Study Protocol

Improving the care of Gout –Self-Management Aiming to Reach Target urate (Gout-SMART) –feasibility study

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Amendment classification and number:	**Summary of change(s)**
Amendment number 1	1) Addition of stool and urine samples at baseline for faecal and urinary metabolomics and gut microbiota characterization using shotgun metagenomic sequencing. 2) Change from use of the Edinburgh Clinical Trials Centre (ECTU) to host the GoutSMART webportal to the Edinburgh Parallel Computing Centre (EPCC) 3) Change in the urate meter device used from HumaSens to BeneCheck 4) Editing of PIS and CF version 1.1 (29/3/18) to reflect the above – now version 2.0 (30/11/18). 5) New inclusion of PIS and consent form (V2.1) to include control subjects which are first degree, near relatives or age- and gender-match non-relative controls for once-off stool, urine, dietary and serum

	urate and bioprofile analysis. 6) Revised study protocol – previously v1.2 (29/3/18), now v2.0 (30/11/18) **7)** Additional promotional email of the study for Lothian GP v1.0 (30/11/18)
Amendment number 2	1) Specification of anthropometric measurements at visits added 2) Addition of 24 hour urine collection and blood sample for renal function as paired samples for analysis of urate metabolism 3) Editing of PIS and CF version 2.0 (30/11/18)_Patients and PIS and CF version 1.0 (30/11/18)_Controls to reflect the above –now versions 3.0 and 2.0 (15/02/19), respectively
Amendment number 3	1) Specification of use of SHARE for participant recruitment within protocol 2) Clarification that all referrals will be considered. 3) Further promotional email for Lothian GP v2.0 (30/06/19)
Amendment number 4	1) Changes to protocol in light of COVID-19 risk assessment ; for the 24 and 52 week study visits the option of telephone consultations is now included to allow continued participation despite requirements for social distancing or self-isolation. At these study assessments capillary rather than serum urate will be used to assess achievement of urate target, and tophus assessment will be made by review of submitted images.
Amendment number 5	1. Change to study procedures 6.1.1 to allow payment of reasonable expenses to participants in the study 2. Changes to protocol to allow extended participation in the study. Changes made to Background and rationale, Study design and Endpoint Sections
Amendment number 6	1) Changes to protocol to allow recruitment of participants into long term monitoring arm of study. Changes made to Study design Sections 3.2, Study population Section 4.1, Sample size calculation 8.1

CONTENTS

LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
EPCC	Edinburgh Parallel Computing Centre
GP	General Practitioner
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
PI	Principal Investigator
PIL	Participant Information Leaflet
QA	Quality Assurance
REC	Research Ethics Committee
RDU	Rheumatic Diseases Unit
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SHARE	Scottish Health Research Registry
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
WGH	Western General Hospital

Study title:	
Type of study	Feasibility study
Trial participants	Patients with diagnosis of gout requiring urate lowering therapy
Planned sample size	60 participants and 60 non-gout controls
Follow-up duration	1 year for GoutSMART study, further 2 years if participating in GoutSMARTER extension
Planned trial period	2 years (4 years in total with GoutSMARTER extension)
Primary objective	Assessment of supported self-management of gout
Secondary objectives	Measurement of gout flare frequency and health related quality of life Evaluation of cost effectiveness and safety of the approach Assessment of treatment adherence Identification of uric acid load in faecal samples and correlation with gut microbiome characteristics. Assessment of compliance with dietary modification and impact on serum urate levels.
Primary endpoint	Proportion of participants achieving urate levels of ≤0.3mmol/L at 24 weeks
Secondary endpoints	Proportion of participants achieving urate levels of ≤0.3mmol/L at 52wks (and for extension 104wks and 156wks) Medication compliance assessed by patient self-report and serum oxypurinol Number of days of self-reported gout flare Size in mm of the largest tophus (index tophus) and number of clinically evident tophi Self-reported quality of life during/following gout flare evaluated using the EQ-5D-5L questionnaire Number of days lost at work and number of scheduled and unscheduled medical appointments or hospital admissions due to gout Proportion of patients achieving a dose reduction of urate lowering therapy in the extension phase Proportion of patients achieving sustained dietary modifications and relative reduction of urate lowering therapy in the extension phase.
Device name	BeneCheck plus
Manufacturer name	General Life Biotechnology Co Ltd, Taiwan
Principle intended use	Self-management of gout by patients in the community managed by the general practitioner

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 (Khanna J, 2012). 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. High levels of serum urate can result in the formation of urate crystal deposits under the skin (called tophi) which are a marker of severe disease. These will resolve if serum urate levels are held low for a sustained period of time. Tight control of gout with a target of urate at or below 0.3mmol/l should achieve disease remission (clearance of all crystals from the body), but once this has been achieved recent guidelines suggest that keeping urate levels at or below 0.36mmol/l should prevent recurrence of disease. There is no consensus on how long tight control of urate is required, nor is there published experience of long term disease related outcomes in gout patients that have achieved target urate levels.

A new paradigm of care for patients is required. Providing patients with the means to measure their own levels of serum urate would reduce the requirement for review appointments needed to guide escalation of therapy to achieve target, and possibly reinforce patient adherence to treatment. Suitable monitoring devices for urate self-testing are already available and have been reported to show excellent reliability in comparison to gold standard laboratory diagnostics (Paraskos J, 2016). Within our unit there is already experience in the use of applications for smart phones facilitating patient feedback of self-testing results, and the interactive nature of this approach provides additional opportunity for providing support to patients at time of need. This could help establish a patient led approach to gout management, similar to the ‘treat to target’ approach adopted in the management of diabetes.

We also aim to understand the contribution of the gut microbiome to the pathogenesis of gout. Little is known about the factors that contribute to uric acid and purine availability within the gut lumen. Some preliminary evidence (Guo Z, et al. 2016) has suggested that gut bacteria resident in patients with gout is different than controls. We would like to challenge and develop this hypothesis by quantifying the availability of purine and urate metabolites within the gut as well as the metabolic potential of gut microbes known to play a role in uric acid and purine metabolism. This section of the study may pave the way for future development of anti-microbial, dietary modification or probiotic agents that may contribute to reducing uric acid availability within the gut and the burden of gout in the wider population.

It has long been suggested that certain lifestyle factors including dietary factors impact the risk of hyperuricaemia and gout. The British Society for Rheumatology Guidelines for Management of Gout (Hui M, et al. 2017) includes that all patients with gout should be encouraged to follow a well-balance diet low in fat and added sugars, high in vegetables and fibres specifically advising the avoidance of sugar-sweetened soft drinks containing fructose, high-purine foods and reducing alcohol intake. However, implementing this knowledge and routinely including this step in the management of patients with gout is challenging due to a variety of factors including limited time resources in primary care. The GoutSMART application provides the opportunity to educate patients of beneficial lifestyle modifications and encourage implementation with direct feedback through control of urate levels and regular review by the healthcare professional, Lifestyle changes may ultimately allow the use of lower doses of urate lowering therapy. During an extension phase, we aim to offer individualised dietary advice based on a Food Frequency Questionnaire for those patients with 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.

2 STUDY OBJECTIVES

2.1 Objectives

2.1.1 Primary Objective

- To assess supported self-management of gout using an application on a smart phone and self-testing of serum urate.

2.1.2 Secondary Objectives

- To measure gout flare frequency and health related quality of life.
- To assess treatment adherence measuring oxypurinol, the active metabolite of Allopurinol
- To evaluate the cost-effectiveness and safety of the approach by gathering data including hospital and GP visits and work absenteeism, and adverse events.
- Identification of uric acid load in faecal samples and correlation with gut microbiome characteristics.
- To assess feasibility of implementation, compliance and impact of dietary modification on serum urate levels.

2.2 ENDPOINTS

2.2.1 Primary Endpoint

- Proportion of participants achieving urate level≤ 0.30mml/L at 24 weeks.

2.2.2 Secondary Endpoints (assessed at week 24 and 52, and for extension study also at week 104 and 156)

- Proportion of participants achieving urate level ≤0.3mmol/l and ≤0.36mmol/l
- Prospectively gathered number of days of self-reported gout flare over course of study
- Size in mm of the largest tophus at baseline (index tophus)
- The number of clinically evident tophi
- Prospectively gathered self-reported quality of life during/following gout flare evaluated using the EQ-5D-5L questionnaire over course of study
- Prospectively gathered data on days lost at work due to gout flare over course of study
- Prospectively gathered number of scheduled and unscheduled medical appointments/ hospital admissions due to gout over course of study
- Self report of number of doses of medication omitted in preceding 2 weeks will be collected at all study visits
- Plasma oxypurinol levels will be measured at study visits where possible
- Proportion of patients achieving a dose reduction of urate lowering therapy in the extension phase whilst maintaining target urate levels.
- Proportion of patients achieving sustained dietary modifications with reduction of urate levels, and/or further reduction of urate lowering therapy dose in the extension phase.

3 STUDY DESIGN

3.1 Original study

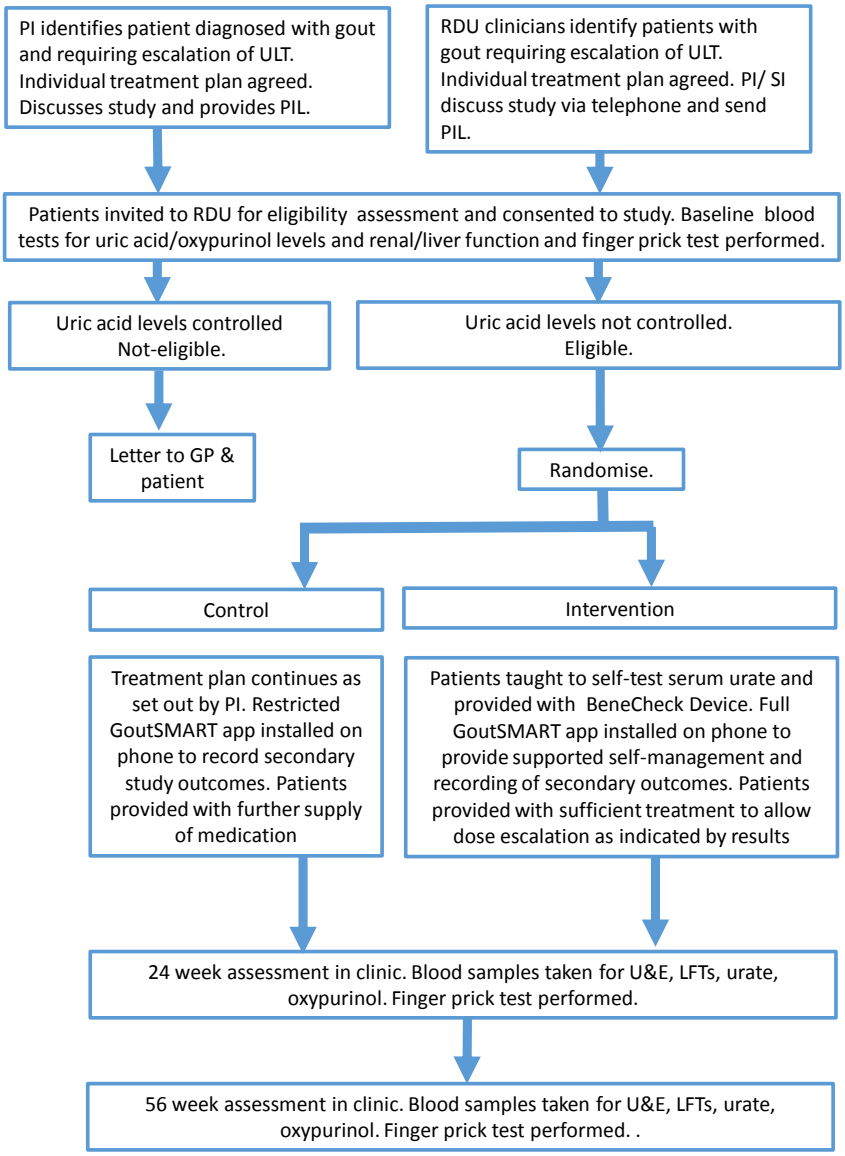
This is a feasibility study. A total of approximately 60 patients will be recruited from rheumatology clinics or rheumatology on-call services in NHS Lothian. Participants will be randomized to the intervention group in a 2:1 ratio. Based on baseline renal function and serum urate levels, and in line with local protocol, an individual treatment plan will be drawn up for all participants with the goal to achieve serum urate level of ≤0.30mm/L. A sample from a 24 hour urine collection and paired serum creatinine and urate sample from each participant will be analysed for urate metabolites. The treatment plan will be communicated to the patient and their general physician.

All participants will have a smart phone application developed by IT specialists in the EPCC uploaded to their smart phones. Control participants will have a limited version of the GoutSMART application installed with background information about gout and providing a means for participants to enter details of gout flare frequency and quality of life through the trial. Subjects in the intervention group 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 incorporating advice on urate monitoring and medication titration. Participants will be prompted to check their serum urate on two separate days and enter the results into the GoutSMART application. The application will respond by a) a suggestion to increase urate lowering therapy or b) to stay on the current dose of allopurinol. If the patient needs to increase allopurinol there will be an automatic reminder two weeks after any increased dose of urate lowering therapy prompting the patients to test their own urate levels on two separate days and submit updated readings 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 until 3 consecutive target readings have been obtained. 6 months is given until review reflecting current practice.

The main outcome will be urate levels at week 24, with a secondary outcome being urate levels at week 52. Where participants are able to attend hospital then both serum and capillary urate will be obtained and the serum urate will be used as the study outcome, however we anticipate that a capillary urate only will be obtained in participants required to self-isolate or maintain social distancing during the coronavirus pandemic and this will be used to determine the urate level at week 24 and 52 for affected participants. To assess treatment compliance drug metabolite levels will be tested from serum samples obtained at week 24 and 52 visits where possible, and by self report in all participants. All patients will be assessed for tophi at baseline by clinical exam, and again at week 24 and 52. This will be by examination if participants are able to attend hospital, or by review of submitted images where attendance at hospital is not appropriate due to coronavirus restrictions. All participants will be asked once per month to record flares, measurements of quality of life, number of hospital and GP visits as well as days off work via the application. The study is designed for a total (post-randomization) duration of 52 weeks. Subjects who withdraw or disengage before the 24 week visit will not be considered to have completed the study.

For the gut microbial aspect of this study, eligible participants will fill in an online semi-quantitative food frequency questionnaire (FFQ, Scottish Collaborative Group – see Zgaga et al, PLOSone 2012). Patients will also provide an early morning urine sample for urinary metabolomic analysis and a fresh faecal sample for subsequent faecal metabolomics and shotgun metagenomics. To provide suitable controls, patients will be asked whether they are happy that a family member be contacted to provide control samples for this analysis. In this case, first or secondary sex-matched controls without gout will be contacted by the study team for a once-off visit (Medical history, bloods – serum urate LFTs, renal function, FFQ and urine and stool samples). Patients can opt out of having a family member involved if they wish in which case local controls (age-similar and sex matched) will be recruited from the staff of the University of Edinburgh.

Figure 1: Study Design



3.2 Extension phase

Urate-lowering therapy requires a long term commitment from the patient and health care provider. We know that levels of medication adherence in gout are unusually low (Dehlin M, 2017 and Briesacher BA, 2008). A recent randomised controlled trial comparing specially trained nurses leading care versus usual care in the UK, showed that with dedicated surveillance and monitoring, the use of urate lowering therapy is significantly higher at 1 and 2 years in the nurse-led compared to the usual care group (Doherty M, 2018). The GoutSMART approach may provide an alternative means for patients to monitor their disease and increase awareness of the role and importance of long-term urate lowering therapy for disease control thereby increasing adherence. At the 12 month study visit all participants will be invited to participate in a 2 year extension to the study which will evaluate long term compliance with medication along with clinical outcomes. Additional participants will be invited to take part in

this long term monitoring arm of the study and will be randomised 1:1 to active monitoring or routine care. All participants taking part in this extension study will have their medication optimised using the GoutSMART approach to ensure that their urate level is at target of 0.3mmol/l or less.

For participants in the active care arm of the study ongoing monitoring of self-reported urate will be performed until participants meet criteria for disease remission. For the purposes of this study we will define disease remission to have been achieved if all three of the following outcomes have been achieved:

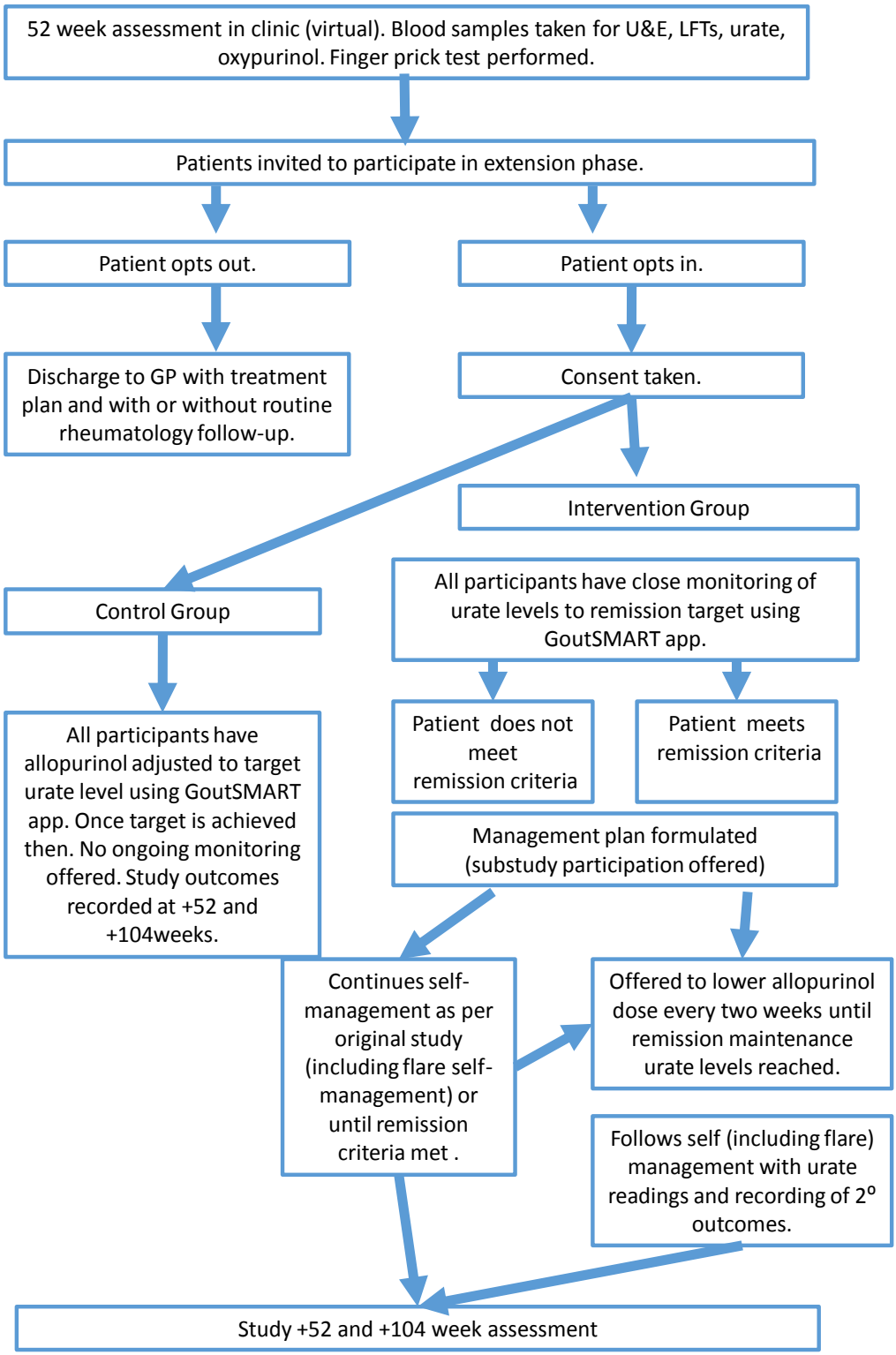
1) Resolution of clinically evident tophi
2) Urate levels at or below 0.3mmol/l over preceding 12 months (with minimum of 3 separate readings obtained in different months.
3) Resolution of gout flares (self-reported) for 12 months

When remission has been achieved by these criteria then participants will be given the option to reduce their dose of allopurinol in line with current best practise guidelines which suggest that maintaining urate below 0.36 mmol/l is sufficient to maintain remission, and that long term urate levels should not be held below 0.18mmol/l.

Participants that were assigned to usual care will have their care optimised using the GoutSMART approach until they have achieved a urate at or below the target of 0.3mmol/l, but in line with usual clinical practise will have no further titration of their medication or outpatient clinical review after this point. Outcomes will be reviewed at 12 months, 24 months, and 36 months as part of the extension study.

In addition, all patients in the active care arm will be invited to participate in a dietary modification substudy during the extension phase. Those in whom aspects of dietary discordance with current BSR guidelines have been identified utilising the Food Frequency Questionnaire, will be offered an individualised plan of dietary modifications to be implemented over a period of time lasting up to three months. Regular measurements of urate levels and diet feedback will monitor progress.

Figure 2: Study Design Extension Phase



3.3 COVID -19

Any research activity continues to be effected by the current 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. In practice this will require adaptations in most activities. 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.

4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

We aim to recruit approximately 60 participants. Recruitment will remain open until sufficient numbers of recruited participants has been reached. Additional participants satisfying the same inclusion and exclusion criteria (but without any urate threshold requirement) will be recruited into the extension study to ensure sufficient power is maintained). An equal number of control participants will be recruited for the purposes of the gut microbiota analysis.

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.
- Confirmed clinical diagnosis of gout as per ACR/EULAR criteria (Neogi T, 2015).
- Physician recommendation that initiation or escalation of urate lowering therapy (Allopurinol or Febuxostat) is required guided by further monitoring of serum urate levels.
- No previous adverse reaction to Allopurinol or Febuxostat.
- Serum urate >0.36mm/L.
- Patient has a smart phone and is able to use application.

For the gut microbiota part of this study control participants must be:

- Adult male or female aged ≥18 years.
- Evidence of a personally signed and dated informed consent document indicating that the subject (or a legally acceptable representative) has been informed of all aspects of the study.

For the extension study

- Patient has completed week 52 of original study
- Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all aspects of the extension study.

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 where therapy cannot be escalated further
- Severe renal failure (eGFR <30) or established liver disease

- Current prescription of medication known to interact with xanthine oxidase inhibitors such as azathioprine or mercapto-purine.

For the gut microbiota part of this study - subjects are excluded from the control group if any of the previous or following are present:

- Have a history of gout
- Taking urate lowering therapy
- Have a history of inflammatory bowel disease or colorectal cancer
- Have had oral antibiotics in the previous 3 months
- Have had a total colectomy previously
- Have suffered an infective gastro-intestinal illness in the previous 6 weeks.
- No face to face visits or samples will be arranged for participants that have ever tested positive for, or had symptoms suggestive of, COVID-19

4.4 CO-ENROLMENT

Co-enrolment will not be allowed in any circumstances.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Participants will be identified by the principal investigator or the sub-investigator following assessment by the NHS Lothian Rheumatology service. It is anticipated that most participants will be identified following routine and acute-care referrals to NHS Lothian Rheumatology services by the participants' general practitioner or secondary care physicians, however any appropriate referral will be considered including referrals from out with NHS Lothian. Additional participants will be sought through SHARE - The Scottish Health Research Register which is a register of adults and children aged 11 and over who are willing to be invited to take part in medical research.

Posters raising awareness of the study will be placed in the rheumatology outpatient department, and in Acute receiving units at Western General Hospital and Royal Infirmary of Edinburgh. An email will be sent to General Practitioners in NHS Lothian inviting referral of suitable patients to the rheumatology service.

In the case of control participants for the microbiota analysis, patients can opt in or out of having a family member as a control participant. If the patient agrees, he/she will be asked to pass the Patient Information Leaflet (PIL – control version) to their relative who will be invited to contact the study team if they are interested in participation. Family members can be first degree or second degree relatives of the same sex. In the event that no family member is suitable or willing to be involved then an age-similar, sex-matched control may be recruited from the staff of the University of Edinburgh, the Western General Hospital or SHARE.

Study participants in both the GoutSMART, as well as the microbiome part of the project who fail screening will be considered for re-screening within one month of initial screening. Subjects of the microbiome control group will be considered for re-screening up to 3 months from initial screening.

All patients of the GoutSMART active and control arm completing the study at week 52 will be invited to participate in the extension study.

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. A copy of the signed Informed Consent will be given to the participants. The original signed form will be retained at the study site.

Patients invited to participate in the extension phase of the study will be provided with written information about the extension via email or in the post with at least 48 hrs time to read the information pior to there week 52 review. Consent will be obtained either during the face to face visit. To minimise COVID-19 exposure, consent may be obtained following a telephone review. The participant may sign the PIL at home and email or post this back to the researcher.

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 Baseline visit

Written and informed consent will be obtained. A history will be taken, basic anthropometric measurements taken (blood pressure, weight, waist circumference) and physical examination be performed. Full medication history will be obtained from participants. Blood samples will be taken for measurement of urate, full blood count, renal and liver function and oxypurinol levels. A finger prick testing for urate levels will be carried out. Participants will be asked to collect urine over a period of 24hrs to hand into the lab as soon as feasible after the baseline visit. A blood sample for creatinine and urate will be taken at that point for paired analysis with urine. Eligible subjects will be randomised at a 1:2 ratio to usual care or supported self-management using a web-based randomisation tool.

For the purposes of the microbiome analysis, patients will provide a once off stool and urine sample at baseline in addition to filling an online food frequency questionnaire. For control subjects for the microbiome analysis, participants will attend on one occasion to provide written informed consent, medical history review, FFQ, blood samples for urate, renal and liver function and oxypurinol levels. In addition they will provide an early morning urine sample and a fresh faecal sample. They will also be asked to collect urine over the 24hour period and a paired serum renal function and urate blood sample will be taken when handing the collection in. No further follow-up visits are planned.

No payment shall be made for participation in the study but compensation for costs of travel to the Western General Hospital shall be offered to control participants up to a value of £30

6.1.2 Intervention procedures

Based on the baseline renal function and serum urate levels, and in line with local protocols, an individual treatment plan will be drawn up for all participants in both groups. This includes a management plan for a potential episode of gout-flare and offering of flare prophylaxis. The treatment plan will be sent to the general practitioner and the patient copied in. All participants will be examined at baseline and the number and size of tophi (if present) will be recorded.
All participants will have the GoutSMART application installed on their phones, and be taught 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 importance of controlling serum urate levels. All participants will be prompted once per month to enter information about their disease severity including the number of days of flare per month, health related quality of life during and after flares, number of days lost at work and the number of health care appointments attended.
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 (including that of the plan set during baseline clinic consultation) to test their own urate levels and submit updated readings. If urate levels remain above target, written advice to increase the dose of urate lowering will be sent to the patient and supervising physician advising up-titration of therapy, with this confirmed also by text message. 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 sent on a monthly basis until three consecutive target readings have been obtained. Six months are allowed to ensure that all participants have the opportunity to escalate to maximum therapy and potentially switch to alterative urate lowering therapy if required.

6.1.3 End-of study visit week 24

Participants will be invited to the RDU clinic, or alternatively if hospital attendance is not appropriate due to recommendations to self-isolate or maintain social distancing due to the coronavirus pandemic then this assessment will be made by telephone. The patient diaries generated by the GoutSMART application will be reviewed and any adverse advents recorded. Participants will complete a questionnaire on their experience with standard care or the testing device and the smart phone application. All participants will be asked to record the number of doses of medication missed in the preceding 2 weeks. A physical examination will be performed to assess the size and number of tophi, or submitted images will be reviewed Finger prick and/or serum urate will be measured along with blood tests of full blood count, renal and liver function tests and oxypurinol levels. A letter will be written to the GP of all participants summarising the disease course and management throughout the past 24 weeks and proposing further management advice. All participants will retain access to the smart phone application and be asked to enter information about the disease course on a monthly basis until week 52.

6.1.4 Follow-up visit week 52 (and for extension study week 104 and 156)

Participants will be invited to the RDU clinic for review of secondary outcomes, or alternatively if hospital attendance is not appropriate due to recommendations to self-isolate or maintain social distancing due to the coronavirus pandemic then this assessment will be made by telephone. The patient diaries generated by the GoutSMART application will be reviewed and any adverse advents recorded. All participants will be asked to record the number of doses of medication missed in the preceding 2 weeks. A physical examination will be performed to assess the size and number of tophi or submitted images will be reviewed. Finger prick and/or serum urate will be measured along with blood tests of renal and liver function tests and oxypurinol levels.

All participants completing the study at week 52 will be offered participation of the extension phase of the study. Written information will have been provided prior to their week 52 review about the extension. Consent will be gained from those choosing to participate in the extension phase. A treatment plan will be formulated for all participants. Participants of the intervention arm in remission will be offered to reduce the dose of their urate lowering medication and self-reassess every two weeks (update urate levels, entering disease activity

data) until remission maintenance is achieved. Feedback will be provided in the usual GoutSMART application manner. Participants of the control arm will continue as per routine care. Once remission maintence is achieved monthly urate reading will be requested. The participant will be asked to enter additional urate readings and QoL information during flares.

For those opting into the dietary lifestyle intervention arm, a personal management plan with dietary adjustments where appropriate will be formulated based on the Food Frequency Questionnaire which each participant will fill in at baseline. Participants will be asked to perform weekly urate measurements, weight measurements and report on flares via the app. Feedback will be provided by the research team at least weekly for the first 4 weeks, then monthly for three months. Participants will be asked to fill in the Food Frequency Questionnaire at extension baseline, monthly for three months and at the end of study.

A letter will be written to the GP of all participants summarising the disease course and management and proposing further management advice including the information of continued participation in trial if agreed. Participants opting out of participation of the extension phase who have achieved target levels of serum urate will be discharged back to care by their primary care physician. Participants who have not yet achieved control of their serum urate by week 52 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 and physical examination will be carried out at the specified time points. This includes basic anthropometrics weight, height, waist circumference and blood pressure. We will be recording the presence of tophi and take measurements of the largest tophus. Details of the duration of disease, frequency and pattern of flares will be recorded.

6.2.2 Laboratory assessments

Serum FBC, U&Es, LFTs, urate and oxypurinol levels will be collected by venepuncture.

6.2.3 App assessments

The smart phone application will collect the following data monthly over the 52 weeks of the study

- Number of days of self-reported gout flare
- Self-reported quality of life during/following gout flare evaluated using the EQ-5D-5L questionnaire
- Number of days lost at work due to gout flare
- Number of scheduled and unscheduled medical appointments/ hospital admissions due to gout

6.2.4 Questionnaires

We will use the EQ-5D® standardized instruments EQ-5D-5L to evaluate health outcomes. Study specific questionnaires will be completed at week 24, week 52, week 104, and week 156 visits.

Participants will fill an online version of the Scottish Collaborative Group food frequency questionnaire (FFQ) – see Zgaga et al, PLOSone 2012. This comprises a semi-quantitative measure of approximately 150 commonly consumed food items. The questionnaire will also be used for the extension substudy at week 52 and week 3 months and end of study for the extension phase. Participants of the substudy will also fill in a short dietary compliance report.

6.2.5 Biomarker analysis

Participants will be asked to provide an additional sample of about 50ml of venous blood at the baseline visit. In most cases the blood sample will be taken on this single occasion only, but selected participants who have previously consented may be approached and asked to provide an additional blood sample if there is a technical problem with processing the original

sample. The sample will be used for DNA extraction and serum will be separated and stored for biochemical analysis. Analysis of candidate genes thought to be involved in the pathogenesis and response to treatment of gout will be performed using standard methodology. The genes to be studied will include variants identified in the analysis of the Febuxostat versus Allopurinol Streamlined Trial (FAST study) that are found to be associated with response to treatment with urate lowering therapy.

6.2.6 Urinary metabolomics

Fresh urinary samples will be provided in a standard universal container. Samples will be the first void on the morning that the sample is provided.

6.2.7 Faecal samples

Fresh and formed faecal samples will be provided by participants ideally on the day of measurement. Participants will be provided with instructions and equipment to safely and effectively collect and deliver the sample to the research staff.

6.3 STORAGE AND ANALYSIS OF SAMPLES

Routine serum biochemistry samples for U&Es, LFTS, urate and oxypurinol will be analysed and stored by local NHS Lothian laboratories. Samples will be discarded as per local protocols.

For biomarker analysis, DNA extraction will be performed in the research laboratories at the Centre for Genomics and Experimental Medicine, at the Institute of Genetics & Molecular Medicine according to standard procedures. The DNA samples will be stored frozen in these facilities or in another suitable storage facility. It is anticipated that the samples and associated clinical information will be stored indefinitely to allow replication of future genetic studies identifying variants involved in the pathogenesis and response to treatment of gout.

For urinary metabolomic analysis, urinary samples will be centrifuged and aliquoted into 2mls containers. These will be stored at -80 degrees Celsius at the research laboratories of the Centre for Genomics and Experimental Medicine, at the Institute of Genetics & Molecular Medicine.

Formed stool samples will also be delivered by study staff to the research laboratories of the Centre for Genomics and Experimental Medicine, at the Institute of Genetics & Molecular Medicine. Here, DNA extraction will be performed on arrival according to a standardized protocol and samples will be aliquoted before being frozen at -80 degrees Celsius. Urinary samples will subsequently be analysed en masse to quantify levels of metabolites related to purine and uric acid metabolism. Likewise, faecal water will be used to quantify levels of metabolites related to purine and uric acid metabolism. DNA extracted from faecal samples will also be used to characterise the gut microbiome using shotgun metagenomic sequencing.

7 DATA COLLECTION

Data will be collected at baseline, week 24 and 52 visits as well as via the smart phone application on a monthly basis. Data will be collected by the principal investigator and the sub-investigators. We will use the EQ-5D® standardized instruments EQ-5D-5L 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.

7.2 Case Report Forms

A paper case report form will be generated for each patient and kept 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 is a feasibility study which is intended to establish whether the proposed self-management approach can be realised in practice, and if so to inform the design of a larger study that would look to establish the cost-effectiveness of this approach.

The numbers chosen are based on previous audits in primary care performed which revealed that only 24% of gout patients reached a target of 0.30mmol/l of serum urate when receiving standard care by GPs who were given an algorithm for management of gout beforehand. We have assumed that about 25% of patients assigned to routine care will achieve the target of 0.3mmol/l in the control group. We are anticipating that we will achieve target levels of urate in 75% of patients in the intervention group which though ambitious is still well below the 92% achieved in a recent UK study (Rees, F. 2013). Based on these estimates a sample size of n=34 in the intervention group and n=17 in the control group (2:1 randomisation) provides 82% power to detect an effect of 25% in the control group and 75% in the intervention group (assuming a two-sided 5% significance level), after taking into account a 15% drop-out rate.

For the extension study we have assumed that 90% of participants in the Smart care arm of the study remain adherent to therapy, compared with only 50% in the usual care arm. These figures are conservative compared to 95% compliance reported in Doherty et al (2018) and 36.8% medicine possession ratio reported in Briesacher et al (2008). A sample size of 20 in each allocation yields 81% power, and 30 in each treatment allocation 94% power to detect such a difference. Due to observed drop outs from the feasibility study and restrictions in recruiting participants during the COVID pandemic we will recruit additional participants into the extension phase of the study to ensure sufficient power is achieved.

8.2 PROPOSED ANALYSES

The primary outcomes of the study will be the proportion of participants achieving urate level ≤0.3mmol/l at 24 weeks in participants receiving supported self-management compared to those receiving usual care. Comparison of proportions will be performed 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).The proportion of participants achieving serum urate level ≤0.3mmol/l at all subsequent assessments will be analysed in the same fashion. Patients with undetectable levels of oxypurinol will be deemed to be non-compliant and a similar analysis will compare the proportion of participants in each treatment allocation that are non-compliant. 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.

Continuous outcome measures include the size in mm of the largest tophus at baseline (index tophus) measured at 52 weeks, and the number of clinically evident tophi evaluated at 52 weeks. Further continuous outcomes include the number of days lost at work due to gout flare, number of scheduled and unscheduled medical appointments/ hospital admissions, self report of number of doses of medication omitted in 2 weeks prior to study visits at week 24 and 52. Two-tailed independent student t-tests will be applied for between group comparisons of normally distributed data. Results will be 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). Although a nominal value of significance of $p<0.05$ for these exploratory measures will be adopted, given the number of secondary outcomes listed a Bonferroni correction will be applied and reported alongside each result.

Although health reported quality of life data will be gathered this is exploratory data that will not be analysed directly but be used to inform the design of a larger health economic study.

Statistical analysis will be performed using Minitab version 16 (Minitab Inc., Pennsylvania, US) or the Statistical Package for Social Services version 19 (SPSS IBM Corp, NY State, 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 of3 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 feasibility study will be published in their own right, 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). The immediate goal of the study however, is to inform the design of a fully powered randomised controlled study into the utility of this approach. If this study should in turn 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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