A Multifactorial 'Urica Cor Intervention' to Prevent Cardiovascular Disease in People with Gout: Protocol for the Multicentre, Randomised Controlled, Blinded Endpoint URICORI Trial.

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TRIAL REGISTRATION

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MM, TE, ALS, RC, KSL, BBL and LS participated in the conception and design of this protocol.
RC provided statistical advice for the design and draft analysis plan.
MM, TE, ALS, RC, KSL and LS drafted the protocol.
MM, TE, ALS, RC, KSL, TL, BBL and LS critically reviewed the manuscript for important intellectual content and approved the final version.

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KEYWORDS

Gout, Cardiovascular disease, randomised clinical trial, cardiovascular risk factors.

ABSTRACT

Introduction: Gout has been associated with a number of comorbidities including cardiovascular disease (CVD). Mounting evidence suggests that hyperuricaemia and gout are associated with a high risk for CVD. Gout is closely related to hypertension, dyslipidaemia, obesity and metabolic syndrome, all well-known factors contributing to the development of CVD. Gout management guidelines all agree that comorbidity screening is relevant and thus should be implemented in contemporary gout management. However, no specific strategy for management of CVD risk factors, in a gout population, exists.

Objective: The objective of the Urica Cor Intervention (URICORI) trial is to evaluate the effectiveness of a one-year, intervention of modifiable risk factors for CVD administered in a rheumatology outpatient clinical setting, compared with conventional (GP) treatment for modifiable risk factors for CVD in people with gout.

Design: The study is a randomised, open label, blinded endpoint trial, with balanced randomisation (1:1) conducted in four rheumatology outpatient clinics in Denmark. We aim to recruit 266 people with gout, fulfilling the current ACR/EULAR gout classification criteria. Eligible patients will be randomised to receive either conventional (control group) treatment for CVD risk factors administered by their general practitioner (GP) according to national guidelines (NG) versus the URICORI programme, administered at the rheumatology department, targeting the same CVD risk factors according to NG. Both groups will be treated for gout at their local department of rheumatology.

End Points: primary end point is a composite endpoint. By inclusion in the URICORI programme all participants will be considered a member of one of four categories derived from the Systematic Coronary Risk Estimation (SCORE)[1,2] screening programme designed to assess the 10 year risk of fatal cardiovascular disease in European low risk population. As a consequence, participants will be classified as responder after 12 months if all national treatment targets for LDL cholesterol, HbA1c, Blood pressure (systolic and diastolic), according to their SCORE risk profile, is met and no commencement of smoking. If not, participants will be classified as non-responders.

Key secondary end points: Change from baseline of LDL cholesterol, HbA1c, systolic blood pressure, diastolic blood pressure, smoking status and change from baseline in serum urate.

Exploratory end points: Proportion of participants achieving treatment target for LDL cholesterol, HbA1c, systolic blood pressure, diastolic blood pressure, change in smoking status (commencement

and cessation) and proportion of participants achieving serum urate < 36.0 mmol/l or serum urate < 0.30 mmol/l for tophaceous disease.

After year 1 and year 5, the first occurrence of any serious cardiovascular event (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke or urgent revascularization due to unstable angina) during the URICORI trial will be registered. Death and hospitalisation during the URICORI trial will also be evaluated after year 5 (fig.2 and fig.3). Events will be determined by medical record review and evaluated by the endpoint adjucation committee. The Outcome Measures in Rheumatology (OMERACT) endorsed Core Domain Set for us in trials in gout will measured during and after the one-year URICORI intervention trial (table.4).

Ethics and dissemination: The local ethics committee in the region of southern Denmark, the Danish data agency in the region of southern Denmark will approve this protocol prior to commencement. Dissemination will occur through presentations at National and International conferences and publications in international peer-reviewed journals. We anticipate that this study will bring new insights to the clinical management of cardiovascular risk factors in people with gout.

INTRODUCTION

Background

Gout is the most common inflammatory arthritis among men and postmenopausal women with prevalence between 2-4% in the United States and the prevalence of hyperuricaemia (precursor to gout) is more than 21%[3]. A recent register based study in Denmark report gout prevalence of 0.68 in 2015 and an increase of the annual incidence rate of 80 % between 1995 and 2015[4]. Gout is characterised by deposition of monosodium urate crystals in tissues and fluids. The response to these crystals results in an acute inflammatory arthritis that is characterised by sudden and severe attacks of red, swollen and painful joints. Gout usually affects only one joint at a time but eventually it can become chronic and affect several joints. It is considered to be one of the most painful forms of arthritis and is a source of disability for many in accordance with the high prevalence[5].

Gout has been associated with a number of comorbidities including cardiovascular disease (CVD)[6]. Mounting evidence suggests that hyperuricaemia and gout are associated with a high risk for CVD[7]. Hyperuricaemia, as a predisposing factor for gout[8], is closely related to hypertension, dyslipidaemia, obesity and the metabolic syndrome, all well-known factors contributing to the development of CVD[9]. The exact nature of the association between hyperuricaemia and CVD remains unclear and it is yet to be determined whether the relationship is causal or whether urate is indirectly related to CVD through other established risk factors. A large number of prospective cohort studies have addressed this issue, but no consensus about the relation between CVD, hyperuricaemia and gout has been stated[10-26]. Mendelian randomisation studies have reported conflicting results regarding adverse cardiovascular outcomes with one reporting hyperuricaemia being causally related to adverse cardiovascular outcomes, particularly sudden cardiac death and the other reporting no association[27,28].

Prospective clinical research regarding treatment of comorbidities in gout is sparse. A meta-analysis of six studies including people with gout reported a risk of CVD related mortality HR 1.29 (95% CI, 1.14-1.44) this was based upon 4 studies (comparing patients with gout to those without gout). Coronary heart disease related mortality was based upon 3 studies (comparing people with gout to those without gout); HR 1.42 (95% CI, 1.22-1.63) and in conclusion the results point to an increased mortality in gout patients due to CHD and CVD[29]. Research in this area has focused on how common CVD and coronary heart disease (CHD) is in people with gout, however no studies have focused on the management and the effect of managing CVD risk factors in people with gout.

There is an unmet need for elaborating on the comorbidities and their management in a clinical setting in view of the increasing incidence of gout worldwide[30,31].

Currently there is no international consensus on how to manage risk factors for CVD in a gout population. The American College of Rheumatology (ACR), European League Against Rheumatism (EULAR) and the Evidence, Expertise and Exchange initiative (3E initiative) all agree that comorbidity screening is relevant and recommend screening and management of co-morbidities is an important aspect of gout management with treatment to established CVD risk targets[32,33]. With the acknowledgement of the close relation of gout and a number of comorbidities the URICORI trial focuses on the management of co-morbidities. No randomised trials addressing the effect of treating the risk factors for CVD exists and the need for rigorous designs in this research area is needed. We aim to answer the following question: Does the management of CVD risk factors in people with gout, in a rheumatologic outpatient clinical setting, versus primary care (GP setting as currently) result in better CVD risk factor control and therefor over time fewer CVD events?

Rationale and evidence-based research

To avoid waste in research, a systematic review of existing evidence is recommended[34]. We performed a pragmatic search in PubMed. Eligible studies included: clinical trials performed in a gout population with at least one intervention targeted against cardiovascular disease risk factors. The search was restricted to clinical trials in humans, full text available and English. Publication date from 1993/01/01 to 2018/03/01.

Applying the following search strategy in PubMed: (((cardiovascular OR metabolic OR diabetes OR intervention OR management OR cardiovascular disease OR coronary artery disease OR stroke OR myocardial infarction OR cardiac OR heart OR death OR mortality OR fatal OR hypertension OR elevated blood pressure OR lipids OR metabolic OR metabolic syndrome OR dyslipidaemia))) AND ((gout OR hyperuricaemia OR serum urate OR gouty arthritis OR uric acid)) AND (Clinical Trial[ptyp] AND full text[sb] AND ("1993/01/01"[PDat] : "2018/03/01"[PDat]) AND Humans[Mesh] AND English[lang]).

The pragmatic search revealed that out of 1,239 potentially relevant trials, 26 trials were eligible for abstract screening and 5 trials were left for full text assessment. Out of the remaining 5 papers none were eligible since they did not include gout patients exclusively, rather patients with asymptomatic hyperuricaemia and there was no sub analysis of the gout population.

Table 1.

Study nr.	Title	Year	Author	Reason for exclusion
1	Multicentre, prospective, randomised, open-label, blinded end point trial of the efficacy of allopurinol therapy in improving cardiovascular outcomes in patients with ischaemic heart disease: protocol of the ALL-HEART study.	2016	Mackenzie IS et al.	Not a gout population
2	Comparative effect of interval continuous training programs on serum uric acid in management of hypertension: a randomised controlled trial.	2011	Lamina S.	Not gout population
3	Effects of three strong statins (atorvastatin, pitavastatin, and rosuvastatin) on serum uric acid levels in dyslipidemic patients.	2010	Ogata N.	Not gout population
4	Serum uric acid level and risk for peripheral arterial disease: analysis of data from the multiple risk factor intervention trial.	2007	Baker JF.	Not gout population
5	Serum uric acid, diuretic treatment and risk of cardiovascular events in the Systolic Hypertension in the Elderly Program (SHEP).	2000	Franse LV.	Not gout population

The Steno II study from 2000 has proved that an intensified multifactorial intervention of modifiable factors in patients with type II diabetes mellitus (T2DM) with micro albuminuria is more effective than conventional treatment to prevent cardiovascular death[35-37]. The study involved 160 patients with type 2 diabetes and microalbuminuria who were randomly assigned to receive either conventional therapy or intensified, multifactorial treatment including both behavioural and pharmacological approaches. Intensive treatment was a stepwise implementation of behaviour modification, pharmacological therapy targeting hyperglycaemia, hypertension, dyslipidaemia, and micro-albuminuria. In the URICORI study we want to apply a similar albeit simplified approach in a gout population.

To our knowledge and in accordance with the principles of evidence-based research, this is the first study to assess a targeted multifactorial intervention for cardiovascular risk factors in a gout population.

Aim and Objective

The objective of the Urica Cor Intervention (URICORI) trial is to evaluate the effectiveness of a one-year, intervention of modifiable risk factors for CVD administered in a rheumatology outpatient clinical setting, compared with conventional (GP) treatment for modifiable risk factors for CVD in people with gout.

METHODS

Trial design and setting

The study is a Randomised Open, Blinded End-point trial, with balanced randomisation (1:1). In total 266 people with gout will be enrolled; participants will be randomised to receive either conventional management for cardiovascular risk factors provided by their usual GP with the

anticipation that this is done according to NG (control group) or a management of the same CVD risk factors in the rheumatology department according to the same NG as the GP[38-40].

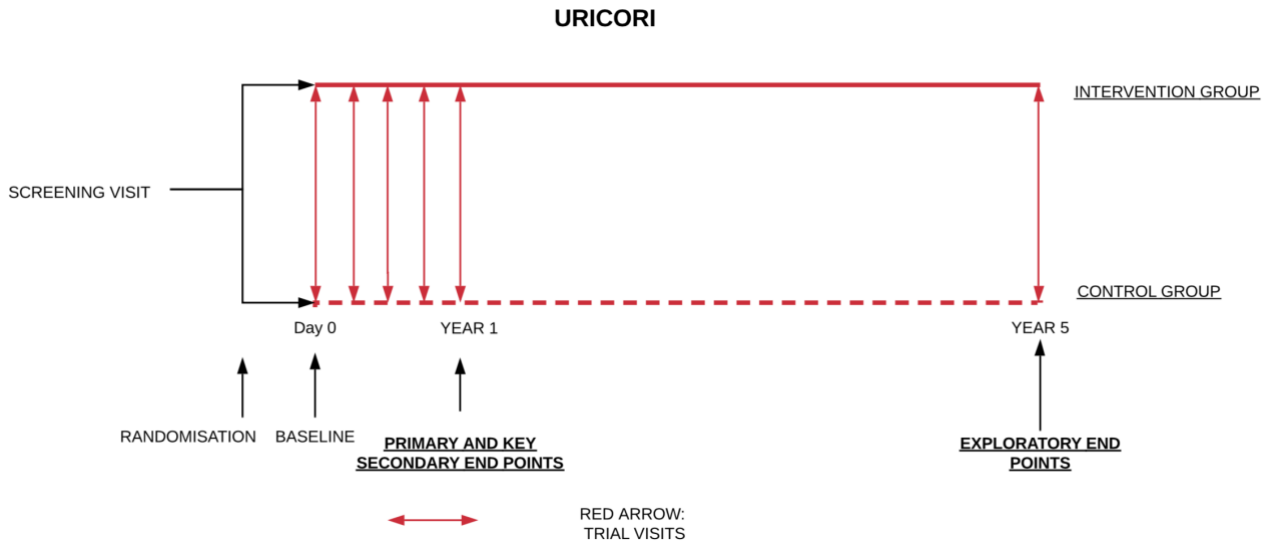
The primary endpoint will be assessed after 12 months, and the follow up period is five years from randomisation. Both groups will be seen at baseline and every third month for one year. From year 1-5 management of CVD risk factors will be provided at the GP. A closeout visit will take place at the end of the five-year study period. Recruitment of patients will begin in 2020. The study will be conducted in four rheumatology outpatient clinics in Denmark; recruiting patients with gout as defined by the ACR/EULAR gout classification criteria[41].

For participants in the intervention group, treatment of gout as well as the modifiable risk factors for CVD will be undertaken by the participant's rheumatologist, while in the comparator group (control = standard of care) the participants GP will be responsible for managing the modifiable risk factors for CVD; the rheumatologist will only manage the gout.

The adjudication for CVE, cause of death and reason for hospitalisation will be based on information from participants records, the death certificate and information from participants usual GP. Two members of the event committee will adjudicate each event individually. In case of disagreement between the two members of the event committee, there will be a meeting between these two members and the chairman of the committee will make a decision in each case.

Both members of the event committee will be blinded to participants treatment allocation.

Figure 1: URICORI trial design, visits and end points.



Participants

The participants will be diagnosed with gout by their treating rheumatologist as defined by the ACR/EULAR gout classification criteria[41].

Eligibility criteria

Inclusion criteria:

- Age over 18 years
- Gout according to current EULAR/ACR gout classification criteria[41]
- Plasma LDL >3.0 mmol/L
- Agreeable to start treatment for CVD risk factors if indicated
- Ability to give informed consent
- Ability to communicate via telephone

Exclusion criteria:

- Other inflammatory diseases requiring immunosuppressant therapy.
- Age >70 years.
- Active cancer (in active treatment).
- Chronic kidney disease (eGFR <30 ml/min/1.73m^2).
- People whose behaviour or lifestyle would render them less likely to comply with the study protocol (i.e., abuse of alcohol, substance misuse or debilitating psychiatric conditions).
- Familial hypercholesterolemia.

The participants should be willing to remain in the study throughout the one-year trial period and participate in the closeout visit five years from randomisation.

Interventions

At screening visit potential participants will be assessed according to the eligibility criteria. Blood samples will be obtained as outlined in table 5. If eligibility criteria are met, they will be invited to participate in the URICORI trial.

At baseline visit, after written consent is obtained, participants will be randomised to receive either:

(1) Treatment of modifiable risk factors, managed by the rheumatologist, to prevent CVD, involving strict treatment goals according to NG regarding CVD risk factors; dyslipidaemia, diabetes and hypertension[38-40]. Including behavioural risk factors for CVD and with the possibility of being referred to specialists[7,42].

(2) Treatment of modifiable risk factors managed by the GP with the anticipation that this is done according to the same NG regarding CVD risk factors. The GP will receive an electronic notification to treat diabetes; hypertension or CVD if risk factors are identified in blood samples or measurements at screening implies so. The patient will be told to arrange an appointment with the GP.

Both groups will adhere to the same treatment algorithm in accordance with NG for CVD risk factors and diabetes and if the guidelines should change so will the treatment in the URICORI trial. The treatment targets/approach in the URICORI study is specified in table 2.

Table 2. Treatment goals for intervention group and control group in URICORI study.

SCORE at baseline	LDL mmol/L	HbA1C mmol/mol	Systolic blood pressure mmHg	Diastolic blood pressure mmHg
Low Risk	<3.0	<48	< 135	<85
Moderate Risk	<3.0	<48	< 135	<85
High Risk	<2.6**	<48	< 130	<80
High Risk and Diabetes	<2.6**	<48*	< 130	<80
Very high Risk	<1.8***	<48*	< 130	<80
Very high Risk and Diabetes	<1.8***	<48*	< 130	<80

* HbA1c < 48 mmol/mol in the first years of diagnosis. HbA1c < 53 mmol/mol later on when tight control may be a challenge due to risk of hypoglycaemia. HbA1c < 58 mmol/mol patients with varying glucose levels, and tendency to hypoglycaemia, long duration of diabetes and macrovascular complications. HbA1c < 58-75 patients where the primary goal is the absence of symptoms. At baseline HbA1c target for participants will be defined.
**OR 50 % reduction with LDL 2.6-5.2. ***OR 50 % reduction with LDL 1.8-3.

Management of CVD risk factors

The ***intervention group*** will be treated with stepwise introduction of pharmacological therapy targeting A: dyslipidaemia, B. hypertension, C: hyperglycaemia and D: Behavioural advice regarding CVD risk factors. Drug modifications will be managed by the project team (Doctor or nurse):

A: Dyslipidaemia[38,39]. Patients will be evaluated according to their risk group by the SCORE[1] screening programme. Participants will accordingly be divided into 4 categories. Low, medium, high and very risk for CVD. The target is LDL cholesterol is <3.0 mmol/L (low and medium risk) or < 2.5 mmol/L (high risk) or <1.8 mmol/L (very high risk). Before initiation of lipid lowering drug therapy, lipids will be measured twice (with minimum 1-week interval). Initial lipid lowering treatment is 20-80 mg atorvastatin. Patients with adverse effects to first line statin will be treated with 10-40 mg Rosuvastatin and subsequently treated with Ezetimibe 10 mg in combination with a statin or alone if statin is not tolerated. If LDL cholesterol target is not reached, patients will be referred to a specialist (cardiologist) at the site/hospital of inclusion.

B: Hypertension[39,43]. Antihypertensive drug therapy will be titrated to achieve target blood pressures (<135 mmHg systolic and <85 mmHg diastolic) for patients without diabetes and (<130 mm Hg systolic and < 80 mm Hg diastolic) for patients with diabetes or kidney disease. At study entry, blood pressure will be measured after sitting quietly for 5 minutes. If blood pressure (systolic or diastolic) is not within target, participants will have their blood pressure measured at home with a blood pressure device. The measurements will obtained 3 times a day for 3 days, and a mean will be calculated before any intervention will be commenced[44].

The primary drug of choice will be an angiotensin-II receptor antagonist at the maximal recommended or maximum tolerated dose. If target is not reached, combination therapy with a calcium antagonist or thiazide can be added. Thiazide diuretics can cause elevation of SU and will be avoided if possible. Combination treatment with an angiotensin-II receptor antagonist and an ACE inhibitor or a renin inhibitor will not be advised. If target BP is not reached, patients will be referred to a specialist (cardiologist) at the site/hospital of inclusion. Patients where hypertension is diagnosed during the URICORI study period will, in accordance NG, undergo home blood pressure measurement or 24-hour blood pressure measurement, ECG, and urine/albumin creatinine ratio[44]. If abnormalities are found, patients will be referred to the department of cardiology for further investigations/treatment.

C: Hyperglycaemia[40]. For those participants with HbA1c levels above 48 mmol/mol (6.5%) treatment with metformin will be recommended at standard clinical doses. If resistant to treatment HbA1c above 48 mm/mol (6.5%) the patients will be discussed with a local relevant specialist and if needed referred to a specialist for further treatment.

D: Behavioural advice regarding CVD risk factors. Lifestyle recommendations according to the European Heart Society[45] are no smoking, weight reduction if body mass index (BMI≥ 25 kg/m2), especially if BMI ≥ 30 kg/m2, 30 min of moderately vigorous exercise on most days of the week and a healthy diet. Smokers will have free access to smoking cessation initiatives. Physical activity with vigorous exercise on most days of the week will be recommended. Also recommended will be a healthy diet that includes a wide variety of foods and energy intake adjusted to avoid weight gain. It will be recommended that the diet consist of fruits and vegetables, wholegrain cereals and bread, fish (especially oily), lean meat, low fat dairy products and replacement of saturated fat with monounsaturated and polyunsaturated fats. Hypertensive patients will be advised to reduce salt intake. Regarding alcohol: The Danish National Board of Health advises no more than 14 units of alcohol per week for men and 7 units per week for women[42].

Participants in the ***intervention group*** have in-person contact with the study team every third month with measurement and response to LDL cholesterol, HbA1c and blood pressure for the first year. If targets for hypertension, dyslipidaemia and HbA1c are not reached within the first year of entering the URICORI study, patients will be referred to the relevant specialist. Every 6 months, a counselling session regarding diet, smoking, alcohol use and exercise habits will be provided by the study team (doctor or nurse). Additional phone calls between the scheduled visits will be provided if further counselling regarding treatment is required.

In comparison, the ***comparator (control) group*** will be managed by the participants usual GP and the treatment and referral to another specialty for CVD risk factor modification will be entirely at the discretion of the GP. After the 1-year intervention period, both intervention and control group will have their CVD risk factors managed by the GP (or relevant specialist if required). The GP will receive an electronic notification.

Gout management

Urate lowering treatment: For all participants (comparator/control and intervention group) urate-lowering treatment (ULT) will be initiated according to national/international guidelines[46]. The team members (doctor/nurse) will up-titrate the ULT monthly (3-5 weeks) during a telephone

consultation. The study team nurses will receive training in management of gout according to NG national/international guidelines. Target SU is defined as < 0.36 mmol/L and <0.30 mmol/L for those with tophaceous disease. When target SU is reached participants will have SU monitored every six months during the 5-year trial period[47].

Urate lowering treatment will be prioritized in the following order:

- Allopurinol uptitrated to maximum licensed/tolerated dose.
- Allopurinol (maximum licensed/tolerated dose) and in combination with probenecid or Lesinurad.
- Benzbromarone (in combination with allopurinol if tolerated)

Febuxostat will not be applied in the URICORI study since the secondary and exploratory end points are cardiovascular endpoints. In a recent study published in New England Journal of Medicine on cardiovascular safety of febuxostat in patients with gout showed that all-cause and cardiovascular mortality were higher in the febuxostat group than in the allopurinol group (hazard ratio for death from any cause, 1.22 [95% CI, 1.01 to 1.47]; hazard ratio for cardiovascular death, 1.34 [95% CI, 1.03 to 1.73][48]. Thus, we have excluded the use of febuxostat from our treatment algorithm to avoid potential harm and bias.

Allopurinol will be uptitrated monthly (3-5 weeks) until SU target is met. The initial dosage will be 50 mg/day increased by 50 mg/day monthly for those with CrCL <60 mL/min and start dosage of 100 mg/day in those with CrCL ≥60 mL/min and increased monthly by 100mg/day until target SU is reached. Probenecid can be added to allopurinol if implied. The initial dosage of Probenecid will be 250 mg/day increasing to 500 mg twice daily until target SU is reached. During the first 2 weeks of Probenecid treatment sodium bicarbonate 1g 2-4 times daily is recommended in order to prevent concrements in the urinary tract. Lesinurad in doses of 200mg/day (in combination with allopurinol) may be applied instead of probenecid if SU target is not reached. Benzbromarone can be applied in the dosage of 50- 100mg/day.

Gout flare prophylaxis: Patients initiating urate-lowering therapy will receive 0.5mg colchicine once a day for 8 weeks as the first-line option for anti-inflammatory prophylaxis[49,50]. If not tolerated NSAID or prednisone can be administered.

Treatment of gout flares: All patients will receive a personalised gout flare treatment plan that will be agreed upon entrance in the URICORI study. The gout flare treatment will consist of either colchicine, NSAID or prednisone alone or in combination. The medication and dose will be agreed by the participant and the investigator upon entrance in the URICORI study and will be

determined by the participant's comorbidities, concomitant medications and previous response to treatment.

End Points

Primary End point:

The primary end point is a composite endpoint. By inclusion in the URICORI programme all participants will be considered a member of one of the four categories derived from the SCORE screening programme; the SCORE was designed to asses cardiovascular disease risk[51]. As a consequence, participants will be classified as responder after 12 months if all 5 of the following treatment targets is met:

Table 3. Response criteria URICORI trial

Participant is responder if all 5 criteria are met					
	Criteria: 1	Criteria: 2	Criteria: 3	Criteria :4	Criteria: 5
HeartSCORE at baseline	LDL mmol/L	HbA1C mmol/mol	Systolic blood pressure mmHg	Diastolic blood pressure mmHg	Smoking
Low Risk	<3.0	<48	< 135	<85	No commencement of smoking
Moderate Risk	<3.0	<48	< 135	<85	No commencement of smoking
High Risk and *no* diabetes	<2.6**	<48	< 130	<80	No commencement of smoking
High Risk and diabetes	<2.6**	<48*	< 130	<80	No commencement of smoking
Very high Risk and *no* diabetes	<1.8***	<48*	< 130	<80	No commencement of smoking
Very high Risk and diabetes	<1.8***	<48*	< 130	<80	No commencement of smoking

* HbA1c < 48 mmol/mol in the first years of diagnosis. HbA1c < 53 mmol/mol later on when tight control may be a challenge due to risk of hypoglycaemia. HbA1c < 58 mmol/mol patients with varying glucose levels, and tendency to hypoglycaemia, long duration of diabetes and macrovascular complications. HbA1c < 58-75 patients where the primary goal is the absence of symptoms. At baseline HbA1c target for participants will be defined.
**OR 50 % reduction with LDL 2.6-5.2 ***OR 50 % reduction with LDL 1.8-3.5

Key secondary end points:

- Change from baseline of LDL Cholesterol.
- Change from baseline of HbA1c.
- Change from baseline Systolic blood pressure.
- Change from baseline Diastolic blood pressure.
- Change in smoking status.
- Change from baseline in serum urate.

Exploratory end points

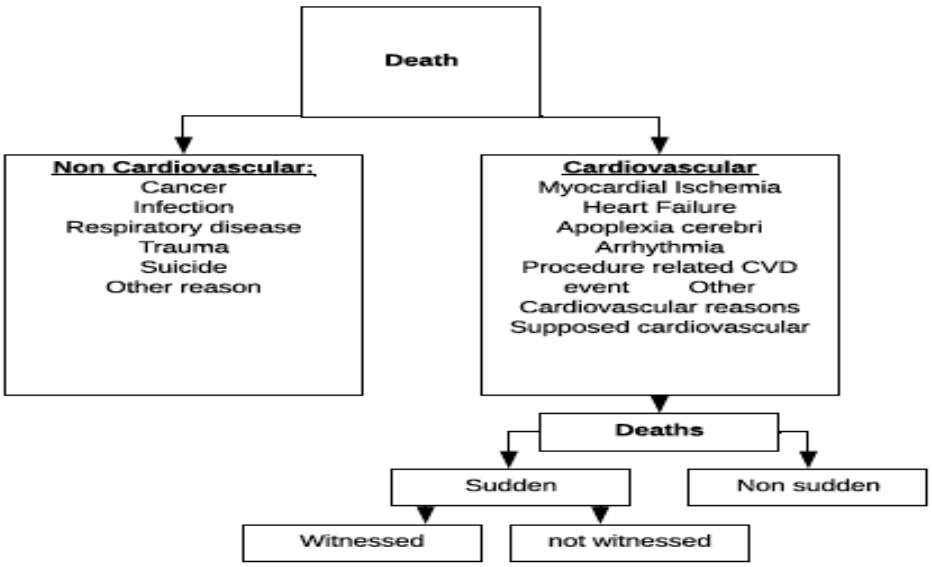
- Proportion of participants achieving treatment target for LDL cholesterol
- Proportion of participants achieving HbA1c treatment target.
- Proportion of participants achieving treatment target for systolic blood pressure.
- Proportion of participants achieving treatment target for diastolic blood pressure.
- Proportion of participants with change in smoking status (commencement and cessation)
- Proportion of participants achieving serum urate < 36.0 mmol/l or if tophaceous disease serum urate < 0.30 mmol/l
- Proportion of participants with any serious cardiovascular event during the first year of the URICORI trial*.
- Proportion of patients with any serious cardiovascular event during the 5-year URICORI trial*.
- Death from any cause
- Hospitalisation due to elective or acute cardiovascular reasons during the URICORI trial.

* cardiovascular death, nonfatal myocardial infarction, nonfatal stroke or urgent revascularization due to unstable angina. Gaede et al. have validated the method of using medical record review for evaluating cardiovascular events and the method has been used in several other studies[36,52-54]

Death: will be classified as either: *Cardiovascular* or *non-cardiovascular.*
If no cause can be established, it will be considered as being cardiovascular. Cardiovascular deaths will be further classified in relation to time as either sudden or non-sudden. Sudden deaths are described as either: witnessed and instantaneous or occurring within 1 hour of new symptoms or

unwitnessed with no apparent cause (found dead). The remaining cardiovascular deaths will be classified as non-sudden.

Figure 2. Classification of death in URICORI



Non-cardiovascular death will be classified as either caused by cancer, primary infectious disease, respiratory disease, trauma/accident, suicide or other causes for non-cardiovascular death
Cardiovascular deaths will be sub-classified as caused by:

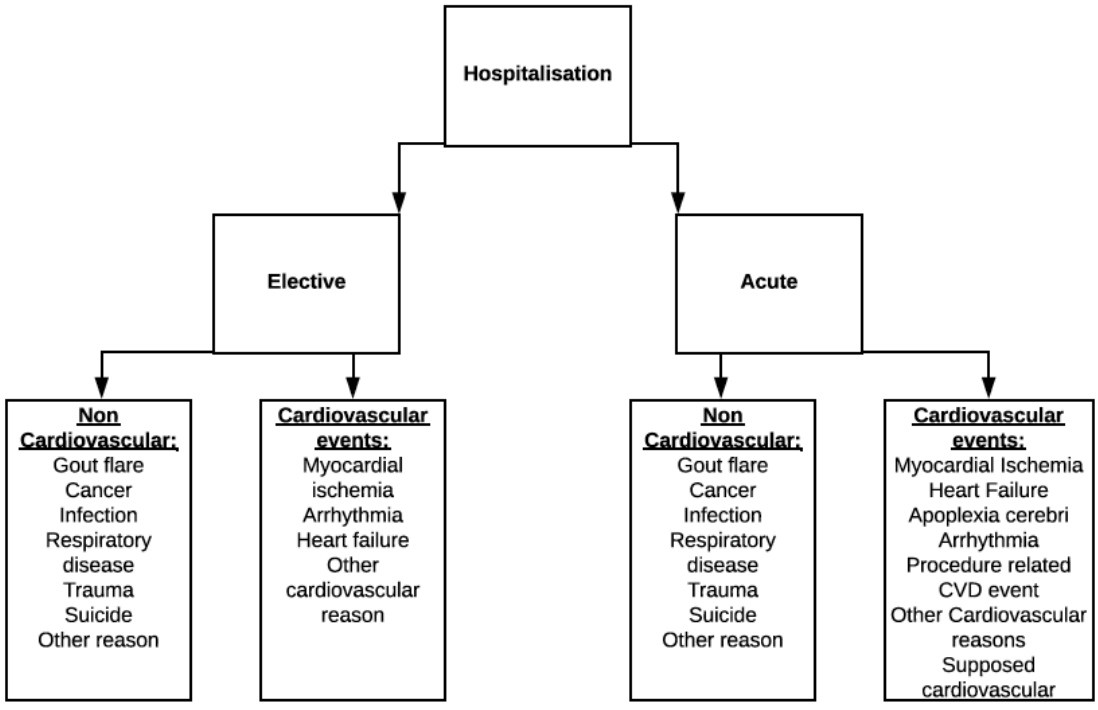
A. myocardial infarction
B. heart failure
C. stroke
D. documented arrhythmia
E. procedure-related
F. other cardiovascular causes including pulmonary embolism,
G. assumed cardiovascular death.

A) Death due to MI is defined as a primary fatal event that occurs within 7 days of a documented MI by autopsy or a MI defined according to national and international guidelines.
B) Death due to heart failure/or worsening heart failure is defined as death occurring after a period of increasing symptoms and signs of heart failure.

C) Death due to stroke is defined as development of acute severe neurological deficit with or without documentation by computer tomography scans. Deaths occurring within 2 weeks of a stroke where no other competing causes can be identified are classified as death due to stroke. Death from stroke occurring as a direct consequence of an investigation/procedure/operation will be classified as procedure-related death.
D) Death due to documented arrhythmia is defined by a documented arrhythmia is the primary cause of death.
E) Death due to procedure-related death is defined as death following a cardiovascular investigation/procedure/operation within 24 hours.
F) Death due to other cardiovascular causes is death occurring after other cardiovascular events like e.g. pulmonary embolism, ruptured aortic aneurysm etc.
G) Presumed cardiovascular death is all deaths not attributed to the above categories of cardiovascular deaths or not attributed to a documented non-cardiovascular cause. This category includes deaths from unknown cause.

Hospitalisation: will be classified as either elective or acute and further subdivided as non-cardiovascular or cardiovascular.

Figure 3. Classification of Hospitalisation



Elective hospitalisation will be subdivided as either:

- non-cardiovascular (gout flare, cancer, infection, respiratory diseases, trauma, suicide and other)
- cardiovascular, which is further divided as follows:
    1. Myocardial ischemia
    2. Arrhythmia
    3. Heart failure
    4. Other

Acute hospitalisation will be subdivided as either:

- non-cardiovascular (gout flare, cancer, infection, respiratory diseases, trauma, suicide and other).
- Cardiovascular hospitalisation

1. Myocardial ischemia:
    A. Non-fatal or fatal myocardial infarction defined by national and international guidelines.
    B. Fatal myocardial infarction is defined as a primary fatal event within 7 days, documented by post mortem autopsy, or by the definition of myocardial infarction according to European guidelines[55].
    C. Death of myocardial infarction as a consequence of medical examination/procedure/surgery will be classified as procedure-related death.
    D. Acute coronary syndrome includes acute ischaemic symptoms with eventual elevation of biomarkers or electrocardiographic changes which does not fulfil the criteria of acute myocardial infarction.
    E. Angina pectoris.
    F. Revascularisation procedures (percutaneous coronary intervention or coronary artery bypass graft).
2. Heart failure:
    A. Patients with non-elective hospitalisation or death, minimum one overnight stay, with symptoms or findings of heart failure.
    B. Death due to heart failure is defined as escalating heart failure symptoms before death.
3. Arrhythmias:

A. Atrial fibrillation or flutter, supraventricular tachycardia and others.
B. Ventricular tachycardia, ventricular fibrillation and others.
C. Death due to arrhythmia requires documentation or example, telemetric transcript, pacemaker output or electrocardiogram.

4. Stroke:
   A. Cerebral haemorrhage, cerebral thromboembolism, transitory cerebral ischemia and others.
   B. Stroke is defined as abrupt severe neurological deficits, eventually with CT documentation. Death within 14 days after symptom-onset of stroke, and without other obvious reasons, is classified as caused by stroke.
   C. Death from stroke as a consequence of medical examination/procedure/surgery, and without other obviously reasons, is classified as caused by stroke.
5. Procedure-related event:
   A. Any cardiovascular event within 24 hours after cardiovascular medical examination/procedure/surgery.
6. Other cardiovascular hospitalisations:
   A. Hospitalisation caused by other cardiovascular events for example, pulmonary embolism, rupture of aortic aneurism, etc.
7. Supposed cardiovascular hospitalisation:
   A. Hospitalisations without any documented non-cardiovascular cause.
   B. All deaths, which are not defined by the cardiovascular reasons, mentioned above, and which are not caused by well-documented non-cardiovascular death.
   C. All deaths without known reason.

Recruitment:

Recruitment will begin in 2020.

Inclusion of patients is estimated to take 1.5 year. The trial Period is 5 years from randomisation.

By 2025 the URICORI study is expected to conclude from its 5-year follow-up visit.

METHODS

Randomisation and allocation concealment

Eligible patients will at baseline, after oral and written information is given and written consent is obtained, be randomised to control or intervention group. The randomisation sequence will be computer generated and stratified by study site (Odense University Hospital, Odense University Hospital-Svendborg, Vejle Hospital and Silkeborg Hospital) and by SCORE (low and medium risk group vs high and very high-risk group). The sequence will be generated by an independent biostatistician using PROC PLAN (SAS Studio 3.7), a random number generator with a 1:1 allocation using varying block sizes between 2 and 6. Randomisation codes will be entered into REDcap database (project-redcap.org) provided by OPEN (Odense Patient data explorative network).

Blinding

Both participating patients and rheumatologists will be aware of the allocation and treatment arm. Outcome assessors and data analysts will however be kept blinded.

Data collection, management and analysis

Demographics and clinical features:

- Age
- Sex
- Duration of gout, years
- Height, cm
- Body weight, kg
- Body mass index, kg/m2
- Gout flares in the preceding year
- History of kidney stones
- Cardiovascular disease
- Diabetes
- Hypertension
- Dyslipidaemia

Gout assessments:

These are the Outcomes in Rheumatology Clinical Trials (OMERACT) endorsed Core Outcome domains for studies of chronic gout[56].

Table 4. Endorsed Core Outcome Domains for chronic gout

Domain	Instrument/measure
Serum urate	mmol/l
Gout flares	self-reported
Tophus burden	tophus count
Health related quality of life (HRQOL)	SF-36
Functional disability/activity limitation	HAQ-DI
Pain	VAS
Patient global assessment	VAS

Assessment of gout flare frequency: number of flares in the last month. Gout flares will be self-reported and defined as flares requiring treatment. This definition has been used in other studies of gout.[57,58]

Biochemical Measurements

The following groups of tests will be performed as indicated in section describing outcomes. These are standard biochemical measurements taken routinely at the department of rheumatology and at the general practitioner. Biochemical measurements will *not* be collected and stored in a biobank.

- Lipids: triglycerides, HDL-, LDL-, VLDL-, and total cholesterol
- Haemoglobin, white cell count and platelet count
- Serum biochemistry for safety monitoring- creatinine, liver function tests (ASAT, GGT, ALP), creatinine kinase
- Serum urate
- HbA1c
- Microalbuminuria

- Blood pressure (Systolic and Diastolic)
- Smoking status (ever smoker, former smoker, smoker, new smoker)
- Alcohol (women: more than 7 drinks per week y/n, men: more than 14 drinks per week y/n)

Table 5. Trial visits and outcomes

						Primary, secondary and exploratory end points evaluation	**Exploratory end point evaluation**
Time in months:	**-0.5 to 0**	**0**	**3**	**6**	**9**	**12**	**60**
Visit No.	1	2	3	4	5	6	7
Visit type	Screening visit	Study	Study	Study	Study	Study	Close out visit
Informed Consent	√ (verbal and written)	√ (written)					
Inclusion/Exclusion Criteria	√						
Randomisation		√					
General practitioner advised of study entry		√					
General practitioner advised of URICORI exit.						√	
Baseline demographics (Age, gender etc.)		√					
Gout history recorded: History of gout (age onset, number of flares in preceding 6 months, family history, previous treatments, associated medical conditions (e.g. hypertension, diabetes), alcohol		√					
Decision on flare rescue treatment		√					
Medical record review		√				√	√
Blood pressure (systolic and diastolic)	√	√	√	√	√	√	√
Smoking status (ever smoker, non-smoker, smoker, commencement of smoking)		√	√	√	√	√	√
Height (cm)		√					
Weight (kg)		√		√		√	√
Concomitant medication		√	√	√	√	√	√
Gout flare questionnaire including activity limitation		√	√	√	√	√	√
Need for gout flare rescue therapy recorded		√	√	√	√	√	√
Prescription provided		√	√	√	√	√	√

OMERACT Endorsed outcome domains							
Serum Urate (mmol/L)		√	√	√	√	√	√
Flares (self-reported)		√	√	√	√	√	√
Tophus burden (count, using homunculus diagram)		√	√	√	√	√	√
Health related quality of life (HRQOL-SF-36 version 1)		√	√	√	√	√	√
Pain (100mm Visual Analog scale VAS)		√	√	√	√	√	√
Activity limitations Health Assessment Questionnaire disability index HAQ -DI)		√	√	√	√	√	√
Patient global assessment (5-point Likert scale)		√	√	√	√	√	√
Laboratory tests							
Serum urate	√	√	√	√	√	√	√
Blood cell count (Hgb, leucocytes and differential count, platelets)	√	√	√	√	√	√	√
ASAT/GGT/ALP	√	√	√	√	√	√	√
Cholesterol (total cholesterol, triglycerides, VLDL, LDL, HDL)	√	√	√	√	√	√	√
CRP	√	√	√	√	√	√	√
Creatinine Kinase	√	√	√	√	√	√	√
HbA1C		√	√	√	√	√	√
Microalbuminuria		√	√	√	√	√	
Harms and adverse events (AEs):							
Adverse Events recorded			√	√	√	√	√
Withdrawal, y/n			√	√	√	√	√
Withdrawal due to AEs, y/n			√	√	√	√	√
Number of serious adverse events, count			√	√	√	√	√
Death, y/n			√	√	√	√	√

Sample size and power considerations

It is anticipated that 266 participants can be recruited at the four centres, during a period of 18 months. A sample size of 266 participants is considered sufficient to test the null hypothesis (H_0): That an intensified intervention targeting known and modifiable risk factors for cardiovascular disease in people with gout does *not* lead to improved cardiovascular outcomes when treated in a rheumatologic setting compared to general practice, by the assumption that 25% in the intervention (URICORI) group and 10% in the control group will be categorised as responders after 1 year a good statistical

power (90%) to detect a difference between the groups using Pearson's Chi-square statistic with a Chi-square approximation with a 2-sided significance level of 0.05 (P<0.05).

Table 6. Power and sample size corresponding to different scenarios (i.e. number of patients, and assumed incidence rates)

Scenario	**Proportion of responders in control group**	**Proportion of responders in intervention (URICORI) group**	**N total (1:1)**	**Statistical power**
1	0.10	0.25	266	0.901
2	0.10	0.25	228	0.851
3	0.10	0.25	200	0.802
4	0.10	0.30	266	0.986
5	0.10	0.20	266	0.621
6	0.05	0.25	266	0.997

Data will be analysed according to a pre-established statistical analysis plan (SAP). The analysis will be analysed based on the Intention-to-treat population. The treatment groups that include all participants randomised will be compared. All analyses will be analysed and reported as two-sided, done at a 5% significance level.

Statistical methods

All analyses will be based on the Intention-to-treat (ITT) population: The ITT principle asserts the effect of a treatment policy (that is, the planned treatment regimen) rather than the actual treatment given (i.e. it is independent of adherence). This has the consequence that participants allocated to a treatment group will be followed up, assessed and analysed as members of that group irrespective of their compliance to the planned course of treatment (i.e. independent of withdrawals and cross-over phenomena). Thus, the primary analyses based the ITT population will use data from the full-analysis set, which include all patients who are randomised, and have at least the outcome of interest assessed at baseline.

The primary statistical model (from baseline to 12 months) will consist of repeated measures linear mixed models, which state that observed data consist of two parts; fixed effects and random effects. Fixed effects define the expected values of the observations, and random effects define the variance and covariances of the observations. In this study participants are randomly

assigned to treatment groups (URICORI vs Standard of Care), and observations are made at five time points (0, 3, 6, 9, and 12) for each participant. Basically, there will be two fixed-effect factors: group and time. Random effects result from variation between and within participants. We anticipate that measures on the same patient at different times are correlated, with measures taken close together in time being more highly correlated than measures taken far apart in time; observations on different participants will be assumed independent. Data will be analysed with the particular outcome variable at baseline level as a covariate - using a multilevel repeated measures random effects model with participants as the random effect factor based on a restricted maximum likelihood (REML) model.

For continuous outcomes, the change from baseline will be the dependent variable, and the baseline value (one for each participant), treatment group (two levels), and time (five levels) will be included as covariates, as well as the interaction between treatment group and time (treatment × time), and Patient ID as a random effect. This statistical model holds all between-group comparisons at all assessment points (incl. baseline) and allows for evaluation of the average effect, as well as the trajectory over the time period from baseline to 12-month follow-up[59]

Categorical outcomes for dichotomous end points (incl. the primary end point) will be analysed with the use of logistic regression with the same fixed effects and covariates as the respective analysis of covariance (i.e. using Generalized Linear Mixed Models). Since Odds Ratios (ORs) for outcomes of common incidence either over- or under estimate the corresponding risk estimate, we will convert all the calculated OR values and 95% confidence intervals into approximate Risk Ratios[60].

In the Statistical Analysis Plan (SAP), which will be developed before data are revealed to the trial statistician, both a hierarchy of the secondary outcome measures will be provided (gatekeeping rule), as well as a framework for sensitivity analyses, to assess the robustness of the primary analyses; incl. multiple-imputation analyses (model-based), non-responder imputation, and complete case analysis.

<u>Stratified analyses (exploring contextual factors at baseline):</u>

- the highest tertile of SU versus other.
- participants with tophaceous disease versus no tophaceous disease.

We will analyse subgroups of study participants in order to explore possible heterogeneity of treatment effects in subgroups of patients. By applying stratified tests for interaction, we will create

"subgroup analysis," evaluating the risk of having a serious CVD event according to subgroups of patients defined by their baseline characteristics. For the primary outcome, the difference between proportions where and missing data will be manually imputed (non-responder imputation [i.e. baseline observation carried forward]). The heterogeneity of treatment effects among the levels of a baseline variable will be based on a statistical test for interaction. The URICORI trial will highly likely lack the power to detect heterogeneity in treatment effect; thus, the inability to find significant interactions will not show that the potential treatment effect observed overall necessarily applies to all subjects with gout; we will consider a p-value <0.10 be indicative of a contextual (subgroup) effect.

Safety and harms

Adverse events (AE) and serious adverse events (SAE) will be systematically registered and reported to the Danish Health Authorities. AE will be coded according to CTCAEv5[61]. Enquiry regarding adverse events will be made at each study visit. CVD events will be treated as an adverse event/ serious adverse event. Participants in the trial will be treated according to national guidelines and in case any patients suffer from harm from trial participation, they will be referred to the patient compensation association independent of group allocation.

ETHICS AND DESSIMINATION:

All patients must give their written informed consent at entrance to the URICORI study and again before the close out visit 5 years after randomisation. The protocol is be approved by the local ethics committee and performed in accordance with the declaration of Helsinki[62,63] and Oviedo. The local ethics committee and the Danish Data Protection Agency has approved the protocol. A medical record review is part of the URICORI trial. Participants will before they sign the written consent form, be informed that this allows the sponsor, and representatives of the sponsor, admittance to perform medical record review and retrieve data from the patients' medical record and give these to the researcher. The type of data is described on page 20-23. The data protection law and the data protection regulation will be respected. The project will be registered at the University of Southern Denmark and at the region of Southern Denmark.

Patient and public involvement (PPI) will be in accordance with the EULAR and GRIPP2 reporting checklists for involvement patient representatives in research[64,65]. PPI was initiated with the perspective of having people with gout involved in the trial design phase as early as possible. Patient partners were invited to discuss the purpose, content and patient relevant outcome measures and have been resourceful in the design of the study protocol. PPI have been resourceful and especially the contribution to and editing of the participant information. Overall the PPI found that the project was relevant, acceptable (regarding aim, measurements and trial visits) and feasible furthermore they found that the project would have utility.

Auditing: The Early Rheumatoid Arthritis Cor Intervention study (ERACORI)[53] with a similar intervention in people with Rheumatoid Arthritis has not been required to have auditing, by the Danish national health authorities as well as the scientific committee, since the intervention is according to national guidelines and do not introduce new medications. The study protocol will be sent to the local ethics committee in the region of southern Denmark, the Danish Health and Medicines Authority and the Danish data agency in the region of southern Denmark for approval of the protocol/study.

The project was initiated by Professor Torkell Ellingsen and Melanie Birger Morillon. The project is supported by grants from the Danish Rheumatism Association: 500.000kr, from the Region of Southern Denmark: 580.000kr and The University of Southern Denmark (490.000kr). The funds are administered centrally from Odense University Hospital, the funds office. The funding is used for VIP salary and project running costs. The sponsor and researchers in the URICORI project do not have disclosures regarding the above-mentioned funds.

Recruitment of participants will be at the departments of Rheumatology at the four inclusion sites. There will be posters available in the waiting areas, if a person would like to hear more about the project, they can ask the secretary, nurse or doctor for more information. Furthermore, people will be asked during their routine consultation at the department of rheumatology if they would like information about the URICORI study. If a person would like more information about the URICORI study. A team member (doctor or nurse) will give the oral and written information in appropriate surroundings ensuring that the information can be given without interruptions. If the person would like an assessor to be there when the oral and written information is given, a consultation for that exact purpose will be planned. If the person after oral and written consent is given, would like to proceed and participate in the URICORI trial, then a

consultation will be scheduled after 1-2 weeks, ensuring sufficient time to consider before signing the written consent form and proceed to the randomisation process.

Author contributions:

MM, TE, ALS, RC, KSL, BBL and LS participated in the conception and design of this protocol.
RC provided statistical advice for the design and analysis.
MM, TE, ALS, RC, KSL and LS drafted the protocol.
MM, TE, ALS, RC, KSL, TL, BBL and LS critically reviewed the manuscript for important intellectual content and approved the final version.

Other information

Registration: The trial will be registered in ClinicalTrials.gov.
Dissemination: 1-year data from the URICORI programme (primary outcome) will be published by peer-reviewed publication. The intended audience will include health care researchers, policymakers and clinicians.

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