This study is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (NIHR130580). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

This protocol is for prediction modelling (work package 2) of the grant:

The development of risk-stratified, cost-effective, and acceptable blood-test monitoring strategies for inflammatory conditions treated with commonly used immune suppressing drugs: a multi-method study using evidence synthesis, modelling and qualitative research (NIHR130580).

Please see below for a description of the other work-packages

Question: What is the optimum strategy of blood testing after the first 6 month of immune-suppressing drug prescription?

Objectives: [1] Investigate association between different strategies of testing and target-organ damage detection. [2] Identify prognostic factors associated with target-organ damage. [3] Develop a prediction model for target-organ damage conditional on the prognostic factors. [4] Evaluate cost-effectiveness of risk-stratified testing strategies. [5] Assess patients' and clinicians' views and experiences of current testing strategies, and the acceptability of recommended strategies.

Methods: The study will be delivered in 3 interlinked work packages (WPs) with patient and public input throughout.

WP 1 (Evidence synthesis): Delivers objectives 1-2. A conventional (Review 1) and prognostic (Review 2) systematic review will be performed adhering to the York CRD guidance and PROGRESS framework respectively. Cochrane Risk of Bias, ROBINS-I and QUIPS checklists will be used for quality assessment as appropriate. Data on patient characteristics, monitoring strategies, adverse events, drug discontinuations (Review 1); and prognostic factors for developing adverse events (Review 2) will be extracted. Evidence will be assessed using the GRADE and meta-analysed using random effects model if appropriate.

WP 2 (Prediction, health economic modelling): Delivers objectives 3-4. Routine healthcare data from Clinical Practice Research Datalink (CPRD) Gold and Aurum will be used to develop and validate a prognostic model. CPRD is an anonymized, longitudinal database of UK primary-care records established in 1987. It provides data on demographics, lifestyle factors, diagnoses, blood test results, and GP prescriptions. Data on prognostic factors identified in WP1 (Review 2) will be extracted from the CPRD and used to develop a risk-score

using a penalized flexible parametric survival model. Risk thresholds to be used in the health economic models will be agreed using decision curve analysis and with patient and clinician involvement. After this, a mathematical model will be formed to compute cost-effectiveness of frequency of testing at different levels of risk. The model will be in line with the NICE reference case using a lifetime horizon and estimating a cost per QALY gained for alternative frequency of testing strategies. The uncertainty of results will be explored with confidence intervals, cost-effectiveness planes and cost-effectiveness acceptability curves.

WP 3 (Qualitative): Delivers objective 5. Patients and healthcare professionals will be recruited to explore their views on current and recommended monitoring strategies. Both purposive stratified and maximum variation sampling will be employed to include patients with different diseases, treatments, and at varying risk of adverse-events. Semi-structured interviews will be conducted using interview topic guide created with PPI input. Data will be transcribed verbatim, anonymised, and analysed using inductive thematic analysis.

Study title: The development of risk-stratified blood-test monitoring strategies for common inflammatory conditions treated with immune suppressing drugs

Section 1: General Information

Research area Drug Safety, Pharmacoepidemiology
Does this protocol describe an observational study using purely CPRD data? Yes

Additional information from GPs and contact with patients

Does this protocol involve requesting any additional information from GPs, or contact with patients? No

Section 2: Research team Applicant's role

Role: Corresponding applicant
Email: georgina.nakafero@nottingham.ac.uk
Name: Dr Georgina Nakafero
Statistical experience: Yes
Experience of handling large datasets: Yes
Experience of practicing in UK primary care: No
Will the applicant be analysing the data?
Yes

Chief investigator
Chief investigator's email: abhishek.abhishek@nottingham.ac.uk
Will this person be analysing the data?: Yes
Status: Confirmed
Name: Professor Abhishek Abhishek
Statistical experience: No
Experience of handling large datasets: Yes
Experience of practicing in UK primary care: No

Collaborators
Collaborator's email: d.van.der.windt@keele.ac.uk
Will this person be analysing the data?: No
Status: Confirmed
Name: Professor Danielle van der Windt
Statistical experience: Yes
Experience of handling large datasets: No
Experience of practicing in UK primary care: No

Collaborator's email: r.riley@keele.ac.uk
Will this person be analysing the data?: No
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Name: Professor Richard Riley
Statistical experience: Yes

Experience of handling large datasets: No
Experience of practicing in UK primary care: No

Collaborator's email: Tim.Card@nottingham.ac.uk
Will this person be analysing the data?: No
Status: Confirmed
Name: Dr Timothy Card
Statistical experience: Yes
Experience of handling large datasets: Yes
Experience of practicing in UK primary care: No

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Will this person be analysing the data?: No
Status: Confirmed
Name: Professor Christian Mallen
Statistical experience: No
Experience of handling large datasets: No
Experience of practicing in UK primary care: Yes

Collaborator's email: Matthew.Grainge@nottingham.ac.uk
Will this person be analysing the data?: No
Status: Confirmed
Name: Dr Matthew Grainge
Statistical experience: Yes
Experience of handling large datasets: Yes
Experience of practicing in UK primary care: No
Access to data

Section 3. Access to data
Sponsor: University of Nottingham
(Sponsor information is retrieved automatically as the chief investigator's affiliation)
Funding source for the study

Is the funding source for the study the same as Chief Investigator's affiliation? No

Funding source for the study
Funding source for the study: National Institute for Health Research - NIHR London Office
Institution conducting the research

Is the institution conducting the research the same as Chief Investigator's affiliation? Yes

Method to access the data
Indicate the method that will be used to access the data Institutional multi-study licence
Is the institution the same as Chief Investigator's affiliation? Yes

Extraction by CPRD

Will the dataset be extracted by CPRD? No

Data processors

Data processor is: Same as the chief investigator's affiliation
Processing: Yes
Accessing: Yes
Storing: Yes
Processing area: UK

Section 4. Information on data
Primary care data: CPRD GOLD, CPRD Aurum

Do you require data linkages?
Yes - I do require data linkages
Patient level data
HES Admitted Patient Care

Area level data
Do you require area level data? No

Withheld concepts
Are withheld concepts required? No

Linkage to a dataset not listed
Are you requesting a linkage to a dataset not listed? No

Patient data privacy

Does any person named in this application already have access to any of these data in a patient identifiable form, or associated with an identifiable patient index? No

Section 5. Protocol information

Lay summary

Medicines such as methotrexate suppress the immune-system and are used to treat conditions like rheumatoid arthritis (RA) that result from an overactive immune-system. Patients treated with these medicines may develop side-effects such as blood, liver or kidney damage, and, fortnightly to monthly blood tests are performed to detect them early, before any permanent damage can occur. However, these side-effects become less common after the first few months of treatment. Nevertheless, monitoring with periodic blood tests is continued indefinitely for all patients treated with these medicines. The benefit from such long-term monitoring is not known, and, whether all patients should undergo regular blood-tests indefinitely needs to be determined.

We want to find out the best strategy for long-term monitoring of people with inflammatory conditions (e.g. RA, psoriasis, inflammatory bowel disease etc.) treated with immune-suppressing medicines, specifically, methotrexate, sulfasalazine, aminosalicylates (e.g. mesalazine), azathioprine, and mycophenolate.

For this, we will use anonymized information from a healthcare database (Clinical Practice Research Datalink), which includes information on the treatment and monitoring of adults registered with a large number of general practices in the UK. We will use information about risk factors such as age, sex, body mass index, other illnesses, lifestyle factors (such as alcohol intake, smoking) and prescription of other medicines to develop a score to calculate the risk of blood, liver, or kidney damage over a 5-year time-period for people treated with these medicines. A separate risk score will be calculated for each medicine of interest named in the previous paragraph.

Technical summary

Background: The optimal monitoring strategy for adults with common inflammatory conditions treated with long-term immune-suppressing drugs is not known.

Question: What is the optimum strategy of blood testing after the first six months of primary-care immune-suppressing drug prescription?

Objectives: [1] Develop and validate a prediction model for estimating an individual's risk of target-organ damage conditional on their values of multiple prognostic factors available at 6 months of primary-care immune-suppressing drug prescription, [2] Identify incidence of drug discontinuation for any reason, and due to abnormal monitoring blood test results in each year of prescription.

Methods: Data from Clinical Practice Research Datalink (CPRD) Gold and Aurum will be used. We will utilise CPRD-HES linked data to validate the sensitivity of outcome definition in primary-care data alone.

People with common inflammatory conditions treated with immune-suppressing drugs, will be followed up electronically from day 180 of the first primary-care prescription of a drug of interest until the earliest of target-organ adverse event, drug discontinuation, death, moving to a different practice, 5-year follow-up time, or 31/12/2019 (study end date).

A penalized flexible parametric survival model will be used to develop a risk prediction score for drug discontinuation due to target organ damage using CPRD Aurum given its larger sample size, accounting for competing risks as necessary, and with internal validation using bootstrapping to quantify and adjust for optimism. The predictive performance of the score will be validated in CPRD Gold. GP practices contributing data to both CPRD Aurum and GOLD will be excluded from the validation cohort. Separate risk scores will be developed and validated for each drug of interest. Risk thresholds will be agreed using decision curve analysis and with patient and clinician involvement. Incidence (per 1,000 person-years) of treatment discontinuation in each 12-month of primary-care prescription will be estimated.

Outcomes to be measured
Primary outcome: Drug discontinuation due to target organ specific adverse event. This will be defined as drug discontinuation with either (a) abnormal blood test results due to target-organ damage, or (b) target organ damage based on clinical code allocation.

Drug discontinuation due to abnormal monitoring blood test results will be defined as present when there is:

(a) a gap between two prescriptions, or between the last prescription date and earliest of death date, moving to a different practice, 5-year follow-up time, or 31/12/2019 (study end date) of ≥ 90 days, and
(b) the last prescription is preceded in up to 15 days by abnormal blood test results (to account for any delay in acting on abnormal results) or followed by an abnormal test result in the next 45 days.

Abnormal blood test results will be defined according to the British Society for Rheumatology DMARD monitoring guidelines1, and CKD progression will be defined as per the Kidney Disease Improving Global Outcomes guideline 20122:

- White blood cells <3.5x109/L,
- Neutrophils <1.6x109/L,
- Platelets <140x109/L,
- Alanine Transaminase and/or Aspartate Transaminase >100 units/L,
- CKD progression defined as creatinine difference > 26 micro mol/L above the first or second preceding blood-test result or chronic kidney disease stage progression.

In addition to the above blood-test abnormalities, in people with psoriasis, methotrexate discontinuation will be defined to be due to blood-test abnormalities if (i) serum amino-terminal pro-peptide of type III procollagen (PIIINP) is > 8 mg/L on two previous occasions; (ii) if three previous PIIINP measurements were >4.2 mg/ L in the previous 12-month period; or (iii) if previous PIIINP measurement was > 10 mg/L as per guidelines for the British Association of Dermatologists [3].

Secondary outcome: Drug discontinuation due to any reason.
Defined as present if there is a gap between two prescriptions, or between last prescription date and earliest of death date, moving to a different practice, 5-year follow-up time, or 31/12/2019 (study end date) of ≥ 90 days.

Objectives, specific aims and rationale

The overall purpose of this study is to ascertain the optimum strategy of blood testing for adults with common inflammatory conditions treated with immune-suppressing drugs after the first six months of primary-care prescription. By strategy we mean the optimum frequency of testing, and how the frequency of testing should alter according to the individual's risk.

The objectives are to:

[1] Develop and validate a prediction model estimating an individual's risk of target-organ damage conditional on their values of multiple prognostic factors available at six months of immune-suppressing drug prescription.

[2] Identify incidence of drug discontinuation due to any reason and due to abnormal monitoring blood test results in each year of prescription.

Synergy with ongoing research: We have an ISAC approved study (reference number 19_275R) developing a risk-prediction score for liver, blood or kidney damage from methotrexate and leflunomide in people with auto-immune rheumatic diseases, using data from the Clinical Practice Research Datalink (CPRD).

We are seeking approval for additional work to [1] conduct prediction modelling for azathioprine, sulfasalazine, aminosalicylates (such as mesalazine), and mycophenolate, and [2] expand analysis of methotrexate to include patients with psoriasis (without psoriatic arthritis) and inflammatory bowel disease.

Leflunomide is only licenced for the treatment of RA and psoriatic arthritis and we do not propose to expand the modelling to other common inflammatory conditions for this drug for this reasons.

We can confirm that these analyses were not included in our previously approved application.

Study background

A. What is the problem being addressed?

Rheumatoid arthritis, inflammatory bowel disease, psoriasis +/- arthritis, ankylosing spondylitis and systemic lupus erythematosus affect 1 in 30 adults in the UK, and are treated with immune suppressing drugs such as methotrexate, azathioprine and sulfasalazine etc. [4-9]. These medicines can cause symptomatic side-effects such as nausea, vomiting, headache, infections etc., and asymptomatic side-effects such as acute liver or kidney injury, or low blood cell count. Clinical experience and research studies identified in our scoping review suggest that both symptomatic and asymptomatic side-effects generally occur within the first six months of starting treatment [10-14], and, because of this increased risk of drug toxicity, treatment is initiated in a hospital clinic with dose escalation guided by disease activity, and fortnightly-to-monthly tests of full blood count, renal and liver function performed to detect any asymptomatic abnormalities early. Unless there are early side-effects and the treatment is stopped, most patients achieve their target dose between three to four months of starting treatment. Just after this, the responsibility for prescribing and monitoring, including with three-monthly blood tests is handed-over to the patients' general practitioner (GP). The intended purpose of such monitoring is to facilitate early detection of an abnormality, allowing the offending treatment to be stopped before any permanent damage occurs. However, there is scant evidence that long-term use of these immune suppressing medicines causes blood, liver, or kidney damage [10-14]. Thus, this strategy for long-term monitoring with periodic blood tests for all patients appears to be based on convention, inertia, and perceived safety, rather than on a robust evidence base.

Moreover, the recommendations for monitoring differ across specialties. For example, the British Association of Dermatology recommends measuring serum amino-terminal pro-peptide of type III procollagen (PIIINP), a biomarker of liver fibrosis for methotrexate prescriptions, while the British Society for Gastroenterology and British Society for Rheumatology do not recommend such testing [1,15,16]. Such inconsistencies cause confusion, and may result in excessive monitoring or in monitoring not being done. Similarly, while the summary of product characteristics and clinical guidelines recommend more frequent haematological and biochemical monitoring in individuals with comorbidities, such as excess alcohol use, extremes of body mass index (e.g. <18 or >35 kg/m2), old age and renal impairment, the way in which these factors interact with drugs to produce target organ damage such as low blood count, or kidney or liver injury varies across studies, and, has not been systematically reviewed [17-22]. A risk prediction model incorporating these factors has not been developed, and the optimum monitoring strategy in terms of frequency, and the tests to include is not known.

How does the existing literature support this proposal?

There is no published systematic review of the evidence for long-term blood-monitoring. A review just on methotrexate toxicity is ongoing since 2013 (CRD42015020254) according to a search of PROSPERO on 29/07/2019. Our scoping review suggests that monitoring tests are rarely abnormal after the first year of treatment. In clinical trials, fewer than 2% of people prescribed methotrexate and none prescribed leflunomide discontinued treatment

due to blood test abnormalities after the first year (n=1,198) [10, 23, 24]. Similar findings were observed in other observational studies of leflunomide and methotrexate treatment [11,25]. Thus, the greatest utility of these monitoring blood tests appears to be in the first year of treatment, with the risk reducing with increasing treatment duration.

Although renal function testing is included in regular monitoring for methotrexate, low-dose methotrexate, as used in the treatment of autoimmune inflammatory diseases has a low rate of acute kidney injury e.g. 1.9/1000 person-years in a nationwide Danish study (mean follow-up period 4 years), with three-quarter of such events occurring within the first eight months of treatment [26]. In keeping with the above, >98% of liver and bone marrow adverse events due to azathioprine occurs within the first year of treatment as observed in previous systematic reviews [12,27]. Similarly, a cohort study of 739 people with inflammatory bowel disease followed-up for up to 11 years, reported only two cases of clinically severe leukopenia (less than 2000/µL) after the first 12 month of treatment [13]. Many of the drug discontinuations reported in these older studies would not occur in clinical practice nowadays as these were relatively early clinical trials, and the current threshold for drug discontinuation due to abnormal blood-test results e.g. alanine transferase (ALT) more than 3 times the upper limit of normal, are significantly higher than those used in these studies e.g. ALT more than 1.2-1.4 times the upper limit of normal [28]. Generally, drug-induced liver injury occurs within the first few months of drug initiation. For instance, in one study, the median (inter-quartile range) time between first drug prescription and liver injury, defined as liver enzyme levels >5 times normal was only 42 (20–117) days, and 5.5% of the 254 liver injuries were due to immune-suppressing drugs [14]. There are no data demonstrating that routine periodic blood test monitoring after a year of treatment is effective in preventing serious adverse drug reactions, compared to symptom-driven testing [29]. Additionally, small observational studies suggest that cumulative dosing of medicines such as methotrexate does not correlate with toxicity [30-33]. Our limited review suggests that most blood, liver, and kidney-related adverse events occur within first few months of treatment, and only a small proportion of drug discontinuations occur due to these after the first year. Ongoing regular monitoring can be onerous for patients, incurs costs, and false positive results prompt unnecessary testing and treatment. There is variability in guidance across disciplines. Hence, there is need for a study to determine optimal monitoring strategy.

We propose to use existing data from routine treatment of people with inflammatory diseases prescribed selected immune-suppressing drugs in the UK to develop risk prediction models.

Study type
Pharmacoepidemiology study, drug-safety study.

Study design
Prospective cohort study.

Feasibility counts According to a feasibility count using data from 731 GP practices (n=3,023,253 adults contributing to CPRD Gold) in the year 2018, there were over 40,000 participants in receipt of at-least one primary-care prescription for the drugs of interest.

Please see Table 1 for individual drugs. As we will utilise data from 2007-2019, we anticipate greater number of participants. For instance, in our ongoing study (ISAC reference number 19_275R), 24,871 people in CPRD Gold dataset were prescribed methotrexate between the years 2007 and 2019 of which 15,670 incident users were included in the analyses after applying the inclusion and exclusion criteria. Among these participants, there were 1,262 methotrexate discontinuations for acute kidney, liver or bone-marrow toxicity. Of the discontinuations due to abnormal blood test results, a random sample of 505 cases demonstrated that 95% discontinuations could not potentially be explained by another underlying illness, its treatment, or complication recorded in the CPRD.

Sample size considerations
Proportion discontinuing drugs due to abnormal blood-test results:
Based on data from our ongoing study, there are 15,670 people with auto-immune rheumatic diseases prescribed methotrexate of which 8% discontinued methotrexate due to blood-test result abnormalities. Assuming a similar discontinuation rate for all inflammatory conditions, we should be able to estimate the same proportion with a margin error based on 99% confidence interval of +/- 0.55%. Values for other drugs in Table 1 should be estimated with similar or greater precision as the source population (Aurum) will be larger.

Risk prediction model:
Sample size for prediction modelling should aim to minimise overfitting and estimate key parameters precisely. This is the premise of Riley et al [34] sample size criteria. Assuming a mean follow-up of 1 year and a rate of 0.02 per person year such that at 6 months outcome risk is 1%, then the max R squared is 0.18. Conservatively assuming that 15% of variation is explained by our model (model R squared is 0.027), then with 50 candidate predictor parameters, the criteria of Riley et al [34] suggests 6.57 events per parameter, therefore 329 outcome events are required, and 16,416 participants are needed for developing the prognostic model.

We will use data from CPRD Aurum to develop the prognostic model for mesalazine, sulfasalazine, azathioprine, and mycophenolate. We are reasonably confident that there will be sufficient sample size to develop a prognostic model for all drugs of interest with the exception of mycophenolate.

Our ongoing ISAC approved study (ISAC reference number 19_275R) has used data from CPRD Gold to develop a prognostic model for methotrexate toxicity in patients with autoimmune rheumatic diseases, and is validating it using data from the CPRD Aurum. To maintain synchrony with ongoing research we will include data for patients with psoriasis and inflammatory bowel diseases treated with methotrexate in CPRD Gold database in the model development dataset and from CPRD Aurum database when validating prognostic model for methotrexate toxicity.

Planned use of linked data and/or withheld concepts
HES admitted patient care:

We anticipate that serious blood, liver or renal organ system drug toxicities may lead to hospitalisation and these outcome events may not be ascertained using primary care

dataset alone if the abnormal blood-test result is not recorded in primary care. However, our clinical experience suggests that such outcomes are very rare. Due to sample size limitations (as 68.5% and 65.7% of CPRD Gold and Aurum respectively have linkage to HES), an analysis restricted to CPRD-HES linked data is not appropriate, as a third of sample-size will be lost with only a few outcome events gained. Therefore, a sample will be drawn from the study population with HES linkages to validate the sensitivity of outcome definition using primary-care data alone.

Data on reason(s) for hospitalisation will be tabulated and ICD-10 codes that imply drug-induced target organ damage will be selected. This process will involve initial review of the potentially eligible ICD-10 codes by AA (CCT in rheumatology and general medicine) to screen out obvious unrelated diagnoses, followed by a review by a panel of all clinical co-investigators. Hospitalisations with such ICD-10 codes will be combined with episodes in which there are primary-care prescription gap of 90-days or more to define outcomes of interest i.e. drug discontinuation due to target organ damage will be ascertained.

The sensitivity of outcome definition using primary-care data alone contained in the CPRD (i.e. abnormal blood test results and/or GP Read code indicating target organ damage with a prescription gap of 90 days or more) will be calculated against primary-outcome defined using both primary-care and secondary-care dataset (HES) for the randomly selected participants. This will be calculated separately for each drug included in this study.
Based on results from the ongoing work, only 8% discontinued methotrexate due to blood-test abnormalities. If the sensitivity is >90%, the potential for misclassification is <1% (1.11 x 0.08). As this is small, we will proceed as planned. If it is <80% the potential for misclassification is larger and we will consider using CPRD-HES linked data to define outcomes in consultation with the independent funder (NIHR) mandated study steering committee, and if between 80-90% we will seek advice from the same independent study steering committee, review event rates, before proceeding further. However, given our clinical experience we anticipate the sensitivity of using primary-care data alone to be above the 90% threshold.

Why is this study important?
This study will develop a prognostic model to identify people at-risk of target organ damage from immune suppressive drugs. If implemented in clinical practice, it will ensure better targeted drug monitoring blood-tests ultimately reducing the burden on patients and the NHS caused by frequent testing with potential cost-saving for the NHS.
Definition of the study population
Data source: Data from the Clinical Practice Research Datalink (CPRD) will be used. CPRD is an anonymised longitudinal database of UK general practice records and was incepted in 1987. It provides data on two platforms:
• CPRD Gold: 18,389,105 participants ever registered with 887 GP surgeries, using the Vision® GP software.
• CPRD Aurum: 39,043,877 participants ever contributing data to 1,485 GP practices using the EMIS GP software.
Both Gold and Aurum databases include information on patient demographics, lifestyle factors, diagnoses, and results of investigations including blood tests, hospital referral, and details of all GP prescriptions [35]. The medication data includes information about dose

and date of prescription and are stored as product codes mapped onto British National Formulary codes in the CPRD Gold and the Dictionary of Medicines and Devices in the CPRD Aurum.

Diagnostic and clinical data in the CPRD Gold are recorded as medical Read codes whereas these data are stored using a mixture of Read version 2, SNOMED and local EMIS® codes in the CPRD Aurum database [36]. Diagnosis, prescription, test and observation (e.g. BMI) data in CPRD Gold are stored in the clinical, therapy, test and additional files respectively. Data for diagnosis, test results and observations such as BMI are stored in the observation file of CPRD Aurum, while prescription data are stored in drug issue file.

The data in the CPRD undergo thorough quality checks and are of a reliable research standard with a high validity of recorded diagnoses, including a median proportion of cases with a confirmed diagnosis of 89% for 183 different conditions including chronic auto-immune diseases [37].
We will develop the prediction model for Mesalazine, Sulfasalazine, Azathioprine and Mycophenolate using data from CPRD Aurum, and externally validate using data from CPRD Gold as the former has substantially more participants.

For methotrexate, we will use CPRD Gold for model development as (a) this was approved in the previous ISAC application and we are at advanced stages of model building for this drug, (b) there were 1,262 outcome events for patients with autoimmune rheumatic diseases prescribed methotrexate in CPRD Gold providing adequate power, and (c) inclusion of participants with psoriasis or inflammatory bowel disease (proposed in the current application) will further increase the power.

Approximately 200 general practices that have moved from Vision to EMIS GP software have contributed data to both platforms. However, these practices are identified by CPRD in a bridging file, and will be excluded from the validation cohort.

Study start date: 01/01/2007
Study end date: 31/12/2019

Cohort entry and start of follow-up: At first prescription and day 180 of the first primary-care prescription of a drug of interest respectively. Separate cohorts will be built for each drug.

Cohort exit: Earliest of target-organ adverse event, drug discontinuation, death, moving to a different practice, 5-year follow-up time, or 31/12/2019 (study end date).

Inclusion criteria:
[1] Diagnosis of any common inflammatory disease i.e. RA, inflammatory bowel disease, psoriasis +/- arthritis, ankylosing spondylitis, systemic lupus erythematosus, or reactive arthritis. These are the commonest inflammatory conditions treated with immune-suppressive drugs.
[2] Age ≥18 years at diagnosis.

[3] At least one GP prescription of methotrexate, azathioprine (or mercaptopurine), aminosalicylates, sulfasalazine, mycophenolate. These are the most commonly prescribed immune-suppressing drugs for which blood test monitoring is recommended.
[4] Meeting CPRD data quality standards (UTS for Gold and acceptable flag for Aurum) and with a continuous registration for at least one year before the first date of diagnosis of inflammatory disease in CPRD Gold and CPRD Aurum.

The requirement to have one-year disease free registration in the CPRD prior to first date of inflammatory disease diagnosis is to allow for the identification of incident cases, and those newly commenced on immune-suppressing drugs. This will exclude prevalent cases of inflammatory diseases on long-term hospital prescribed immune-suppressive drugs who have recently switched to GP prescription due to implementation of primary-care/secondary-care shared care prescribing in their area.

Exclusion criteria: Presence of any of the below prior to cohort entry:
[1] eGFR < 15 ml/min or chronic kidney disease stage 4 or 5.
[2] Chronic liver disease: Autoimmune hepatitis, hepatitis B or C, cirrhosis
[3] Pre-existing hematological abnormalities: Myelodysplasia, primary hematological diseases causing neutropenia or thrombocytopenia.
[4] Prescription of the immunosuppressive drugs listed above before first inflammatory disease diagnosis date.
[5] Registered in GP practices not meeting CPRD data quality standard at cohort entry.

Selection of comparison group(s) or controls
A comparison group is not applicable in the context of risk prediction modelling.
Exposures, outcomes and covariates
Predictors of drug discontinuation: Candidate prognostic factors will be identified using two approaches:
[1] Theory driven based on prior knowledge: A list of recognised prognostic factors for abnormal monitoring blood test results have been developed based on the research teams' clinical experience. The a priori agreed prognostic factors include: age, sex, body mass index, alcohol consumption, smoking, CKD stage 3, type 2 diabetes, and prescription of selected drugs that increase risk of acute kidney injury or transaminase elevation at baseline.

[2] Evidence based, based on systematic review: A systematic review of existing literature is currently underway to identify other prognostic factors. This will provide additional candidate predictors (PROSPERO: CRD42020208049).

The presence of comorbid and lifestyle prognostic factors will be ascertained using primary-care diagnoses and lifestyle data collected in the two-years preceding cohort entry. The presence of prescription prognostic factors will be ascertained using primary-care prescriptions in the 180 days preceding cohort entry.

Outcomes
Primary outcome: Target organ specific adverse event resulting in drug discontinuation from 6 months of initial primary-care prescription to until 5-years after the initial prescription.

This will be defined as drug discontinuation with either (a) diagnosed with target organ damage based on clinical code, or (b) significant abnormal blood test results.

Drug discontinuation due to abnormal monitoring blood test results will be defined as present when there is:
(a) a gap between two prescriptions, or between last prescription date and earliest of death date, moving to a different practice, 5-year follow-up time, or 31/12/2019 (study end date) of ≥ 90 days, and

(b) an abnormal blood-test result in the 15 days preceding or 45 days after the last prescription date. The 15-day preceding window is to allow for any delay in acting on abnormal blood-test results.

Abnormal blood test results will be defined according to the British Society for Rheumatology DMARD monitoring guidelines 1, and CKD progression will be defined as per the Kidney Disease Improving Global Outcomes guideline 20122:

- White blood cells <3.5x109/L,
- Neutrophils <1.6x109/L,
- Platelets <140x109/L,
- Alanine Transaminase and/or Aspartate Transaminase >100 units/L,
- CKD progression defined as creatinine difference > 26 micro mol/L above the first or second preceding result or chronic kidney disease stage progression.

In addition, in people with psoriasis (but without arthritis), methotrexate discontinuation will be defined to be due to blood-test abnormalities if (i) serum amino-terminal pro-peptide of type III procollagen (PIIINP) is > 8 mg/L on two previous occasions; (ii) if three previous PIIINP measurements were >4.2 mg/L in the previous 12-month period; or (iii) if previous PIIINP measurement was > 10 mg/L as per guidelines for the the British Association of Dermatologists [3].

Primary outcome identification: Study participants who have the outcome of interest will be identified as follows:

Step 1: All participants with drug discontinuation as defined above will be identified.

Step 2: The results of their blood tests from up to 15 days before and 45 days after the last DMARD prescription date, and the dates of blood tests will be extracted.

Step 3: All other Read code entries in the clinical and investigation files indicating abnormal blood test results within this 60-day period (-15 to + 45 days), and the date of such entry will be extracted.

Step 4: Participants with abnormal blood test results or a Read code specifying abnormal blood test results within this period and their date of event will be ascertained.

Secondary outcome: Drug discontinuation due to any reason. Defined as a gap between two prescriptions, or between last prescription date and earliest of death date, moving to a different practice, 5-year follow-up time, or 31/12/2019 (study end date) of ≥ 90 days.
Data/statistical analysis
Mean (standard deviation), and n (%) will be used for descriptive purposes.

Derivation and validation of the risk prediction model:

The theory driven and systematic review derived prognostic factors will be included in a flexible parametric survival model, to identify the prognostic factors (predictors) of the outcomes of interest i.e. target organ specific adverse events or drug discontinuation due to abnormal monitoring blood test results. Multiple imputation using chained equations will be used to deal with missing data. The number of imputations will depend on the extent of missing data. All of the data available in the CPRD Aurum (except for methotrexate where we will continue to use CPRD Gold for model development) will be used to develop the risk prediction model. All candidate predictors will be included. We will form the risk equation for the outcome of interest by a function of the estimated β coefficients multiplied by values of the corresponding predictors included in our model together with the baseline hazard function. This process ultimately leads to an equation for the predicted absolute risk over time. We will examine the performance of this final model in terms of discrimination by calculating the c-statistic and calibration by plotting agreement between predicted and observed risks across the whole range of predicted risk at relevant time-points (calibration plot with smoothed calibration curves, with measures of calibration-in-the-large and calibration slope, as estimated using pseudo-observations). As part of the process of internal validation, to account for optimism caused by over-fitting, for each imputation separately, we will develop a model separately within 100 samples of the derivation data with replacement of the same size of the original sample (bootstrap samples). From this the optimism will be estimated by comparing the performance of the model in the bootstrap samples with the same model in the original sample. We will then estimate the overall optimism averaged over all 100 models in each imputed dataset and estimate a uniform shrinkage factor, equal to the average of the calibration slopes from each of the bootstrap samples. The process will be repeated for each imputed dataset, and the final uniform shrinkage calculated by averaging across the estimated shrinkage estimates from the imputations. Then, to account for over-fitting during the development process, we will multiply (penalize) the original β coefficients by the uniform shrinkage factor. At this point, the baseline hazard will be re-estimated on the basis of the shrunken β coefficients to ensure that overall calibration is maintained, producing a final model. Outcomes affected by competing events (e.g. discontinuation due to renal or liver abnormalities) will be accounted for using a competing risks and multi-stage modelling framework, within the flexible parametric framework via a subdistribution (Fine and Gray) approach [38]. Continuous predictors will not be categorised and potential non-linear effects examined using fractional polynomials.

Independent external validation of the model using the same time horizon and study periods will be performed using data from the CPRD Gold except for the methotrexate model which will be validated using CPRD Aurum. CPRD Aurum contains data for practices using EMIS software, unlike CPRD Gold, which contains data from GP surgeries using Vision

software. A bridging file provided by CPRD will be used to exclude practices which contribute data to both CPRD Gold and Aurum from the validation dataset. Although CPRD Gold has become smaller over time especially after 2015, this will not be problematic for model validation because the monitoring recommendations in the UK have not changed after 2007 [1]. Code search strategies will be developed by the study team and applied to generate code lists for both the CPRD Gold and Aurum databases simultaneously in order to accommodate data coding differences between CPRD Gold and Aurum. We will use the same search strategy to build the code list for both databases. Cluster-specific performance will also be examined using internal-external cross-validation [39].

Decision curve analysis: To evaluate the use of the developed models in practice, decision curve analysis is important (in addition to traditional validation measures of calibration and discrimination) to summarise clinical utility (whether one model offers greater net benefit than another when used to inform clinical decision making based on a threshold of predicted risk). The net benefit of our developed models will be plotted against different risk thresholds to produce a decision curve [41,42]. To obtain the curve, the prediction model is evaluated at different probability thresholds, where the threshold is taken as a point above which a patient would be monitored frequently, and below which a patient would not be monitored as frequently. The curve can then be compared against the 'monitor all' and 'monitor none' strategies to see the range of probabilities at which the model may be useful. Decision curves can also be plotted for different models on the same graph for comparison, and to help decide which model offers the most benefit. The model with the highest curve (over a range of clinically relevant thresholds) is considered to have the greatest net benefit.

Incidence of drug discontinuation: Survival analysis will be undertaken to calculate the incidence rate of drug discontinuation (95% confidence intervals (CI)) per 1,000 person-years for entire study period, first 12-months of follow-up, and the subsequent period. Life tables will be constructed to estimate the cumulative incidence at 1-year and 5-year follow-up. Cumulative hazards will be plotted using Nelson-Aalen graphs. Data management and analysis will be performed in Stata MP v16.

Plan for addressing confounding

Bias due to transferring GP surgeries: To minimise bias due to prevalent users appearing as incident users in a new GP surgery, data for participants who receive a prescription of a DMARD within one year of their current registration in a GP surgery will be excluded from the cohort. This will minimise the chance of prevalent long-term users of these medicines entering the cohort as new incident-users.
Plans for addressing missing data
Multiple imputation using chained equations will be used to deal with missing data. We expect BMI, alcohol intake, smoking and ethnicity to have missing values. The number of imputations will depend on the extent of the missing data.

Missing data on blood test results: The CPRD has data about blood test results. However, it is possible that in some instances of drug discontinuation due to abnormal monitoring blood test results, the numerical blood test results are not available in the CPRD. However, just as

for other clinical events, the occurrence of abnormal blood tests is recorded using Read codes such as R144.11 (kidney function test abnormal), KO4..12 to KOE.0 (acute kidney injury) etc.; R148.00 and 44D2.00, 44G2.00 etc. (liver function test abnormal or abnormal liver enzymes); and D400.12 and 42J2.00 etc. (neutropenia) and D400600 and D400211 etc. (drug induced neutropenia); D315.00 D313z00 and 42P2.00 (thrombocytopenia). To reduce the risk of missing data, we will use either numerical blood test results or Read codes to define the outcome of interest. To minimise the risk of bias from missing data, participants with only one full blood count, liver function test and renal function test in the first year of drug prescription in primary care will be excluded from analysis. Similar steps will be taken in CPRD Aurum where applicable. For example, cleansedreadcode which define the occurrence of abnormal blood tests such as 44J3000 (serum creatinine abnormal), KO4..00 (acute renal failure); R148.11 (LFT's abnormal) and 44D2.00 (liver function test abnormal); and 42J2.00 (Neutropenia), 42J4.00 (Neutrophil count abnormal); 42H2.11 (Leucopenia) and 42P2.00 (thrombocytopenia) will be used in instances of missing numerical blood test results in Aurum.

Patient or user group involvement

The PPI panel will review and feedback on the performance of risk scores, with information presented in a way that is accessible to lay members. The risk prediction calculation will be applied to hypothetical case scenarios and the results presented to the PPI members to gauge initial acceptability. They will also comment on the net risk and net benefit from different monitoring strategies compared to no testing or testing all.

Plans for disseminating and communicating study results

The results of this study will be presented at speciality and primary-care scientific meetings. They will be published in open access peer-reviewed journals. We will disseminate the findings to the wider medical community through publication in newsletters such as Pulse, and emails to the entire memberships of the British Societies for Rheumatology, Dermatology, Gastroenterology, Hepatology, Nephrology, Haematology, Pharmacology, Geriatrics, Royal College of Physicians, and the Royal College of General Practitioners. We will also disseminate the results to the National Patient Safety Agency as they are a key stakeholder. We will engage with Rheumatology, Dermatology, General-Practice, and Gastroenterology guideline writing groups to bring about a change in their national guidelines. Several coinvestigators already have strong links with these guideline writing groups. We will engage with MHRA and drug manufacturing authorisation holders to edit relevant monitoring recommendations in the British National Formulary, and, summary of product characteristics respectively. We will lobby NICE to see if an overarching monitoring guideline can be produced. We will also disseminate the findings directly to patient groups. We will work with Versus Arthritis, Arthritis and Musculoskeletal Alliance (ARMA), Crohn's and Colitis UK, British Skin Foundation and Psoriasis Association to disseminate the results to people with these conditions. As above several co-investigators have links with these patient societies. We will also publicise the study results directly to patients, through existing networks such as social media and Twitter accounts to maximise impact. We will be supported by the East Midlands AHSN, Versus Arthritis Pain Centre, and Nottingham NIHR-BRC in this endeavour. Finally, we will engage with traditional media, such as radio, TV, and newspapers to disseminate our study findings. The PPI volunteers will advise on the content of all public facing content for Dissemination.

Conflict of interest statement

None.

Limitations of the study design, data sources, and analytic methods

Limitation of data source:

[1] Lack of information about biologic prescriptions in the CPRD: Biological agents (such as anti-TNF agents) are prescribed exclusively by hospital specialists, and this information is not recorded in the CPRD. Thus, it is possible that some individuals who discontinue non-biologic immune-suppressing treatment with a preceding abnormal blood test result, actually had an adverse drug reaction to the biological agent and the treating physician discontinued both treatments as a precaution. This will result in a higher rate of outcome i.e. drug discontinuation with a preceding blood test abnormality than the true outcome rate. Although not ideal, this is better than a bias in the opposite direction, as the results of our study have important patient safety implications.

[2] Drug discontinuation without any data for monitoring blood test results in the period of interest: It is possible that in some instances of drug discontinuations due to abnormal monitoring blood test results, the data for monitoring results are not available in the CPRD, in either the clinical or the observation files as Read codes and as numeric values respectively. This will reduce the annual rate of outcome of interest.

[3] There is a possibility that people at a very high risk of drug-toxicity, e.g. due to pre-existing chronic liver or renal disease, or cytopenia due to bone marrow or peripheral consumption, may be prescribed immune-suppressing therapies directly by the hospital specialist, and these prescription details will not be available in the CPRD. Thus, our sample may be biased towards participants at a lower risk of side-effects. However, it is very rare to prescribed potentially hepatotoxic, nephrotoxic and myelotoxic drugs to patients with such serious illnesses and, our results will maintain broad generalisability.

[4] It is possible that for some patients on long-term methotrexate, the decision to discontinue therapy is based on non-invasive tests of fibrosis such as transient elastography. This would be a confounder and may increase the discontinuation in a later phase of treatment i.e. after 2 years, but, not due to abnormal liver enzymes. Data on transient elastography are included in hospital clinic letters and not available in the CPRD as a test result value. This would be a limitation to the risk prediction model.

[5] Sample size: Our study has small sample size for less often prescribed drugs and we may not be able to build and validate a prognostic model for mycophenolate.

[6] Data on doses is commonly missing in the CPRD and we will not be able to include dose reduction in the analysis.

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