Component	Target trial	Emulated trial using real-world data
Design	Multicentre open-label two-arm parallel group superiority randomised trial	Same
Setting	Primary care	Same
Aim	To compare the risk of cardiovascular events among patients with gout who initiate treat-to-target (T2T)-ULT versus fire-and-forget ULT	To compare the risk of cardiovascular events among patients with gout who initiate ULT and achieve the serum urate target of ≤360 micromol/L within 12 months (T2T-ULT) versus those who initiate ULT and either do not meet this target or have no recorded serum urate measurement of ≤360 micromol/L within 12 months after ULT initiation (fire-and-forget)
Eligibility	1. patients diagnosed with gout meet the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for gout 2. aged ≥18 years at trial entry 3. indicated for ULT initiation 4. serum urate ≥360 micromol /L	1. English and Swedish patients with a new primary-care or hospital recorded diagnosis of gout and contributing data to the CPRD and VEGA databases respectively. 2. age ≥18 years at ULT prescription 3. newly prescribed ULT for gout on or after the date of the first primary care consultation or hospital admission for gout 4. latest serum urate ≥ 360 micromol/l.
Treatment strategies	1. T2T-ULT with target serum urate ≤360 micromol/l 2. Fire-and-forget-ULT	1. T2T-ULT aiming to achieve the serum urate target of ≤360 micromol/l within 12 months after ULT initiation. The achievement of the serum urate target will be ascertained by considering the earliest serum urate measurement reaching ≤360 micromol/l within 12 months after ULT initiation. 2. Fire-and-forget-ULT. No recorded serum urate measurements of ≤360 micromol/l within 12 months after ULT initiation or no serum urate measurements.
Treatment assignment	Patients are randomly assigned to either strategy	Patients receive a treatment strategy in a non-random manner. Randomisation is emulated using a cloning, censoring, and weighting approach.
Treatment implementation	In the T2T-ULT arm, ULT dose is monthly up-titrated to meet serum urate targets. In the fire-and-forget-ULT arm, ULT is prescribed without further adjustment based on serum urate levels or where dose adjustments are made, they are not aimed at achieving a treatment target.	12-month grace period to allow for ULT escalation to meet serum urate targets. Previous randomised controlled trials showed that the serum urate target can be achieved within 6 months from the first ULT prescription [2–4]. However, the proportion of patients achieving the serum urate target in clinical practice is expected to be lower [5]. Therefore, we will allow 12 months of grace after ULT initiation for participants to achieve the SU target.
Outcomes (main)	Cardiovascular events defined as non-fatal myocardial infarction, non-fatal stroke (i.e., ischaemic or haemorrhagic), or cardiovascular death (i.e., fatal myocardial infarction, fatal stroke, cardiac arrest, death due to heart failure, death due to aortic dissection, death from arrhythmias).	Same
Outcomes (secondary)	**Secondary outcomes**: first-ever CVE, cardiovascular death, CVE requiring hospitalisation or leading to death, acute myocardial infarction, stroke, first gout flare requiring consultation in primary care or hospitalisation, number of gout flares over the study period.	Same secondary outcomes. **Negative control outcomes**: acute bronchitis, appendicitis, and cataract. Control outcomes are required to test the risk of bias or residual confounding [6].

Type of outcome	Time to event for all outcomes other than the number of gout flares. Count outcome for the number of gout flares over the study period.	Same
Follow up	Follow-up starts at ULT initiation, equivalent to randomisation and treatment assignment	Follow-up starts at ULT initiation; however, it does not correspond to treatment assignment. The cloning, censoring, and weighting approach considers this point by creating a clone for each patient and censoring them when the treatment assignment of the patient is known.
Censoring	Loss to follow-up, death, outcome date, 5 years after ULT initiation	Death, administrative censoring (last consultation date, transfer out of practice date, study end date), outcome date (except for gout flares' count), 5 years after ULT initiation.
Adjustment variables	Randomisation will be stratified by the following factors and they will be included in the analysis model. • Prior cardiovascular events • Sex • Age-group (<40, 41-65, >65) • Smoking status (current smoker, past smoker, non-smoker), • Body Mass Index	These covariates ascertained on or before the first ULT prescription will be used to build the inverse probability of censoring weighting: • demographics: age, sex (male or female), latest body mass index (BMI) available only in CPRD, socioeconomic deprivation assessed using the index of multiple deprivation (IMD) in CPRD and income and educational level in VEGA, latest smoking status (current, past, or non-smoker) available only in CPRD, latest alcohol intake (current, past, or no intake) available only in CPRD, • gout-related variables: gout duration (years), presence of subcutaneous tophi, number of anti-inflammatory prescriptions (colchicine, NSAIDs, and corticosteroids) in 12 months before ULT initiation, number of consultations in primary care for gout and number of hospitalisations for gout in the 12 months before ULT initiation, ULT molecule (i.e., febuxostat, allopurinol, uricosurics) and dose (high vs low starting dose), co-prescription of gout flare prophylaxis with colchicine and/or non-steroidal anti-inflammatory drugs on the date of ULT initiation (i.e., prescription length ≥21 days); • general health and other cardiovascular comorbidities: Charlson Comorbidity Index [15], cardiovascular comorbidities not included in the Charlson Comorbidity index (i.e., hypertension, atrial fibrillation, and hypercholesterolemia), heart failure, diabetes with and without target organ damage, chronic kidney disease (stage 3,4,5), dementia, peripheral vascular disease, COPD, cancer, HIV/AIDS European Society of Cardiology cardiovascular risk (high/very high vs moderate/low), history of cardiovascular events before ULT initiation, number of consultations in primary care for any reason and number of hospitalisations for any cause in the 12 months before ULT initiation, • measure of treatment adherence: proportion of days covered by ULT between the date of the first ULT prescription and the end of the grace period, • medications (low-dose acetylsalicylic acid (ASA), non-ASA antiplatelet agents, statins, fibrates, other lipid-lowering agents, potassium-sparing diuretics, thiazides, loop diuretics, beta-blockers, calcium-channel blockers,

		angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, other anti-hypertensive agents, nitrates, and oral anticoagulants. Prescriptions will be categorised as current (last prescription within 60 days before ULT initiation in CPRD and last prescription within 120 days before ULT initiation in VEGA) or past/no prescription. The duration was selected based on clinical input as the mean length of prescriptions in the UK and in Sweden differs.
Causal contrast	Intention to treat and per protocol.	Observational analogue of the per protocol effect.
Estimands	Differences in five-year survival and restricted mean survival time at five years between arms	Same In addition, sensitivity analyses will be carried out to test the robustness of the results: - We will consider a SU target of ≤300 micromol/l to define the T2T-ULT arm and we will compare it with fire-and-forget ULT arm, - We will further censor the follow-up when people discontinue ULT, - We will exclude from the FAF-ULT arm, those patients who will not have measured serum urate levels within 12 months after ULT initiation. Also, we will stratify the analyses using the following prognostic factors: - Prior cardiovascular events (yes/no) - Sex (M/F) - Age-groups (<40, 41-65, >65) - Smoking status (current smoker, past smoker, non-smoker), - Body Mass Index categories (≤30 kg/m^2 and >30 kg/m^2)