Al Magnifico Rettore
All'Ufficio Dottorato di Ricerca

Università Politecnica delle Marche

Oggetto: richiesta periodo di soggiorno all'estero

Il sottoscritto Prof. WALTER GRASSI, in qualità di docente tutor nel programma di ricerca del Corso di dottorato di ricerca in Human Health – XXXVII° ciclo, chiedo l'autorizzazione a che il Dott. EDOARDO CIPOLLETTA possa trascorrere un periodo di 12 mesi, a decorrere dal 01/09/2023 al 01/09/2024 presso ACADEMIC RHEUMATOLOGY diretto dal Prof. ABHISHEK ABHISHEK - University of NOTTINGHAM per scopi inerenti la sua attività di dottorando.
Il Dott. EDOARDO CIPOLLETTA è iscritto regolarmente al SECONDO anno del corso di dottorato in Human Health – XXXVI ciclo e sotto la mia supervisione, sta affrontando tematiche riguardanti LA DIAGNOSI E LA PROGNOSI DELLE ARTROPATIE DA MICROCRISTALLI
L'attività per la quale si chiede la mobilità rientra nell'ambito dell'attuazione del programma di studi e di ricerca.

Si chiede pertanto l'incremento dell'importo della borsa di studio così come previsto all'art. 11 commi 5 e 6 del Regolamento Dottorato di Ricerca.

(Firma dottorando) _____ (Firma docente) _____

VISTO SI AUTORIZZA
IL COORDINATORE
Prof. Mario Guerrieri

Full project proposal

1.Title of research
Cardiovascular outcomes of gout flares and treat-to-target urate lowering treatment (clinical).

2.Applicant (name, organisation, position, email address) and anticipated contribution

First name, last name	Dr Edoardo Cipolletta
Professional position	MD, rheumatologist
Affiliation research centre	Polytechnic University of Marche (UnivPM), Ancona, Italy
Email addresses	edoardo.cipolletta@pm.univpm.it - edoardocipolletta@gmail.com
Anticipated contributions	Cipolletta will manage and analyse the study data. He will draft and submit journal articles and conference abstracts. Supervisory team will provide Rheumatology (Abhishek, Dehlin, Fillippucci, Drivelegka), Cardiology (Mamas, Guerra), Primary-care (Avery) and Epidemiology/bio-statistics (Abhishek, Nakafero, Tata) expertise. Abhishek and Fillippucci will provide mentorship and links to international networking opportunities for Cipolletta.

3. Abstract

Background: People with gout have higher cardiovascular disease risk and recent prior gout flares have been associated with a short-term increase in acute cardiovascular events. Long-term treat-to-target urate-lowering therapy (T2T-ULT) prevents gout flares. Whether lowering serum urate with T2T-ULT will prevent cardiovascular events, likely via flares reduction, has not been investigated. Additionally, whether gout flares are associated with arrhythmias, decompensated heart failure, and complications of acute myocardial infarction is unknown. The purpose of this study is to better understand cardiovascular outcomes associated with gout flares and to ascertain if T2T-ULT and colchicine flare prophylaxis prevent cardiovascular events.
Objectives: The objectives are to evaluate among people with gout whether: [1] T2T-ULT that meets serum urate target <360 µmol/L reduces cardiovascular event risk, [2] colchicine flare prophylaxis co-prescribed with ULT reduces cardiovascular event risk, and [3] to explore whether recent prior gout flares are associated with cardiac arrhythmias, decompensated heart failure, and complications of myocardial infarction.
Methods: The study will be delivered in three parts with patient and public input throughout. *Objective-1*: Routine healthcare data from the United Kingdom Clinical Practice Research Datalink (CPRD) and Western Swedish Health Care Register (VEGA) will be used to build a cohort of incident gout patients prescribed ULT for the first time. Landmark analysis in a prospective cohort study design will be used to compare the hazard ratio of cardiovascular events in patients meeting and not meeting serum urate treatment target within 12 months of start of ULT. *Objective-2:* Data from CPRD will be used to build a cohort of incident gout cases prescribed ULT for the first time. Hazard ratio of cardiovascular events will be compared between those co-prescribed colchicine flare prophylaxis and age- sex- matched controls not co-prescribed colchicine flare prophylaxis in a prospective cohort study design using Cox-regression. Data from VEGA will not be used for this objective due to low colchicine usage in Sweden. *Objective-3:* Data from CPRD, and VEGA linked to the SWEDEHEART registry will be used to conduct three separate nested case-control studies and self-controlled case series analyses to investigate the association between recent prior gout flares and (a) cardiac arrhythmias, (b) decompensated heart failure, and (c) complicated acute myocardial infarction. Odds ratios and incidence rate ratios will be used to estimate associations.
Impact and dissemination: The findings will be disseminated to patients, healthcare professionals, and will improve quality of care in gout by better understanding the extra-articular effects of gout flares and potential benefits from T2T-ULT with flare prophylaxis.

4.Background Gout is the commonest inflammatory arthritis with a prevalence of 2.5-4.0% in European adults and is caused by the deposition of monosodium urate (MSU) crystals in articular and peri-articular tissues. Characterised by recurrent painful inflammatory flares, that become even more frequent without long-term treat-to-target urate-lowering treatment (T2T-ULT), it is the only form of arthritis that can potentially be cured - with freedom from recurrent flares - provided long-term T2T-ULT is prescribed and adhered with [1].

Gout has traditionally been conceptualised as an intermittent inflammatory joint disease. However, articular and systemic inflammation during the inter-critical period (i.e. between gout flares) has been described recently [2]. Of greater concern, our recent research using a population sample of 62,574 people with gout demonstrated that flares are temporally closely associated with subsequent cardiovascular events and death due to cardiovascular events in the next 60 days [3]. It is likely that acute inflammation during gout flare causes atherosclerotic plaque instability resulting in cardiovascular events [3]. As T2T-ULT is effective in preventing gout flares after the first year of treatment, it is possible that long-term T2T-ULT may prevent cardiovascular events and cardiovascular mortality by reducing the number of flares [1].

There is considerable controversy over whether T2T-ULT improves cardiovascular outcomes in people with gout, despite the potential for such an effect [4,5]. This may be as clinical trials that recruited gout patients were underpowered [4,5]. Furthermore, confounding by indication and healthcare seeking behaviour bias, the observational studies that evaluated the association between ULT and cardiovascular mortality were biased because patients prescribed ULT were compared with ULT non-initiators [4,5]. Additionally, no attempts were made to ascertain whether the ULT initiators met serum urate treatment target in these studies [4,5].

A recent randomised controlled trial, the ALL-HEART study, showed that allopurinol does not improve cardiovascular outcomes in patients with ischaemic heart disease, but gout was an exclusion criterion for this study [6]. The effectiveness of long-term T2T-ULT that achieves serum urate target in preventing cardiovascular events in gout patients merits urgent assessment given the findings of the ALL-HEART study. Given the association between cardiovascular events and recent prior gout flares, the mechanism for long-term T2T-ULT in preventing cardiovascular events in gout could be reduction in gout flares.

Inflammation has a role in the pathophysiology of arrhythmogenesis and in the progression of heart failure [7]. Thus, it is possible that gout flares could also be temporally associated with other acute cardiovascular outcomes, specifically, cardiac arrhythmias, decompensated heart failure and complications of acute myocardial infarction. These need assessment to develop a greater understanding of the cardiovascular implications of gout flares.

Patients commenced on T2T-ULT are at high risk of gout flares and are recommended to be prescribed gout flare prophylaxis, preferably with colchicine for at-least the first six months of treatment. Colchicine is an anti-inflammatory drug and is effective in secondary prevention of cardiovascular events [8]. Whether co-prescription of colchicine in the context of initiating T2T-ULT would further prevent cardiovascular events has not been evaluated. Whether T2T-ULT and colchicine flare prophylaxis will prevent cardiovascular events in people with gout cannot be evaluated in a randomized controlled trial because these treatments are recommended as part of standard care of people with gout and it would be unethical to randomize patients to not receive these treatments.

5.Research objectives This fellowship will answer three unresolved questions in the field of gout:

- **Question1:** Does T2T-ULT that meets serum urate target prevent cardiovascular events? *Hypothesis:* In gout patients commenced on ULT, those that achieved serum urate treatment target <360 µmol/L will be less likely to experience cardiovascular events.
- **Question 2:** Does colchicine flare prophylaxis with ULT prevent cardiovascular events? *Hypothesis:* In gout patients commenced on ULT, co-prescription of colchicine flare prophylaxis will associate negatively with cardiovascular events.

- **Question 3:** Are gout flares associated with cardiac arrhythmias, decompensated heart failure, and complications of acute myocardial infarction? *Hypothesis:* Recent prior gout flares will be associated with cardiac arrhythmias, decompensated heart failure, and complications of acute myocardial infarction.

6.Research Plan

Data source Electronic health records from the Clinical Practice Research Datalink (CPRD) and the Western Swedish Health Care Register (VEGA) will be used. CPRD is a database of longitudinal anonymized electronic health record from over 34 million patients in the UK. VEGA is an electronic healthcare record database for the Western Sweden (an area inhabited by a sixth of the Swedish population – 1.7 million). Both databases include information on demographic details, lifestyle factors, diagnoses, results of blood tests, primary-care prescriptions, hospitalization and mortality records either directly or via linkages [9]. In addition, VEGA is linked to SWEDEHEART registry for outcomes of acute myocardial infarction [10].

Study period 1st January 2006 to 31st December 2019.

[A] Q1: Does T2T-ULT that meets serum urate target prevent cardiovascular events?

Study design: Cohort study using landmark analysis.
Data source: CPRD and VEGA.
Inclusion criteria: 1) Age ≥18 years. 2) New primary-care diagnosis of gout, defined as registered in database for ≥1 year without gout diagnosis or ULT prescription, thus minimizing the possibility of prevalent cases appearing as incident gout [11]. 3) Prescribed ULT after gout diagnosis.
Landmark date: 1-year after first ULT prescription. Serum urate level closest to landmark date will be used to define the exposed and unexposed status.
Exposed: Achieved serum urate target ≤360 µmol/L within 12 months of start of ULT.
Unexposed: Not achieved serum urate target within 12 months of start of ULT.
Outcomes: Cardiovascular events and death due to cardiovascular events. Cardiovascular event will be defined as either acute myocardial infarction or cerebrovascular accident ascertained in primary care, hospital or mortality records. Linkage across all databases will be used to improve case ascertainment as 25-50% of cardiovascular events are not recorded in at-least one of the three data sources [3].
Follow-up: Patients will be followed-up from landmark date to earliest of outcome date, date of transfer out of GP surgery, death date, 5 years from start of follow-up or study end date.
Data analysis: Multivariable Cox proportional-hazards model using landmark analysis and competing risk regression (where appropriate) will be used to examine associations. Data for Sweden and UK will be analysed separately and then pooled in a meta-analysis. Sensitivity analyses will consider serum urate treatment target ≤300 µmol/L to define the exposed status.
Feasibility count: There are 96,000 patients with incident gout in CPRD [3]. Of them, 48% were ever prescribed ULT (n≈43,000) and, 28% (n≈12,000) and 15% (n≈6,400) respectively achieved serum urate <360 and <300 µmol/L respectively within 1 year of first prescription. Approximately 20,000 patients with an incident diagnosis of gout were ascertained in VEGA [10]. Of them, 42% were prescribed ULT [12]. We assume similar success with T2T-ULT in VEGA as in CPRD. Thus, data for ≈14,000 exposed and 30,000 unexposed patients will be available for analyses.

[B] Q2: Does colchicine flare prophylaxis alongside ULT prevent cardiovascular events?

Study design: Cohort study.
Data source: CPRD. VEGA will not be used due to low colchicine use in Sweden.
Inclusion criteria: Incident gout and a new ULT prescription as described in section 6[A], page 3.
Exposed: Patients co-prescribed colchicine.
Unexposed: Patients not co-prescribed colchicine and age (years), sex matched to exposed participants. One unexposed participant will be matched to each case.
Outcomes: Cardiovascular events and death due to cardiovascular events. Outcomes will be defined as described in section 6[A], page 3.

Follow-up: Patients will be followed-up from first ULT prescription date to earliest of last colchicine prescription date or matched end follow-up date + 28 days in the unexposed, date of transfer out of GP surgery, event date, death date, or study end date.
Data analysis: Propensity score for colchicine prescription will be calculated. Multivariable Cox proportional-hazards model and competing risk regression (where appropriate) will be used to examine associations with the outcomes adjusted for propensity score. Sensitivity analyses will include propensity score-matched and inverse probability treatment weighted analyses. Stratified analyses will consider those who met and did not meet serum urate treatment target < 360 µmol/L.
Feasibility count: ≈43,000 new initiators of ULT were ascertained in the CPRD in our previous research [12]. There were 13,945 patients with gout prescribed colchicine flare prophylaxis in the CPRD ascertained in another study [13]. Thus, we are reasonably confident we will be able to match one unexposed person to an exposed person for sex and age.

[C] Q3: Are gout flares associated with cardiac arrhythmias, decompensated heart failure, and complications of acute myocardial infarction?

(i) Gout flare, arrhythmia and decompensated heart failure nested case-control study

Data source: CPRD and VEGA.
Inclusion criteria: Patients with incident gout as defined earlier in section 6[A], page 3.
Study-1: Gout flare and arrhythmias.
Cases: Patients with a consultation, hospitalization or death due to cardiac arrhythmias.
Controls: Up to 4 patients age, sex, and gout duration matched to index case.
Study-2: Gout flare and decompensated heart failure.
Cases: Patients with hospitalization or death due to heart failure.
Controls: Up to 4 patients age, sex, and gout duration matched to the case.
Exposure: Gout flares in the 0-60 days, 61-120 days, 121-180 days before event. Gout flares prior to 180 days or no gout flares will be the reference category. Gout flares will be defined as present if there was a diagnosis of gout flare in primary-care or hospitalization records, or if there was a primary-care consultation for gout and primary-care prescription of drugs used to treat gout flare on the same date.
Data analysis: Multivariable logistic regression will be used to evaluate the association between recent prior gout flares and each of the outcomes.
Feasibility count: We expect ≈96,000 patients with incident gout in CPRD and ≈40,000 consulted for at least one gout flare [3,10,12]. Assuming a prevalence of heart failure and cardiac arrhythmias of 9% and 10% in people with gout [14], we expect to ascertain ≈8,000 and ≈9,000 cases with heart failure and cardiac arrhythmia respectively and up to four-fold as many controls in study-1 and study-2 respectively.

(ii) Gout flare, arrhythmia and decompensated heart failure self-controlled case series

Data source: CPRD and VEGA.
Study-1: Gout flare and arrhythmias.
Inclusion criteria: Patients with gout flare and a consultation, hospitalization or death due to cardiac arrhythmias and one or more gout flares.
Study-2: Gout flare and decompensated heart failure.
Inclusion criteria: Patients with a gout flare and hospitalization or death due to heart failure and one or more gout flares.
Exposed and reference period: The 180 days after the gout flare will be the exposed period. It will be divided into three 60-day intervals. The 2 years before and after exposed period will be the reference period. Gout flares will be defined as in section 6[C](i) in page 4.
Data analysis: The self-controlled case series involves fitting a Poisson model conditioned on the number of specific outcomes. It is suited for examining the association between a transient exposure and an outcome and implicitly accounts for within-person time-invariant confounding. Age and season adjusted incidence rate ratios with 95% confidence intervals will be calculated for each stratum of the exposed period compared with the reference period.

Feasibility count: We expect ≈96,000 patients with incident gout in CPRD and ≈40,000 consulted for at least one flare [3,10,12]. For estimated rate of decompensated heart failure and incident cardiac arrhythmias in gout patients of 4.0 and 5.0 events/1,000 person-years [14] and median follow-up of 6 years, we expect ≈960 and 1200 eligible patients in studies 1 and 2, respectively.

(iii) Gout flare and complications of acute myocardial infarction nested case-control study

Data source: VEGA linked to SWEDEHEART registry.

Inclusion criteria: Patients with incident gout and hospitalization for acute myocardial infarction.

Cases: Patients hospitalized for acute myocardial infarction and experienced complications specifically ventricular arrhythmia, cardiac failure, cardiac shock, cardiac tamponade, heart rupture, ventricular septal defect (VSD), papillary muscle rupture, or prolonged hospitalization defined as ≥8 and 14 days, or dead within 30 days of acute myocardial infarction.

Controls: Patients hospitalized for acute myocardial infarction and did not experience above complications.

Exposure: Gout flares in the 0-60 days, 61-120 days, 121-180 days before event. Gout flares prior to 180 days or no gout flares will be the reference period.

Data analysis: Multivariable logistic regression will be used to evaluate the association between recent prior gout flares and the outcomes of interest.

Feasibility count: Based on previous research [3,10,12,15], we expect at least 20,000 patients with incident gout in VEGA and ≈8,000 consulted for at least one gout flare. Assuming a prevalence of acute myocardial infarction hospitalisation of 3% in people with gout [14], we expect to ascertain ≈600 patients with gout and an hospital admission for acute myocardial infarction. Given that, and using a case/control ratio of 1 to 4, ≈600 and up to ≈2,400 controls without the outcome of interest will be included in this study. Of them, ≈240 cases and ≈960 controls would experience at least one gout flare.

(iv) Gout flare and complications of acute myocardial infarction self-controlled case series

Data source: VEGA linked to SWEDEHEART registry.

Inclusion criteria: Patients with a new diagnosis of gout and acute myocardial infarction hospitalization and one or more gout flares.

Exposed and reference periods: will be as defined earlier in section 6[C](ii) in page 5.

Data analysis: as described earlier in section 6[C](i) in page 4.

Feasibility count: Based on previous research [3,10,12], we expect to have at least 20,000 patients with incident gout in VEGA and ≈8,000 consulted for at least one gout flare. Hypothesising an incidence of acute myocardial infarction in gout patients of 9.0 events/1,000 person-years and a study period of 4.5 years, we expect to have ≈300 patients with a hospital admission for acute myocardial infarction and at least one gout flare during the study period.

Covariates included in prospective cohort and nested case-control studies Age, sex, body mass index, socioeconomic deprivation, smoking status, alcohol intake, Charlson Comorbidity Index, gout disease duration, number of hospitalizations and primary care consultations in previous 12 months, and prescriptions of antiplatelet drugs, statins, diuretics, antihypertensives, colchicine, non-steroidal anti-inflammatory drugs, and corticosteroids.

7.Relevance to specific FOREUM call This proposal is relevant to the FOREUM international fellowship as it will deliver an European rheumatologist trained in epidemiology and biostatistics; establish a new multidisciplinary research network across three European countries (UK, Sweden, and Italy) and provide evidence to improve gout care by highlighting the adverse health impacts of recurrent gout flares and the beneficial effects of T2T-ULT with colchicine flare prophylaxis.

8.Key anticipated outcomes and proposed metrics to measure success As the main results of the present projects, we expect to publish at-least three high impact novel research papers. Proposed metrics of success will be completion of the work packages as outlined in the Gantt chart, acceptance of manuscripts in high-impact Journals such as Lancet Rheumatol, and ARD.

9.Project organisation and timeline

- *Who is doing what?* Cipolletta will deliver the research project. He will manage datasets, analyse data, and draft manuscripts and abstracts. Abhishek and Filippucci will mentor the fellow and coordinate a multidisciplinary team of supervisors.
- *External help needed?* No external help is needed to complete the research project.
- *Role of Patient (Research) Partners.* UK Gout Society and people with gout from Italy have advised on the research questions. They will co-develop the lay summary of results for the patient community and help disseminate findings including at Scientific meetings.

10.Milestones of the project

These are outlined in the Gantt chart below.

TASK	START	END
Phase 1 - Training at the Host Institution	06/2023	06/2024
Q1 project: data management and code list generation	06/2023	08/2023
Q1 project: data analysis	08/2023	12/2023
Epidemiology MSc at the LSHTM	09/2023	09/2023
Q1 project: manuscript drafting	12/2023	02/2024
Q1 project: PPIE	06/2023	02/2024
Q1 project: submit an abstract at the EULAR congress	01/2024	01/2024
Q1 project: submit the full paper to a Journal	02/2024	03/2024
Q2 project: data management and code list generation	02/2024	04/2024
Q2 project: data analysis	04/2024	08/2024
Phase 2 - Training at the Home Institution	06/2024	06/2026
Q2 project: submit an abstract at the ACR congress	06/2024	08/2024
Q2 project: manuscript drafting	08/2024	10/2024
Q2 project: PPIE	04/2024	10/2024
Q2 project: submit the full paper to a Journal	11/2024	12/2024
Q3 project: data management and code list generation	01/2025	07/2025
Q3 project: data analysis	08/2025	02/2026
Q3 project: submit an abstract at the EULAR congress	12/2026	01/2026
Q3 project: manuscripts drafting	02/2026	06/2026
Q3 project: PPIE	02/2025	06/2026
Q3 project: submit an abstract at the ACR congress	05/2026	06/2026
Q3 project: submit the full papers to the Journals	03/2026	08/2026

LSHTM: London School of Hygiene and Tropical Medicine **PPIE**: Patient and Public Involvement and Engagement **Q1**: does Treat-to-Target Urate-Lowering Therapy that meets serum urate target prevent cardiovascular events? **Q2**: does colchicine flare prophylaxis alongside Urate-Lowering Therapy prevent cardiovascular events? **Q3**: are gout flares associated with cardiac arrhythmias, decompensated heart failure, and complications of acute myocardial infarction?

Appendix I

Please list scientific key references (max. 15) to the research proposal (including full title and all authors)

1.	Doherty M, Jenkins W, Richardson H, *et al.* Efficacy and cost-effectiveness of nurse-led care involving education and engagement of patients and a treat-to-target urate-lowering strategy versus usual care for gout: a randomised controlled trial. *Lancet* 2018;**392**:1403–12. doi:10.1016/S0140-6736(18)32158-5
2.	Diaz-Torne C, Ortiz MA, Garcia-Guillen A, *et al.* The inflammatory role of silent urate crystal deposition in intercritical gout. *Rheumatology* 2021;**60**:5463–72. doi:10.1093/RHEUMATOLOGY/KEAB335
3.	Cipolletta E, Tata LJ, Nakafero G, *et al.* Association Between Gout Flare and Subsequent Cardiovascular Events Among Patients With Gout. *JAMA* 2022;**328**:440. doi:10.1001/JAMA.2022.11390
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5.	Zhang S, Xie Q, Xie S, *et al.* The association between urate-lowering therapies and treatment-related adverse events, liver damage, and major adverse cardiovascular events (MACE): A network meta-analysis of randomized trials. *Pharmacotherapy* 2021;**41**:781–91. doi:10.1002/PHAR.2609
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7.	Grune J, Yamazoe M, Nahrendorf M. Electroimmunology and cardiac arrhythmia. *Nature Reviews Cardiology 2021 18:8* 2021;**18**:547–64. doi:10.1038/s41569-021-00520-9
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9.	Herrett E, Gallagher A, Bhaskaran K, *et al.* Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015;**44**:827–36. doi:10.1093/IJE/DYV098
10.	Drivelegka P, Jacobsson LTH, Lindström U, *et al.* Incident gout and risk of first-time acute coronary syndrome: a prospective, population-based, cohort study in Sweden. *Arthritis Care Res (Hoboken)* Published Online First: 12 September 2022. doi:10.1002/ACR.25018
11.	Kuo CF, Grainge MJ, Mallen C, et al. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. Ann Rheum Dis 2015;74:661–7. doi:10.1136/ANNRHEUMDIS-2013-204463
12.	Abhishek A, Cipolletta E, Nakafero G, *et al.* Serum urate outcomes of treat-to-target urate lowering treatment: results of a nationwide cohort study from 1997 to the COVID-19 pandemic using data from the Clinical Practice Research Datalink. *Ann Rheum Dis* Published Online First: 2022. doi:10.1136/ARD-2022-222668

13.	Roddy E, Bajpai R, Forrester H, *et al.* P145 Safety of colchicine or NSAID prophylaxis when initiating allopurinol for gout: propensity score-matched cohort studies. *Rheumatology* 2022;**61**. doi:10.1093/RHEUMATOLOGY/KEAC133.144
14.	Cox P, Gupta S, Zhao SS, *et al.* The incidence and prevalence of cardiovascular diseases in gout: a systematic review and meta-analysis. *Rheumatol Int* 2021;**41**:1209–19. doi:10.1007/S00296-021-04876-6/TABLES/2
15.	Dehlin M, Drivelegka P, Sigurdardottir V, *et al.* Incidence and prevalence of gout in Western Sweden. *Arthritis Res Ther* 2016;**18**. doi:10.1186/S13075-016-1062-6

Appendix II

1. Does the proposed project, or parts of it, have any co-funding or support from industry or other sources?

   Yes ☐ (please specify in relation to the proposal)

   No ☒

2. Facilities / existing collaborative links available to support the proposed project (no more than 100 words):

Prof Abhishek will mentor the fellow. Abhishek has successfully supervised 10 PhD students to completion and leads Academic Rheumatology in Nottingham. Dr Tata (epidemiology), Dr Nakafero (statistics), Prof Avery (primary-care, co-investigator of the ALL-HEART trial), Prof Mamas (cardiology), Prof Dehlin (rheumatology), Dr Drivelegka (rheumatology), Prof Filippucci (rheumatology), Prof Guerra (cardiology) will form wider mentorship and supervision team. A high-spec computer, office space, peer support from junior career researchers, pastoral support and IT and library access will be provided. The fellow will learn Stata programming, epidemiological and methodological skills during his Master's at the London School of Hygiene and Tropical Medicine.

3. Has this or a related application currently or previously been submitted elsewhere, including FOREUM, EULAR or ACR?

   Yes ☐ (if yes, please give details and state when you expect to hear the outcome)

   No ☒

4. Is the proposed project likely to lead to patentable or commercially applicable data or apparatus?

   Yes ☐ (if yes, please give details)

   No ☒

IMPORTANT: FOREUM expects all of the researchers it funds, both clinical and non-clinical, to adopt the highest achievable standards in the conduct of their research. This means exhibiting impeccable scientific integrity and following the principles of good research practice detailed in the **MRC Good Research Practice Guidelines (2000).**