Targeting Tight Control of Gouty Arthritis

Study Protocol

Effect of tight urate control in gouty arthritis compared to usual care (TICOGA), a randomised clinical trial

Sponsor	The University of Edinburgh/ Lothian Health Board ACCORD The Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ
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REC Number	IRAS ID 314061
Project registration	NCT 05507723 Tight control in gouty arthritis (TICOGA)
Version Number and Date	Version 3.0 Thursday 07.08.2025
Amendment History	
Amendment 1	Amendments to protocol; **1)** The control arm has been changed to 'Usual Care' from a flare based algorithm of treatment escalation. This simplifies conduct of the trial, and ensures the cost-effectiveness analysis has a comparator which reflects current practice. 2) Power calculation revised based on experience of extension trial, recruitment target reduced to 125 participants 3) Qualitative interview component introduced to explore participant experience and attitudes in greater depth 4) Outcome measures revised in line with updated OMERACT (Outcome Measures in Rheumatology Clinical Trials) guidelines for gout trials
Amendment 2	Amendments to protocol 1) Recruitment of patients through patient engagement

	and display of posters in the community 2) Amendments to body of text to ensure consistency with outcome measures specified in Endpoints Section 2.2 (eg use of SF-36/HAQ-DI in place of EQ5D5L) 3) Clarification of methods used to gather data including use of RedCAP software to generate an electronic patient record, and that this software will be used to allow potential participants to express interest in the trial.

CONTENTS

LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
EPCC	Edinburgh Parallel Computing Centre
GP	General Practitioner
GCP	Good Clinical Practice
NHS	National Health Service
PI	Principal Investigator
PIL	Participant Information Leaflet
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture
RDU	Rheumatic Diseases Unit
WGH	Western General Hospital

Study title:	Tight control in gouty arthritis
Type of study	Randomised clinical trial
Trial participants	Patients with diagnosis of gout requiring urate lowering therapy
Planned sample size	125 participants
Follow-up duration	2 years
Planned trial period	3 years (1 year for recruitment, with 2 years of follow up)
Primary objective	Assessment of clinical outcomes with supported self-management of gout
Secondary objectives	Measurement of health related quality of life Evaluation of cost effectiveness and safety of the approach Assessment of treatment adherence Assessment of brief diet and exercise questionnaires, and compliance with lifestyle advice
Primary endpoint	Proportion of participants flare free in 2nd year of trial
Secondary endpoints	Number of flares of gout in year 1, year 2 and over whole course of trial Proportion of participants achieving urate levels of ≤0.3mmol/L or ≤0.36mmol/L at week 52 and 104 Proportion of participants meeting gout remission criteria at week 52 and 104 Medication compliance assessed by patient self-report, and prescription collection Proportion of participants with tophi at week 52 and 104 Self-reported quality of life and pain at week 52 and week 104 Number of days lost at work and number of medical appointments or hospital admissions due to gout Time to last flare of gout and time to resolution of tophi User enagagement with Smartphone app (number of reminders needed for each submission) Cost-effectiveness and cost-utility analysis Activity limitation measured through Haq-DI Patient understanding and attitudes assessed through qualitative interview
Device name	BeneCheck plus
Manufacturer name	General Life Biotechnology Co Ltd, Taiwan
Principle intended use	Supported self-management of gout

1 INTRODUCTION

1.1 BACKGROUND AND RATIONAL

Gout is the most common cause of inflammatory arthritis with prevalence in the UK estimated at 2.5%, and an incidence that is rising globally alongside epidemics of obesity and cardiovascular disease. For patients it is characterised by sudden attacks of pain of great intensity, and is a cause of reduced quality of life, work absence and disability. For health services gout is an increasing cause of emergency attendance, hospital admission, and prolonged hospital stays. Recent guidelines have emphasised the importance of maintaining urate below target levels in order to achieve long term prevention of gout attacks (Fitzgerald 2020). Within clinical trials or with sufficient support it is clear that the vast majority of patients are able to achieve target serum urate levels, though in routine clinical practice patients rarely meet current recommendations.

Suitable monitoring devices for urate self-testing are available and have been reported to show excellent reliability in comparison to gold standard laboratory diagnostics (Paraskos J, 2016). We have developed a supported self-management approach to gout which uses results of urate self-monitoring to guide escalation of treatment to target urate levels, with communication of results and treatment advice sent through a smartphone application (GoutSMART). This approach has been evaluated in a feasibility trial which showed that the approach was well tolerated and resulted in high attainment of urate targets by 6 months (Riches et al 2022). Exploratory results from this trial suggested that active care participants sustained fewer flares; however this needs to be confirmed in a larger trial with flares as the primary outcome. Similarly we were able to show that participants assigned to active care required fewer GP appointments for review of gout, but we still need to formally evaluate the cost-effectiveness of the approach. The GoutSMART application also provides an opportunity to educate patients about beneficial lifestyle modifications and encourage their implementation with direct feedback through better control of urate levels. Once patients are established on effective urate lowering therapy we aim to offer individualised dietary advice to participants identified as having elevated consumption of certain foods, and then review dietary compliance and its impact on urate levels via frequent urate level testing and repeat Food Frequency Questionnaires during a block of intervention.

Although a treat-to-target urate approach to gout is recommended in rheumatology specialty clinical guidelines (Hui 2017, Fitzgerald 2020), the approach has not been endorsed by primary care practice guidelines (Qaseem 2017) which cite a lack of evidence that such an approach is superior to pragmatic escalation of urate lowering therapy based on gout flares. We wish to investigate the clinical and cost-effectiveness of our treat-to-target urate approach incorporating supported self-management in comparison to a usual care strategy.

2 STUDY OBJECTIVES

2.1 Objectives

2.1.1 Primary Objective

- To assess flare frequency in patients allocated to a treat-to-target urate approach incorporating supported self-management, in comparison to a pragmatic usual care approach.

2.1.2 Secondary Objectives

- To measure health related quality of life.
- To measure proportion of participants achieving resolution of tophi
- To assess treatment adherence by measuring oxypurinol, the active metabolite of Allopurinol, as well as by prescription collection rates

- To evaluate the cost-effectiveness and safety of the approach by gathering data including hospital and GP visits and work absenteeism, and adverse events.
- To assess feasibility of implementation, compliance and impact of lifestyle modification.

2.2 ENDPOINTS

2.2.1 Primary Endpoint

- Proportion of participants flare free in 2nd year of trial.

2.2.2 Secondary Endpoints

- Number of flares in year 1, and year 2 of study and total flares experienced over the 104 week course of the study.
- Proportion of participants flare free in 1st year of trial.
- Patient global assessment of health and pain (both all cause and due to gout) at week 52 and 104 and opportunistically during gout flare
- Time to final flare of gout
- Proportion of participants achieving urate level ≤0.3mmol/l and ≤0.36mmol/l at week 52 and 104
- Proportion of participants with tophi at week 52 and week 104. The number of clinically evident tophi and size of largest baseline tophus (index tophus) at week 52 and week 104
- Proportion of participants achieving remission criteria for gout at week 52 and 104
- Quality of life evaluated using Medical Outcomes Study Questionnaire Short Form 36 at week 52 and 104.
- Activity limitation evaluated using HAQ-DI questionnaire at week 52 and 104
- Number of days lost at work due to gout flare at week 52 and 104
- Number of scheduled and unscheduled medical appointments/ hospital admissions both all cause and due to gout assessed at week 52 and 104 through questionnaire and data linkage.
- Cost-effectiveness (cost per flare avoided) and cost-utility (cost per quality-adjusted life year (QALY) gained) will be determined within the trial using healthcare resource use data (from questionnaires and medical records obtained through data linkage) including both all healthcare resource use and resource use attributable directly to gout.
- Wider societal costs such as carers leave, personal time travelling to/from GP appointments and work absenteeism will be measured by questionnaire and again broken down into total costs and gout attributable costs (utilising the Work Productivity and Activity Impairment Questionnaire: General Health V2.0) at week 52 and 104 and opportunistically during the trial after reports of flares.
- Self report of number of doses of medication omitted in preceding week, and prescription collection rates will be evaluated at week 52 and 104
- Number of reminders received per submission on GoutSMART app
- Patient attitudes and understanding assessed through qualitative interview

3 STUDY DESIGN

3.1 Original study

A total of approximately 125 participants will be recruited. We anticipate that most participants will be identified following referral to rheumatology outpatient or on-call services in NHS Lothian, or through NHS Lothian's gout liaison service. Additional patients may indicate their willingness to participate directly in response to study advertisements.

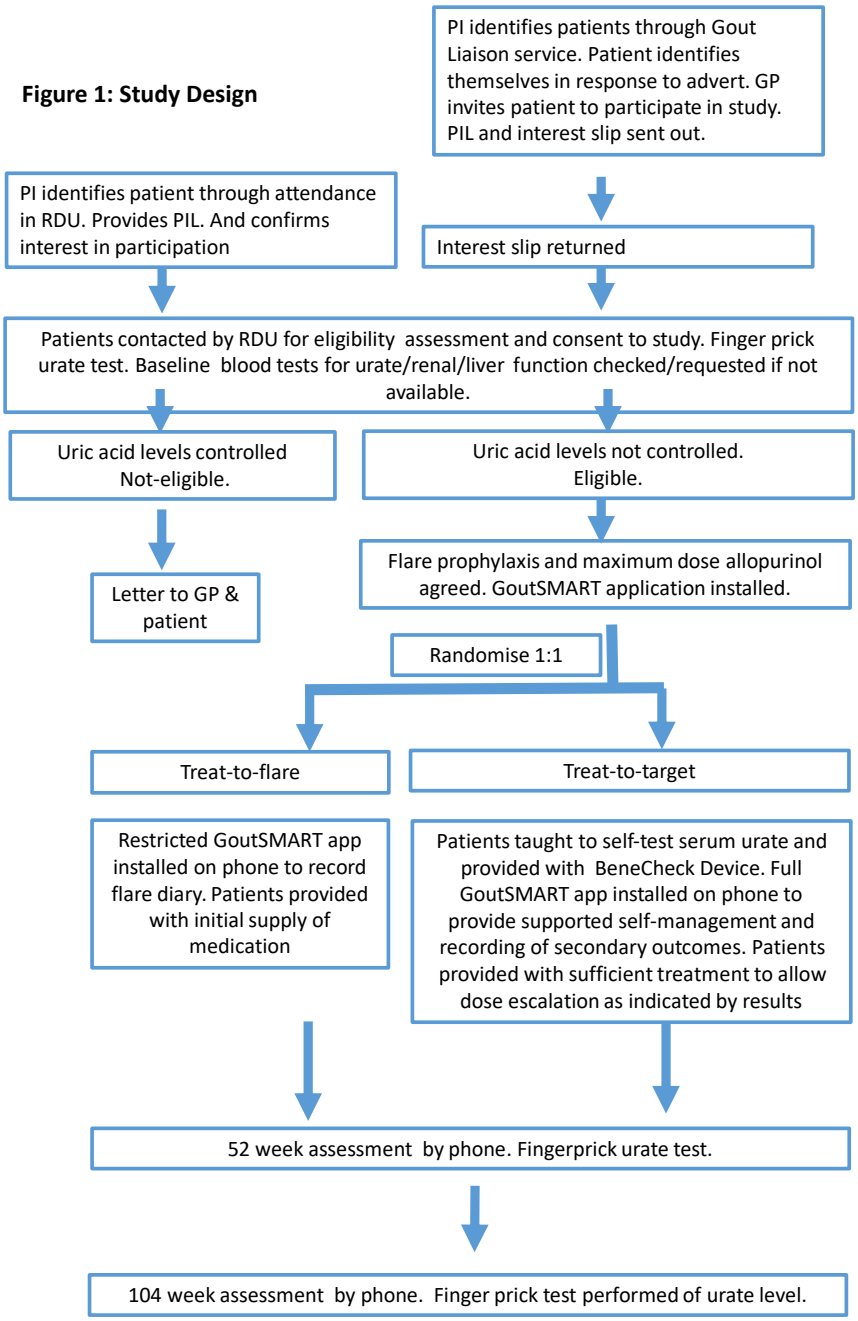
Based on baseline renal function and flare frequency, an individual treatment plan will be drawn up for all participants which will set a ceiling on the maximum dose of allopurinol to be used within the trial and determine the need for flare prophylaxis with colchicine. Participants will be randomized to the intervention group in a 1:1 ratio.

All participants will have a smart phone application (GoutSMART) uploaded to their smart phones. Usual care participants will have a limited version of the GoutSMART application installed which includes background information about gout and provides a means for participants to maintain diaries of gout flares and quality of life. Subjects in the usual care arm of the study will be managed by their GP in line with usual practice. Subjects in the treat-to-target arm will be taught to self-test serum urate using a BeneCheck Plus hand held device and provided with test strips. A full version of the GoutSMART application will be installed with the features mentioned above but also the facility to record a urate diary. Participants will be prompted to check their serum urate and enter the results into the GoutSMART application. Participants reporting a urate level >0.3mmol/l will be advised to increase the dose of allopurinol by 100mg or 50mg depending on renal function, up to the maximum dose of allopurinol specified in their treatment plan. No change will be advised in those whose urate levels are already at target. If the patient needs to increase allopurinol there will be an automatic reminder after two weeks prompting the patients to submit updated self-test results which will be handled in the same way as described above. Conversely for participants achieving target levels this will be acknowledged and a request to resubmit readings will be sent on a monthly basis.

The primary outcome will be the proportion of participants that are flare free in the second year of participation in the trial. Secondary outcomes will include number of flares in year 1, year 2 and over entire trial period, time to last flare, resolution of tophi, urate levels at year 1 and year 2, quality of life measures, compliance measures, and measures of healthcare resource utilisation and societal impact. All reviews will be performed remotely with capillary urate used to assess urate levels at study close to allow social distancing in view of the coronavirus pandemic. To assess treatment compliance drug metabolite levels will be tested from urine samples obtained at week 52 and week 104 visits, and by review of prescription collection. Presence of tophi will be assessed by review of submitted images and patient self-report. All participants will be asked once per month to record flares via the application. The study is designed for a total (post-randomization) duration of 104 weeks. Subjects who withdraw or disengage before the final visit will not be considered to have completed the study.

Cost-effectiveness (cost per flare avoided) and cost-utility (cost per quality-adjusted life year (QALY) gained) will be determined within the trial using healthcare resource use data (questionnaires and medical records obtained through data linkage), primary outcome data and responses to the SF-36. The economic evaluation will assess the cost-effectiveness and cost-utility of treat-to-target with ULT compared to outcomes in the usual care arm. This will take the form of an incremental cost-utility analysis to estimate cost per QALY and an incremental cost-effectiveness analysis to estimate the cost per gout flare avoided over 24 months follow-up. The base-case analysis will be from an NHS and Personal Social Services perspective, with an additional analysis from a societal perspective taking into account productivity losses. The analysis will be report both all healthcare utilisation costs and gout attributable costs.

Figure 1: Study Design



3.2 COVID -19

Research activity continues to be effected by the COVID-19 pandemic. Any research activity will be carried out in compliance with prevailing Scottish and UK Government instructions and guidance as well as the local R&D regulations. This includes continuous risk assessments to minimize the exposure to COVID-19 to any participant, in particular those who are required to socially distance, self-isolate or shield. All scheduled review will be carried out via telephone rather than face to face unless clinically indicated. Consent may not be taken in person but the information is provided prior to a review, discussed via telephone and the participant asked to sign consent in their home forwarding the documents via email or post or online using REDCap software.

4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

We aim to recruit approximately 125 participants. Recruitment will remain open until sufficient numbers of recruited participants has been reached.

4.2 INCLUSION CRITERIA

Subjects must meet all of the following inclusion criteria to enter the study:

- Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all aspects of the study.
- Adult male or female aged ≥18 years.
- Patient has sustained at least one flare of gout in the previous 12 months.
- Confirmed clinical diagnosis of gout as per ACR/EULAR criteria (Neogi T, 2015).
- Serum urate >0.36mm/L.
- Patient has a smart phone and is able to use the GoutSMART application.
- Patient willing to take urate lowering treatment
- Patient is an NHS Lothian patient

4.3 EXCLUSION CRITERIA

Subjects with any of the following criteria will not be accepted into the study:

- Subject is unable to follow consent
- Patient on maximum urate lowering therapy or where therapy cannot be escalated further due to intolerance. Adverse reaction to either allopurinol or febuxostat.
- End stage renal failure (eGFR <15) or previous kidney transplant
- Current prescription of medication known to interact with xanthine oxidase inhibitors such as azathioprine or mercapto-purine.

4.4 CO-ENROLMENT

Co-enrolment may be allowed in purely observational studies, but will not be allowed for any clinical trial involving an investigational medical product.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

We anticipate that most participants will be identified by the principal investigator or the sub-investigator following referral to rheumatology outpatient or on-call services in NHS Lothian, or through NHS Lothian's gout liaison service which identifies NHS Lothian patients that have attended unscheduled care services with acute flares of gout, or have recently been prescribed allopurinol by their primary care physician. Participants may also be identified through attendance at locally held patient information events for gout, or be invited to find out more about the trial through articles published in local media. The GoutSMART website will have a link to the secure REDCap database, (Harris et al., 2009; Harris et al., 2019) where participants can express their interest online. Data submitted via REDCap will be stored on secure, University of Edinburgh managed servers. Potential participants that have been identified by NHS Lothian's rheumatology service, or who have identified themselves as interested in participation, will be invited to participate directly by the study team, or will self-identify through the REDCap database. General practitioners who wish their patients to participate in the study can refer the patient in for outpatient assessment or signpost patients towards online information about the trial. General practices that express an interest in recruiting patients into the study will be designated as Participant Identification Centres and would then be invited to contact potential participants directly.

Posters raising awareness of the study will be placed in the rheumatology outpatient department, and in Unscheduled Care services in NHS Lothian. Further posters may be

displayed with the approval of the relevant authority in primary care healthcare facilities or suitable community locations. These will direct patients to the GoutSMART trial website which hosts a link to the Research Electronic Data Capture (REDCap) database. An email will be sent to General Practitioners in NHS Lothian inviting referral of suitable patients to the rheumatology service. Potential participants who fail screening due to low urate levels will be considered for re-screening within 6 weeks of initial screening based on a repeat urate test.

5.2 CONSENTING PARTICIPANTS

Written and informed consent will be obtained by the principal investigator or the sub-investigator prior to any study-related procedures being undertaken. Verbal and written participant information will be presented to the participant detailing the nature of the study, the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason and without prejudice to future care, and with no obligation to give the reason for withdrawal. The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, the GP or other independent parties to decide whether they will participate in the study. Written Informed consent will then obtained by means of the participant dated signature and dated signature of the person who presented and obtained the informed consent. Consent will be obtained either during a face to face visit, or to minimise COVID-19 exposure, consent may be obtained following a telephone review, or consent may be obtained online via REDCap. If filled out online, the participant will have a chance to contact the research team about any queries about the trial, patient information, or consent form.. The participant may sign the PIL at home and send this physically or electronically via REDCap back to the researcher. A copy of the signed Informed Consent will be given to the participants, and the original or scanned copy of the original be retained at the study site. Alternatively the participant will sign a copy of the consent form electronically on REDCap and a copy of this form will be donwnloaded for inclusion in the participants study file.

5.3 Withdrawal of Study Participants

Participants are free to withdraw from the study at any point or a participant can be withdrawn by the Investigator. Withdrawal by the investigator will be considered when participants are non-compliant with study procedures. At least two attempts will be made to contact the participant to ascertain whether the participant wishes to continue the study.

If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's case report form, if possible. The participant will have the option of withdrawal from
(i) all aspects of the trial but continued use of data collected up to that point
(ii) all aspects of the trial with removal of all previously collected data.
(iii) all aspects of the trial with removal of previously collected and stored participant samples.

6 STUDY PROCEDURES AND ASSESSMENTS

6.1 STUDY PROCEDURES

6.1.1 Screening

Screening will be performed remotely for all participants that have indicated interest in the study either directly, or by return of an interest slip. At this review all inclusion/exclusion criteria will be assessed including confirmation of gout diagnosis, history of gout flares, and willingness to take urate lowering therapy. Blood results will be reviewed for measures of urate, renal and liver function within the last 12 months. For patients in whom necessary baseline blood tests are available the baseline assessment and randomisation can be completed remotely using REDCap's randomisation module. If blood test results are not available then the patient will be invited to attend the rheumatology department to have these parameters assessed in line with normal clinical care. Similarly if in the course of the trial patients are identified as needing switched to Febuxostat they will be invited to attend hospital for updated renal, liver function and urate biochemistry check.

6.1.2 Baseline assessment

The baseline assessment may be completed remotely, or alternatively may be completed at a face to face visit. Written, informed consent to participate in the study will be obtained. Basic anthropometric measurements (weight, height) will be obtained from medical records or estimated by participants, and the presence or absence of tophi documented. A medical and medication history will be obtained with access to the participants emergency care summary. Based on the baseline renal function a maximum dose of allopurinol will be agreed in line with local guidelines. Flare prophylaxis with continuous colchicine for 6 months will be recommended for participants with a history of ≥3 flares in the preceding 6 months. A letter will be sent to the participants general practitioner detailing the treatment plan, where appropriate the recommendation for 6 months supply of colchicine flare prophylaxis, and recommending that both 100mg and 300mg allopurinol tablets be taken as directed by the study team. All participants will install the GoutSMART app onto their phones and will be automatically randomised in a 1:1 ratio to usual care or treatment-to-target. Participants will be randomised using the REDCap randomisation module.

Participants will fill in a baseline questionnaire at the baseline visit, unless there are time constraints, in which the survey will be sent to them to complete at home via REDCap. Questions will include details on previous gout flares within the last year, gout disease duration, lifestyle factors, and healthcare resource use. Work productivity will be measured using the Work Productivity & Activity Impairment – General Health (WPAI:GH) questionnaire, Quality of life will be measured using the Short-Form 36 (SF-36) and Health Assessment Questionnaire Disability Index (HAQ-DI).

6.1.3 Baseline Interventions

Participants allocated to usual care will be supplied with either emergency or continuous use colchicine as determined in their treatment plan. In addition those who are commencing allopurinol will be given a supply of 2 months allopurinol 100mg daily, with those already prescribed allopurinol continuing on their current dose. Participants allocated to treatment-to-target will be given supplies of both 100mg and 300mg allopurinol tablets to facilitate dose titration based on their urate levels. Participants allocated to treatment-to-target will also be provided with a Benecheck urate meter and lancets/test strips and taught how to perform a urate finger prick test.

All participants will have the GoutSMART application installed on their phones, and be shown how to use the application to allow direct communication between the research staff and the participant. All participants will be given access to online resources providing background information on the causes of gout, the likely progression of symptoms, strategies for dealing with acute attacks of gout and the role of urate in gout. All participants will be prompted once per month to update a flare diary through the GoutSMART application. Participants will receive daily reminders to complete these updates, and if this is still not completed by day 7 the trial team will be notified. Adjudication of flares will be performed by trial staff, based on the submitted diaries and in line with the 2018 criteria of Gaffo *et al*.

Participants in the intervention group will receive their treatment plan in the same fashion and will be provided with the BeneCheck hand-held device, taught to perform the serum urate finger prick self-test and shown how to enter this information into the application. Participants will be sent automatic reminders two weeks after any increased dose of urate lowering therapy to test their own urate levels and submit updated readings. If urate levels remain above target the participant will be advised to increase the dose of urate lowering by 100mg or 50mg increments in patients with renal impairment (up to the pre-specified maximum dose of allopurinol). If up-titration is recommended, a reminder to test again will be sent after a further two weeks. Conversely, for participants achieving target levels, acknowledgement will be sent and a request to resubmit readings will be scheduled monthly.

Any participant that requires escalation of therapy in the course of the trial will be recalled to have updated renal and liver function tests in line with normal clinical practice.

6.1.4 Study visit week 52

Participants will be reviewed in person or by telephone at week 52, with in person review preferred for participants with tophi. A finger prick urate test will be performed. The patient flare diaries generated by the GoutSMART application will be reviewed and the number of adjudicated flares recorded. Any adverse advents recorded. All participants will be asked to record the number of doses of medication missed in the preceding 2 weeks, and have prescription uptake reviewed. Quality of life scores will be evaluated using the SF-36 and HAQ-DI questionnaires integrated within the Week 52/104 data collection sheet. The number of days lost at work due to gout flares and the number of scheduled and unscheduled medical appointments/ hospital admissions due to gout will be collected following review of hospital records and through patient self-report. Any adverse events will be recorded.

6.1.5 Final Study visit week 104

Participants will be given their final study review in person or by telephone at week 104, with in person review preferred for participants with tophi. A finger prick urate test will be performed. The patient flare diaries generated by the GoutSMART application will be reviewed and the number of adjudicated flares recorded. All participants will be asked to record the number of doses of medication missed in the preceding 2 weeks, and have prescription uptake reviewed. Quality of life scores will be evaluated using the SF-36 and HAQ-DIquestionnaires. The number of days lost at work due to gout flares and the number of scheduled and unscheduled medical appointments/ hospital admissions due to gout will be collected following review of hospital records and through patient self-report. Any adverse advents recorded. All participants will record a finger prick urate at their final study visit using the Benecheck meter.

A letter will be written to the GP of all participants summarising the disease course and management and proposing further management advice in line with usual clinical practice. Participants who have not yet achieved control of their serum urate by week 104 will be offered further follow up in the gout clinic in line with usual practice.

6.2 STUDY ASSESSMENTS

6.2.1 History and physical examination

A focussed history will be carried out at the specified time points. We will be recording the presence of tophi and take measurements of the largest tophus using supplied callipers at baseline and year 1 and 2 visits. Details of the duration of disease, frequency and pattern of flares will be recorded. Weight and height will be recorded from hospital records or self-report at baseline and weight again at year 1 and year 2.

6.2.2 Laboratory assessments

Serum FBC, U&Es, LFTs, urate will be collected by venepuncture where needed as part of the normal clinical care of the participants.

6.2.3 App assessments

The smart phone application will collect the following data over the 104 weeks of the study

- Number of days of self-reported gout flare, updated monthly through study
- Diary of self-reported urate results

6.2.4 Questionnaires

We will use the SF-36, HAQ-DI and Work Productivity and Activity Impairment Questionnaire: General Health V2.0 to evaluate health outcomes. Study specific questionnaires will be completed at week 52, week 104 and an abbreviated version of this questionnaire after gout flares.

6.2.5 Qualitative Interviews

Patients will be invited to take part in a single semi-structured interview exploring their understanding of gout and its treatment according to a draft interview schedule and at a mutually convenient time during their participation in the trial. The interviews will be conducted face to face within NHS Lothian facilities. Interviews will be recorded using recording devices

meeting AES 256-bit encryption standard. Transcripts of the interview will be prepared using NHS approved transcription software (G2) and these transcripts will be stored on secure servers within NHS Lothian for thematic analysis. Travel expenses will be provided to participants choosing to take part in this aspect of the study.

6.2.6 Linkage

In order to evaluate the full heath economic impact of gout we will contact Public Health Scotland, NHS Lothian primary care pharmacy team or other NHS organisations to identify participant use of healthcare resources through 'data linkage'. This will be linked to the participant CHI number and we expect this information to be available within 6 months of study close.

6.3 STORAGE AND ANALYSIS OF SAMPLES

Where serum biochemistry samples are needed for U&Es, LFTS or urate these will be analysed and stored by local NHS Lothian laboratories. Samples will be discarded as per local protocols.

7 DATA COLLECTION

Data will be collected at baseline, week 52 and 104 visits as well as via the smart phone application on a monthly basis. Data will also be collected opportunistically if participants submit a flare in the GoutSMART app. A shortened version of the study review questionnaires will be sent one week after the start date that a participant has submitted a flare. Data will be collected by the principal investigator and the sub-investigators. The use of REDCap software will be the main source of collecting and storing trial data, though paper copies of questionnaires are also available should the participant wish them. We will use the SF36 and HAQ-DI to evaluate health outcome. To maximise completeness of data collection, every effort will be made to contact participants who have failed to attend scheduled visits, submit requested information via the smart phone application or return questionnaires. Participants will be contacted by telephone on at least two occasions.

7.1 Source Data Documentation

Source documents will be the patient's electronic patient record, electronic data entered into the smart phone application and participant questionnaires completed either on paper or on REDCap.

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7.2 Case Report Forms

An electroniccase report form will be generated for each patient and kept on secure web servers for REDCap, managed by the University of Edinburgh. Any paper documents will be stored in a locked facility at the Rheumatic Diseases Unit at the Western General Hospital Edinburgh.

8 STATISTICS AND DATA ANALYSIS

8.1 SAMPLE SIZE CALCULATION

This clinical trial is intended to establish the clinical-effectiveness of a supported self-management approach, when compared to pragmatic flare based treatment escalation.

The numbers chosen are based on the outcomes observed in our extension trial in which we observed 7.7% of participants sustained flares in the second year of follow up, compared to 33.3% of usual care participants. Based on these values 90% power (alpha 0.05) can be

achieved with a sample size of 100. Similarly for a quality of life analysis based on feasibility trial self-management pain scores of 1.44 +/- 0.57 compared to 1.86 in usual care a sample size of 98 yields 90% power to detect an effect of this size. We will aim to recruit 125 participants assuming 20% drop out rate over the course of 2 years (compared to 10% drop out over 1 year in the feasibility trial)

8.2 PROPOSED ANALYSES

The primary outcome of the study will be the proportion of participants that are flare free in the second year of trial participation. Categorical outcomes will be analysed using the Chi-square test of independence, or Fishers Exact test for where expected values in any cell of the contingency table are less than 5, with results displayed as frequency (percentages). For these analyses an intention to treat analysis will be performed with participants that have dropped out of the study being included as failing to reach target, or non-compliant with medication respectively. Normally distributed continuous study outcomes will be analysed using a T test with results displayed as mean ± standard deviation (SD). A Mann Whitney U test (MWU) will be applied when the variables are not normally distributed, with results given as median (interquartile range IQR). Comparison of number of flares, along with other count data such as number of GP visits will be performed using a 2 sample Poisson rate test. A nominal value of significance of $p<0.05$ will be used for secondary outcomes however given the number of secondary outcomes these will be acknowledged as exploratory. Statistical analysis will be performed using Minitab version 17 (Minitab Inc., Pennsylvania, US).

9 ADVERSE EVENTS

Adverse side effects from allopurinol and febuxostat are rare, with the commonest side effect being of skin rash. All participants will be informed of potential side effects of their treatment in line with usual clinical practice and be able to contact the study team directly to discuss any concerns. The participants' usual primary care physician will be notified simultaneously with details of any medication change to ensure that the primary care records remain accurate and to minimize the risk of drug interactions.

10 OVERSIGHT ARRANGEMENTS

10.1 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of audit or monitoring, the Investigator agrees to allow the representatives of the sponsordirect access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

11 GOOD CLINICAL PRACTICE

11.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

11.2 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. Responsibilities may be delegated to an appropriate member of study site staff.

11.2.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any protocol specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasized that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s).

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant willreceive a copy of this document and a copy filed in the Investigator Site File (ISF) and participant's medical notes (if applicable).

11.2.2 Study Site Staff

The Investigator must be familiar with the protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their trial related duties.

11.2.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

11.2.4 Investigator Documentation

The Principal Investigator will ensure that the required documentation is available in local Investigator Site Files (ISFs).

11.2.5 GCP Training

All researchers will be expected to have undertaken GCP training in order to understand the principles of GCP.GCP training status for all investigators will be indicated in their CVs.

11.2.6 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

11.2.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage,

processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to individuals from the research team treating the participants, representatives of the sponsor(s) and representatives of regulatory authorities.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

12 STUDY CONDUCT RESPONSIBILITIES

12.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Amendments will be submitted to a sponsor representative for review and authorisation before being submitted in writing to the appropriate REC, and local R&D for approval prior to participants being enrolled into an amended protocol.

12.2 MANAGEMENT OF PROTOCOL NON COMPLIANCE

Prospective protocol deviations,i.e.protocol waivers,will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation. All protocol deviation logs and violation forms should be emailed to QA@accord.scot

Deviations and violations are non-compliance events discovered after the event has occurred. Deviation logs will be maintained for each site in multi-centre studies. An alternative frequency of deviation log submission to the sponsors may be agreed in writing with the sponsors.

12.3 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (seriousbreach@accord.scot) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to research ethics committees as necessary.

12.4 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 3 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

12.5 END OF STUDY

The end of study is defined as the last participant's last visit.

The Investigators or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, and R+D Office(s) and co-sponsors within 90 days, or 15days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to resgov@accord.scot.

A summary report of the study will be provided to the REC within 1 year of the end of the study.

12.6 CONTINUATION OF TREATMENT FOLLOWING THE END OF STUDY

All participants will continue on treatment following the end of study in line with usual clinical practice.

12.7 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.
- Sites outwith the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.

13 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

13.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team. For all papers arising from the study the Principal Investigator, and the person who drafted the paper will decide on authorship order and the corresponding author role. Selection of additional authors will remain in line with the criteria of the International Committee of Medical Journal Editors (ICMJE) and that of the Journal to which the article is submitted.

13.2 DISSEMINATION OF RESULTS

The results of the trial will be published, and details of the experience gained disseminated to physicians with an interest in gout attending European and American specialist networking meetings (European Crystal Network and G-CAN (Gout, Hyperuricaemia and Crystal-Associated Disease Network). If this study should be successful then this would represent a substantial development in the delivery of better care in an area of long unmet need. In theory the approach could be adopted very easily, and since the intention is to develop an approach

that requires less intervention but provides better care, it is to be anticipated that this would find favour with policy makers and service users alike. A full cost analysis will be provided in order to facilitate adoption of the approach by policy makers. All participants will be informed of the results of the research by letter.

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