BMJ Open

Risk of Harm in Synthetic & Biological Intervention Trials in Patients with Inflammatory Arthritis: Protocol for A Meta-Epidemiological Study with Focus on Contextual Factors

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-049850
Article Type:	Protocol
Date Submitted by the Author:	05-Feb-2021
Complete List of Authors:	Malm, Esben; SDU, Research Unit of Rheumatology; The Parker Institute, Musculoskeletal Statistics Unit Berg, Johannes; University of Southern Denmark, Research Unit of Rheumatology; Parker Instituttet Nielsen, Sabrina; The Parker Institute Ioannidis, John; Stanford University, USA Furst, Daniel; UCLA Smolen, Josef S Kristensen, Lars Erik; Bispebjerg and Frederiksberg Hospital, The Parker Institute Tarp, Simon; Musculoskeletal Statistics Unit, The Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark. Ellingsen, Torkell; University of Southern Denmark, Rheumatology Christensen, Robin; Parker Instituttet, Musculoskeletal Statistics Unit; University of Southern Denmark
Keywords:	RHEUMATOLOGY, Rheumatology < INTERNAL MEDICINE, EPIDEMIOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

META-RESEARCH **Protocol**

Risk of Harm in Synthetic & Biological Intervention Trials in Patients with Inflammatory Arthritis: Protocol for A Meta-Epidemiological Study with Focus on Contextual Factors

Esben Malm (medical student); Johannes Berg (medical student); Sabrina M Nielsen, MSc, PhD Student; John PA Ioannidis, MD, DSc; Daniel E Furst, MD; Josef S Smolen, MD; Lars Erik Kristensen, MD, PhD; Simon Tarp, MSc, PhD; Torkell Ellingsen, MD, PhD; Robin Christensen, MSc, PhD

Collaborator/Author information

EM: Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, & Section for Biostatistics and Evidence-Based Research, the Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark. esmal14@student.sdu.dk

JB: Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, Denmark & Section for Biostatistics and Evidence-Based Research, the Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark. jober14@student.sdu.dk

SMN: Section for Biostatistics and Evidence-Based Research, the Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark & Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, Denmark. sabrina.mai.nielsen@regionh.dk

JPAI: Department of Medicine, Department of Epidemiology and Population Health, Department of Biomedical Data Science, Department of Statistics, Stanford University, Stanford, CA, USA. jioannid@stanford.edu

DEF: David Geffen School of Medicine, Division of Rheumatology, UCLA, Los Angeles; University of Washington, Seattle; Washington and University of Florence, Florence, Italy. defurst@mednet.ucla.edu

JS: Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, Vienna, Austria. josef.smolen@meduniwien.ac.at

LEK: Department of Rheumatology & The Parker Institute, Frederiksberg, Denmark. lars.erik.kristensen@regionh.dk

ST: Section for Biostatistics and Evidence-Based Research, the Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark. simon.tarp@regionh.dk

TE: Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, Denmark. torkell.ellingsen@rsyd.dk

RC: Section for Biostatistics and Evidence-Based Research, the Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark & Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, Denmark. robin.christensen@regionh.dk

Corresponding author

Robin Christensen, BSc, MSc, PhD; biostatistician & professor

Head of Musculoskeletal Statistics Unit, The Parker Institute, Bispebjerg and Frederiksberg Hospital & Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, Denmark. Mailing address: The Parker Institute, Bispebjerg and Frederiksberg Hospital, Nordre Fasanvej 57, DK-2000 Copenhagen F, Denmark.

e-mail: Robin.Christensen@regionh.dk

Tel: +45 3816 4165/Fax: +45 3816 4159

ORCID iD: 0000-0002-6600-0631/

web: http://www.parkerinst.dk/staff/robin-christensen

Disclaimers

The views expressed in the submitted protocol are the authors' own and not an official position of the institution or funder.

Source(s) of support

The Parker Institute, Bispebjerg and Frederiksberg Hospital is supported by a core grant from the Oak Foundation (OCAY-18-774-OFIL).

Contributions

Study concept and design: EM, SMN, ST, RC, JPAI, ST, PCT, JSS.
Drafting on the protocol: EM, JB, SMN, TE, RC, JPAI, ST, PCT, JSS.
Critical revision of the protocol for important intellectual content and final approval before submission: All authors.
Obtained funding: TE & RC.

Competing interests

This study had no financial competing interests.

Funding

The Parker Institute is grateful for the financial support received from public and private foundations, companies, and private individuals over the years. The Parker Institute, Bispebjerg and Frederiksberg Hospital, is supported by a core grant from the Oak Foundation (OCAY-18-774-OFIL); The Oak Foundation is a group of philanthropic organisations that, since its establishment in 1983, has given grants to not-for-profit organisations around the world.

Amendments

Important deviations from the protocol will be reported in the peer-reviewed publication.

ABSTRACT

Introduction: Inflammatory Arthritis (IA) conditions, including rheumatoid arthritis (RA), psoriatic arthritis (PsA), and axial spondyloarthritis (AxSpA), are characterised by inflammatory infiltration of the joints. Biologic and targeted synthetic disease-modifying antirheumatic drugs (bDMARDs and tsDMARDs, respectively) reduce the effects of proinflammatory cytokines and immune cells to ameliorate disease. However, immunosuppression can be associated with high rates of serious adverse events (SAEs), including serious infections, and maybe an increased risk of malignancies and cardiovascular events. Currently, there is no empirical evidence on the extent to which contextual factors and risk of bias (RoB) domains may modify these harm signals in randomised trials.

Method and analysis: We will search MEDLINE (via PubMed) for systematic reviews published since April 2015 and all Cochrane reviews. From these reviews, randomised trials will be eligible if they include patients with an IA condition (RA, PsA, or AxSpA) with at least one group randomly allocated to bDMARD and/or tsDMARD treatments. A predefined form will be used for extracting data on population characteristics (e.g., baseline characteristics or eligibility criteria, such as medication background), and specific harm outcome measures, such as number of withdrawals, numbers of patients discontinuing due to adverse events, and number of patients having SAEs. RoB in individual trials will be assessed using a modified Cochrane RoB tool. We will estimate the potentially causal harm effects related to the experimental intervention compared to control comparator as risk ratios, and heterogeneity across randomised comparisons will be assessed statistically and evaluated as inconsistency using the I^2 Index. Our meta-regression analyses will designate population and trial characteristics, and each RoB domain as independent variables, whereas the three harm domains will serve as dependent variables.

Ethics and dissemination: Ethics approval is not required for this study. Results will be disseminated through publication in international peer-reviewed journals.

Registration: PROSPERO (CRD: 42020171124).

Strengths and limitations of this study

- This will be an extensive and comprehensive risk of harm analysis of bDMARDs and tsDMARDs across multiple IA diagnoses unlike previous assessments that have been more circumscribed.
- A large array of contextual factors and risk of bias items will be assessed.
- Despite the comprehensive nature of the assessment, some analyses may be underpowered, especially for uncommon harms, and some meta-regression assessments may be affected by ecological bias.

INTRODUCTION

Background

Inflammatory Arthritis (IA) is a heterogeneous group of autoimmune diseases that includes rheumatoid arthritis (RA), psoriatic arthritis (PsA), axial spondyloarthritis (axSpA, including ankylosing spondylitis AS) (1, 2). These diseases are characterised by inflammatory infiltration of the joints (3), resulting in pain, swelling, stiffness and restricted movement (4). Ultimately, they can have a detrimental impact on quality of life, cause progressive disability and premature death (5, 6). Not only are the implications severe, also the diseases are a global concern; RA alone affects about 1% of the world's population (7).

Aside from conventional synthetic (cs) DMARDs including methotrexate, targeted therapies, consisting of biological disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) are considered effective for treating IA *per se* (8-10). Notably, bDMARDs work by targeting specific molecules or receptors (11), such as tumour necrosis factor alpha (TNFα), which is a potent inflammatory cytokine produced by T-cells and macrophages (12, 13). In contrast, tsDMARDs target intracellular pathways and reduce the effect of cytokines known to drive the proinflammatory machinery of cellular immune response (14-16). As such, b- and tsDMARDs are Immunomodulatory; although effective in alleviating symptoms of IA, they also carry risk of harm (defined as: "*the totality of possible adverse consequences of an intervention or therapy*" (17)). Indeed, meta-analyses and an observational cohort study have shown that bDMARDs are associated with higher rates of serious infections (18-20) and potentially dose-dependent increased risk of malignancies (21). Some meta-studies and systematic literature reviews suggest that tsDMARD rates of serious infections and malignancies are no different from those of bDMARDs (16, 22, 23). Recent reviews report a possibly increased risk of venous thromboembolism with tsDMARDs (23, 24).

Randomised controlled trials (RCTs) inevitably vary with respect to eligibility criteria, patient characteristics, and internal validity, which may distort their results (i.e., the harm signal) and thus potentially bias their interpretation (25, 26). If evidence were available on which trial characteristics to adjust for when interpreting harm from meta-research, these covariates would be considered important contextual factors. Currently, a contextual factor is broadly defined as a "…*variable that is not an outcome of the study but needs to be recognized (and measured) to understand the study results. This*

includes potential confounders and effect modifiers" (27). However, we currently have no empirical evidence concerning the extent to which contextual factors, such as population and trial characteristics and risk of bias (RoB) domains, modify the harm signals from trials testing targeted therapies (i.e., bDMARDs and tsDMARDs) across IA diseases.

Rationale

Designing, conducting, and reporting RCTs should incorporate methods—such as concealing randomised allocation, blinding participants and personnel, and appropriately engaging the intention-to-treat population—that avoid biases resulting from incompatibilities between the intervention and control groups. Empirical evidence suggests that the absence of rigorous methodology can lead to biased intervention effect estimates (i.e., net benefits) (28). Contextual factors, such as population and trial characteristics, also have been shown to be possible effect modifiers when assessing benefits (8, 29).

The effect on harms of RoB, trial characteristics and contextual factors (e.g., population characteristics) has yet to be investigated, and using meta-epidemiology is the method of choice for doing so (30). Previous meta-epidemiological research within rheumatology has primarily investigated the effect of methodological quality (internal validity) on treatment effects (benefit) (8, 29, 31, 32). To our knowledge, no one has yet investigated the importance in IA therapies of contextual factors (i.e., population and trial characteristics) and RoB when the outcome is harmful effects.

Aims and objectives

This exploratory meta-epidemiological study aims to improve harm reporting by investigating the influence of RoB domains, trial characteristics, and contextual factors on three generic harm measures (17), as well as mortality among patients with IA who were treated with bDMARDs and/or tsDMARDs. Our objective is to explore whether specific participant and trial characteristics (i.e., contextual factors incl. RoB domains) have a quantitative influence in terms of effect modification and/or distortion due to biases on the observed likelihood of harm from an experimental intervention compared to control comparators in randomised trials. If contextual factors have such an influence, we hope to shed light on their importance to future trial reporting and interpretation of harm when reporting randomised trials (17).

Protocol and registration

This protocol was developed in accordance with the v1.07 2018 Methodological Expectations for Cochrane Intervention Reviews (MECIR) recommendations of the Cochrane Collaboration (33) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Protocols (PRISMA-P) guidelines (34). The study protocol was pre-specified and registered in PROSPERO on 2020-03-27, CRD number: CRD42020171124.

METHODS AND ANALYSIS

This (meta-epidemiological) study combines data from a large representative sample of available trials into a single database by assembling trials already included in published systematic reviews. Generic outcome measures that cover important harm domains (*i:* withdrawals, *ii:* withdrawals due to adverse events [WD d/t AEs], and *iii:* serious adverse events [SAEs] (17)) and mortality will constitute the dependent variable(s) in the database. Harm effects in relation to the use of targeted therapies will be analysed to determine whether they are affected by contextual factors among population and trial characteristics.

Eligibility criteria

We will search MEDLINE (via PubMed) for trials included in published systematic reviews (published since April 2015) or Cochrane reviews. From these systematic reviews, randomised trials will be eligible if they fulfil our inclusion criteria (see table 1 for PICO framework), with at least one group randomly allocated to bDMARD and/or tsDMARD.

The interventions of interest are targeted therapies (i.e., bDMARDs and tsDMARDs) approved by either EMA or FDA to date, treating IA conditions in adult populations. These therapies will include bDMARDs: abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, guselkumab, infliximab, ixekizumab, rituximab, sarilumab, secukinumab, tocilizumab, ustekinumab, and tsDMARDs: apremilast, baricitinib, filgotinib, tofacitinib and upadacitinib.

Only RCTs included in an existing systematic review of patients with inflammatory arthritis (RA, PsA, and AxSpA [incl. AS]) will be considered for eligibility. We will exclude reviews (i.e., not look for trials) that have been withdrawn. Furthermore, only RCTs from the eligible systematic reviews where the full text is available in

English will be included. There will be no restriction on publication year of the individual RCTs.

*Table 1. Research objective described using PICO**

Participants	**Adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), axial spondyloarthritis (axSpA) or ankylosing spondylitis (AS).**
Intervention	Targeted therapies (i.e., bDMARDs and tsDMARDs)
Comparison	Placebo, standard care or waiting list/no intervention, active comparator and unclear.
Outcome(s)	Number of withdrawals (WDs), number of WDs due to adverse events (WD d/t AEs), number of serious adverse events (SAEs) and number of patients who died.

*PICO - participants, intervention, comparison, and outcome.

Information sources and search strategy

We will search MEDLINE (via PubMed) for eligible meta-analyses or systematic reviews of trials published since April 2015 and eligible Cochrane reviews using the search algorithm shown in table 2:

Table 2. Search strategy

(arthritis[tiab] OR spondyloarthritis[tiab] OR ankylosing[tiab] OR psoriatic[tiab] OR Spondylarthropathies[tiab] OR rheumatoid[tiab] OR Psoriasis[tiab])

AND

("disease-modifying antirheumatic drugs"[tiab] OR "biological agent*"[tiab] OR biologics*[tiab] OR DMARD[tiab] OR abatacept[tiab] OR adalimumab[tiab] OR anakinra[tiab] OR apremilast[tiab] OR baricitinib[tiab] OR certolizumab[tiab] OR etanercept[tiab] OR filgotinib[tiab] OR golimumab[tiab] OR guselkumab[tiab] OR infliximab[tiab] OR ixekizumab[tiab] OR rituximab[tiab] OR sarilumab[tiab] OR secukinumab[tiab] OR tocilizumab[tiab] OR tofacitinib[tiab] OR upadacitinib[tiab] OR ustekinumab[tiab])

AND

((“Systematic Review”[pt] OR Meta-Analysis[pt] OR meta-analysis[tiab] OR “systematic review”[tiab] OR meta-analys*[pt] OR meta-analys*[ti] OR metaanalys*[ti] OR meta-regress*[tiab] OR metaregress*[tiab]

AND ("2015/04/01"[Date - Publication]: "3000"[Date - Publication]))

OR “Cochrane Database Syst Rev” [jour])

Study selection

Two independent reviewers (JB and EM, with support from SMN/RC) will screen the systematic reviews based on title and abstract, in accordance with eligibility criteria. The same two reviewers will assess the full systematic review texts for eligibility of the reviews and subsequently select the RCTs from the reviews that are eligible, according to our objectives. We will obtain the full text if at least one of the reviewers considers an RCT to be potentially eligible during the screening process. Disagreements will be resolved by consensus or by consulting a third reviewer (RC). EndNote X9.2 software will be used to manage the reviews and RCT records retrieved from the search.

Data collection process

Two reviewers (JB and EM) will extract data using a predefined, standardised data extraction form, and in case of uncertainty a third reviewer (SMN/RC) will be consulted. If a trial is included in more than one review, the trial will be registered and counted/included once.

Review Level: From the reviews, we will extract data on review registration number, year of publication, first author’s name, number of RCTs eligible for our study, and the condition and intervention studied, according to the review title.

Randomised Trial Level: From the trials, we will extract data on first author’s name, publication ID, trial duration, duration until switch (e.g., relevant for adaptive trial designs), rescue, early escape or cross over, number of participants in each arm, and treatment given in the active and comparator arms (i.e., following the PICO framework). Treatment in the comparator arm will be grouped into the following predefined categories: (*i*) placebo; (*ii*) standard care or waiting list/no intervention; (*iii*) active comparator, or as an ultimate last option; (*iv*) unclear. Outcome measures and data extraction of trial and participant characteristics are specified below and listed in table 3.

Participant characteristics in individual studies

Data on the following trial eligibility criteria will be extracted:

- Binary indicator (0 or 1) of inflammation scored as 1 with ≥1 of the following criteria: erythrocyte sedimentation rate (ESR) ≥28 mm/hour, CRP level ≥0.3 mg/dL, and/or morning stiffness lasting ≥45 minutes
- minimum AND maximum required number of swollen joint counts (SJC)
- minimum AND maximum required number of tender joint counts (TJC)
- minimum AND maximum allowed disease duration
- rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide antibody (anti-CCP) and/or anti-cyclic citrullinated peptide antibody 2 (CCP2) status

In order to stratify trials according to the DMARD history of their included patients, we will ask the following signalling question: Had the participants, prior to inclusion, potentially exhausted the treatment potential of at least one class of DMARD—either conventional synthetic DMARDs (i.e., [csDMARD], bDMARD, or tsDMARD)?

- csDMARD-naïve (patients were either csDMARD naïve or had not exhausted the treatment potential of at least one csDMARD)
- csDMARD-IR (csDMARD inadequate responders), where patients had exhausted at least one csDMARD option previously
- bDMARD or tsDMARD-IR (bDMARD or tsDMARD inadequate responders), patients had inadequate response to at least one previous bDMARD or tsDMARD. Inclusion in this group entails exclusion from other DMARD history groups.

Patients' concomitant medication (background) of DMARDs during the trial period will be ordered in the following three levels:

- methotrexate (MTX)
- csDMARDs other than MTX
- bDMARDs or tsDMARDs

We will extract information about how the three groups were handled at randomisation, potentially enabling us to cluster the trials into one of the following five levels: (*i*) Naïve (i.e., patients had never used the drug[s] of interest); (*ii*) Not using (i.e., the study included only patients who were currently not using the drug[s] of interest); (*iii*) Discontinued (i.e., patients were not allowed to continue drug[s] of interest; (iv) Continued (i.e., patients were allowed to continue drug[s] of interest); and (*v*) Not reported (unclear: no information was reported on this matter). In the case of axSpa, NSAID will be extracted equivalent to csDMARDs.

Data on the following aggregate (average/median) patient baseline characteristics will be extracted: age, female (proportion), disease duration (years), ESR (mm/hour), CRP (mg/dL), Disease activity score, RF positive (proportion), anti-CCP positive (proportion), anti-CCP2 positive (proportion), SJC, TJC, health assessment questionnaire—disability index (HAQ-DI), physician global assessment (e.g., Visual Analogue Scale [VAS]), patient global assessment (e.g., VAS), and patient-reported pain on visual analogue scales of 0–100 mm (e.g., VAS).

Risk of bias and trial characteristics in individual studies

Many published reviews include some form of RoB assessment (i.e., at least for the most frequently used RoB domains) for each individual trial; these assessments will be mapped to the best of our ability to correspond to the Cochrane RoB v.1 (35). The RoB will also be assessed by one of the two reviewers (JB and EM) and subsequently compared with the original bias and internal validity assessments' in the review, from which it was sampled.

Within each full-text trial report, we will apply the following domains of the original Cochrane RoB tool (i.e., RoB v.1.0) (35), which comprise methods for:

- sequence generation/maintaining allocation concealment (selection bias)
- blinding both patients and personnel (performance bias)
- management/analysis/reporting of incomplete outcome data (attrition bias)

Each of these three domains will be rated as high risk, low risk, or unclear RoB (35). In case of uncertainty, another reviewer (SMN/RC) will be consulted. Any discrepancy between RoB assessment sources will be resolved by discussion among the authors.

The following additional bias sources will also be assessed, and data will be extracted from them:

- single *vs*. multi-site trials (36)
- small *vs*. large trials (where small will pragmatically be defined as <100 patients per arm) (37, 38)
- source of funding grouped into one of the following five categories: (*i*) 100% industry (pharmaceutical/device company) funded; (*ii*) mixed funding (e.g., non-industry and

industry; (*iii*) provision of drug only; (*iv*) 100% non-profit funded; and (*v*) unclear/undisclosed funding (39)

Outcome measures

Data extraction for each RCT will include the number of patients who died, and the numbers of patients with any of the following "generic events": (*i*) all withdrawals (WDs); (*ii*) WDs due to AEs; and (*iii*) SAEs (17). If the number of individual patients with SAEs is not reported, we will extract the number of reported SAEs instead.

Where reasons are provided to explain the SAEs, they will be categorised according to MedDRA v.23.0 [(*i*) Infections and infestations; (*ii*) Neoplasms benign, malignant and unspecified (incl. cysts and polyps); (*iii*) Cardiac and vascular disorders; or (*iv*) others]. If patients in the comparison group later are offered the intervention (i.e., switching to the intervention group), the number of events before the switch will be used as the endpoint of choice (i.e., before introducing adaptive trial designs).

Summary measures

For each binary outcome, we will extract data corresponding to the 2×2 table, summarising the number of patients who experienced the outcome in each comparison group as reported in the randomised trial and the total number of patients randomly assigned in each group. For outcomes collected and reported corresponding to different time points, we will select the time point with the longest follow-up while still respecting the primary research design (e.g., before introducing an adaptive trial design, and/or open label extension) (40, 41).

Because all the outcome measures are dichotomous, the relative Risk Ratios (RRs) with 95% confidence intervals (95%CI) will be the preferred measure of relative effect, and these can subsequently be applied to the baseline or control group risks to generate absolute risks (42). When appropriate for the very rare adverse events, we will use a continuity correction (adding to all cells a factor proportional to the reciprocal of the size of the contrasting study group), as suggested by Sweeting and colleagues (43), to take into account zero cell counts in one group only. This continuity correction will be applied when no events are observed in one study arm of a trial. The correction is inversely proportional to the relative size of the opposite of the study (21, 43). Continuity correction for the experimental intervention arm is $1/(R+1)$; R is the ratio of control group to

intervention group sizes (i.e., $R = n_C/n_I$). Similarly, the continuity correction for the control comparator arm is $R/(R+1)$. We expect that most trials will report only a few SAEs and deaths, so the odds ratios and 95%CI's will also (for the purpose of sensitivity analysis) be calculated with the use of the *Peto* method. Because the expected events are sparse and all trials will have similar durations of follow-up for their treatment groups, the use of both risk ratios and odds ratios should represent a valid approach to assessing the risk associated with the use of synthetic or biological intervention in patients with IA. We expect the search to bring around 175 eligible trials (RA: 117, PsA: 15, AxSpA: 43) (44-48). A random sample of 10 eligible studies (49-58) showed typical reported event rates in the placebo and intervention groups for all WD of 14,9% and 12,5%, for WDs due to AEs/TEAEs or SAE of 2,8% and 4,8% and for SAE of 5% and 6,5%, respectively. Simple power estimation showed that a sample group of 7,560 patients was required for a study power of 80%.

Synthesis of results

Outcome events will be coded so that an RR direction of more than 1 indicates a potentially harmful effect of the experimental intervention (i.e., $RR = [r_I/n_I]/ [r_C/n_C]$). Mixed effects Restricted Maximum Likelihood (REML) meta-analyses (59) will be used to combine the harm effects across RCTs (based on their log [*RR*]) (60); we will apply the trial ID as a random effect, while applying the review ID (from which the trial was sampled) as a fixed effect in order to model the hierarchical structure of the data sampling (61).

Heterogeneity across randomised comparisons will be assessed by using the Cochrane Q test (62), interpreted based on the I^2 inconsistency index (63), and quantified by the estimate for between-trial variance (τ^2), estimated as T^2 (64). The effect of population and trial characteristics (listed below) on the between-trial variance will be calculated by univariably adding a factor for the specific characteristic in the model. If introducing a specific covariate into the meta-model reduces the observed between-trial variance (T^2), this result will be considered an indication of a potentially important effect modifier (65).

Table 3. Population and trial characteristics

Trial eligibility criteria:

Minimum and maximum required number of swollen joint counts

Minimum and maximum required number of tender joint counts

Minimum and maximum required C-reactive protein

Minimum and maximum required Erythrocyte sedimentation rate

Minimum and maximum allowed disease duration

Rheumatoid factor

Anti-cyclic citrullinated peptide antibody status

Anti-cyclic citrullinated peptide antibody 2 status

DMARD history:

csDMARD-naïve

csDMARD-IR (csDMARD inadequate responders)

bDMARD or tsDMARD-IR (bDMARD or tsDMARD inadequate responders)

Medication background of DMARDs:

Methotrexate

-Naïve

-Not using

-Discontinued

-Continued

-Not reported

csDMARDs other than methotrexate

-Naïve

-Not using

-Discontinued

-Continued

-Not reported

bDMARDs or tsDMARDs.

-Naïve

-Not using

-Discontinued

-Continued

-Not reported

Aggregate (e.g., average/median) patient baseline characteristics:

Age

Female (%)

Disease duration

Erythrocyte sedimentation rate

C-reactive protein
Disease activity score
RF positive (%)
Anti-CCP positive (%)
CCP2 positive (%)
Swollen joint counts
Tender joint counts
Health assessment questionnaire—disability index
Physician global assessment of disease activity
Patient global assessment of disease activity
Patient-reported pain on visual analogue scales of 0–100 mm

Risk of bias across studies

Stratified meta-analyses will be used for tests of interaction between harms and the trial RoB (listed in Table 4) and trial characteristics collected as described above.

Table 4. Risk of bias

Cochrane risk of bias domains:
· Risk of selection bias
· Risk of performance bias
· Risk of attrition bias
· Overall risk of bias*
Additional bias sources:
· Single vs. multi-site trials
· Small vs. large trials
· Source of funding

*For each trial, the overall RoB will be classified as low (i.e., low RoB for all three domains); high (i.e., high RoB for one or more domains); or unclear (i.e., unclear RoB for one or more domains in the absence of high RoB).

Perspectives

The Outcome Measures in Rheumatology (OMERACT) initiative established the Contextual Factors Working Group to guide the understanding, identification and handling of contextual factors for clinical trials, with most of the current emphasis' being on net benefit inferred from a

rheumatology trial (66). This meta-epidemiological study will work from the original definition of what constitutes a contextual factor, as defined in the introduction. We will explore and hope to reveal the possible impact of contextual factors (i.e., population and trial characteristics) and RoB domains of three different (but related) harm measures, as well as deaths (67). Knowing which factors are associated with a causal model for harms—either as effect modifiers or distortions of the outcome due to bias—is important for improving investigation and reporting of harms in future trials (68). Also, research in this area might identify subgroups among rheumatic disease patients that are at higher risk of experiencing harms. Such information would provide important evidence for future treatment guideline development. Ultimately the doctor will be able to differentiate the risk of intervention based on the patient's characteristics. This has the potential to enhance informed decision-making and effect therapeutic interventions applied in practice, leading to safer treatment of individual patients and increase efficiency in the health care system.

Patient and public involvement

Patients and/or the public were not involved in designing study concept or drafting of the protocol.

ETHICS AND DISSEMINATION

Because our study does not collect primary data, no formal ethical assessment and informed consent are required. First, second and third author (EM, JB and SMN) will draft the paper describing this meta-epidemiological study; the study will be disseminated in a peer-reviewed publication.

References

1. Ledingham J, Snowden N, Ide Z. Diagnosis and early management of inflammatory arthritis. BMJ. 2017;358:j3248.

2. Raychaudhuri SP, Deodhar A. The classification and diagnostic criteria of ankylosing spondylitis. J Autoimmun. 2014;48-49:128-33.

3. Miyabe Y, Miyabe C, Luster AD. LTB4 and BLT1 in inflammatory arthritis. Semin Immunol. 2017;33:52-7.

4. McInnes IB, Schett G. The Pathogenesis of Rheumatoid Arthritis. New England Journal of Medicine. 2011;365(23):2205-19.

5. Janke K, Biester K, Krause D, Richter B, Schürmann C, Hirsch K, et al. Comparative effectiveness of biological medicines in rheumatoid arthritis: systematic review and network meta-analysis including aggregate results from reanalysed individual patient data. Bmj. 2020;370:m2288.

6. Schweikert B, Malmberg C, Núñez M, Dilla T, Sapin C, Hartz S. Cost-effectiveness analysis of ixekizumab versus secukinumab in patients with psoriatic arthritis and concomitant moderate-to-severe psoriasis in Spain. BMJ Open. 2020;10(8):e032552.

7. Hartman L, Rasch LA, Klausch T, Bijlsma HWJ, Christensen R, Smulders YM, et al. Harm, benefit and costs associated with low-dose glucocorticoids added to the treatment strategies for rheumatoid arthritis in elderly patients (GLORIA trial): study protocol for a randomised controlled trial. Trials. 2018;19(1):67.

8. Christensen AW, Tarp S, Furst DE, Dossing A, Amris K, Bliddal H, et al. Most Trial Eligibility Criteria and Patient Baseline Characteristics Do Not Modify Treatment Effect in Trials Using Targeted Therapies for Rheumatoid Arthritis: A Meta-Epidemiological Study. PLoS One. 2015;10(9):e0136982.

9. Callhoff J, Sieper J, Weiss A, Zink A, Listing J. Efficacy of TNFalpha blockers in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis: a meta-analysis. Ann Rheum Dis. 2015;74(6):1241-8.

10. Goulabchand R, Mouterde G, Barnetche T, Lukas C, Morel J, Combe B. Effect of tumour necrosis factor blockers on radiographic progression of psoriatic arthritis: a systematic review and meta-analysis of randomised controlled trials. Ann Rheum Dis. 2014;73(2):414-9.

11. Oo C, Kalbag SS. Leveraging the attributes of biologics and small molecules, and releasing the bottlenecks: a new wave of revolution in drug development. Expert review of clinical pharmacology. 2016;9(6):747-9.

12. Komaki Y, Yamada A, Komaki F, Kudaravalli P, Micic D, Ido A, et al. Efficacy, safety and pharmacokinetics of biosimilars of anti-tumor necrosis factor-alpha agents in rheumatic diseases; A systematic review and meta-analysis. J Autoimmun. 2017;79:4-16.

13. So A, Inman RD. An overview of biologic disease-modifying antirheumatic drugs in axial spondyloarthritis and psoriatic arthritis. Best Pract Res Clin Rheumatol. 2018;32(3):453-71.

14. Gadina M, Le MT, Schwartz DM, Silvennoinen O, Nakayamada S, Yamaoka K, et al. Janus kinases to jakinibs: from basic insights to clinical practice. Rheumatology (Oxford, England). 2019;58(Supplement_1):i4-i16.

15. Sarzi-Puttini P, Ceribelli A, Marotto D, Batticciotto A, Atzeni F. Systemic rheumatic diseases: From biological agents to small molecules. Autoimmun Rev. 2019;18(6):583-92.

16. Winthrop KL. The emerging safety profile of JAK inhibitors in rheumatic disease. Nat Rev Rheumatol. 2017;13(4):234-43.

17. Ioannidis JP, Evans SJ, Gøtzsche PC, O'neill RT, Altman DG, Schulz K, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. Annals of internal medicine. 2004;141(10):781-8.

18. Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, Macdonald JK, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database Syst Rev. 2011(2):Cd008794.

19. Minozzi S, Bonovas S, Lytras T, Pecoraro V, Gonzalez-Lorenzo M, Bastiampillai AJ, et al. Risk of infections using anti-TNF agents in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: a systematic review and meta-analysis. Expert Opin Drug Saf. 2016;15(sup1):11-34.

20. Gron KL, Arkema EV, Glintborg B, Mehnert F, Ostergaard M, Dreyer L, et al. Risk of serious infections in patients with rheumatoid arthritis treated in routine care with abatacept, rituximab and tocilizumab in Denmark and Sweden. Ann Rheum Dis. 2019;78(3):320-7.

21. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006;295(19):2275-85.

22. Salgado E, Maneiro JR, Carmona L, Gomez-Reino JJ. Safety profile of protein kinase inhibitors in rheumatoid arthritis: systematic review and meta-analysis. Ann Rheum Dis. 2014;73(5):871-82.

23. Sepriano A, Kerschbaumer A, Smolen JS, van der Heijde D, Dougados M, van Vollenhoven R, et al. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2019 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2020.

24. Mease P, Charles-Schoeman C, Cohen S, Fallon L, Woolcott J, Yun H, et al. Incidence of venous and arterial thromboembolic events reported in the tofacitinib rheumatoid arthritis, psoriasis and psoriatic arthritis development programmes and from real-world data. Ann Rheum Dis. 2020;79(11):1400-13.

25. Rahman MU, Buchanan J, Doyle MK, Hsia EC, Gathany T, Parasuraman S, et al. Changes in patient characteristics in anti-tumour necrosis factor clinical trials for rheumatoid arthritis: results of an analysis of the literature over the past 16 years. Ann Rheum Dis. 2011;70(9):1631-40.

26. Gluud LL. Bias in clinical intervention research. American journal of epidemiology. 2006;163(6):493-501.

27. Boers M, Kirwan JR, Wells G, Beaton D, Gossec L, d'Agostino MA, et al. Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. J Clin Epidemiol. 2014;67(7):745-53.

28. Savović J, Jones HE, Altman DG, Harris RJ, Jüni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. Annals of internal medicine. 2012;157(6):429-38.

29. Ballegaard C, Jorgensen TS, Skougaard M, Strand V, Mease PJ, Kristensen LE, et al. Trial Characteristics as Contextual Factors When Evaluating Targeted Therapies in Patients With Psoriatic Disease: A Meta-Epidemiologic Study. Arthritis Care Res (Hoboken). 2018;70(8):1206-17.

30. Bae JM. Meta-epidemiology. Epidemiology and health. 2014;36:e2014019.

31. Bolvig J, Juhl CB, Boutron I, Tugwell P, Ghogomu EAT, Pardo JP, et al. Some Cochrane risk-of-bias items are not important in osteoarthritis trials: a meta-epidemiological study based on Cochrane reviews. J Clin Epidemiol. 2018;95:128-36.

32. Dossing A, Tarp S, Furst DE, Gluud C, Wells GA, Beyene J, et al. Modified intention-to-treat analysis did not bias trial results. J Clin Epidemiol. 2016;72:66-74.

33. Higgins JPT LT, Chandler J, Tovey D, Churchill R. Methodological Expectations of Cochrane Intervention Reviews. Cochrane: London, Version 1.06. 2018.

34. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;350:g7647.

35. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.

36. Dechartres A, Boutron I, Trinquart L, Charles P, Ravaud P. Single-center trials show larger treatment effects than multicenter trials: evidence from a meta-epidemiologic study. Ann Intern Med. 2011;155(1):39-51.

37. Nüesch E, Trelle S, Reichenbach S, Rutjes AW, Tschannen B, Altman DG, et al. Small study effects in meta-analyses of osteoarthritis trials: meta-epidemiological study. Bmj. 2010;341:c3515.

38. Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. Ann Intern Med. 2001;135(11):982-9.

39. Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. Cochrane Database Syst Rev. 2017;2:Mr000033.

40. Pickles T, Alten R, Boers M, Bykerk V, Christensen J, Christensen R, et al. Adaptive Trial Designs in Rheumatology: Report from the OMERACT Special Interest Group. J Rheumatol. 2019;46(10):1406-8.

41. Buch MH, Silva-Fernandez L, Carmona L, Aletaha D, Christensen R, Combe B, et al. Development of EULAR recommendations for the reporting of clinical trial extension studies in rheumatology. Ann Rheum Dis. 2015;74(6):963-9.

42. Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, et al. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. J Clin Epidemiol. 2013;66(2):158-72.

43. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med. 2004;23(9):1351-75.

44. JA. S, A. H, E. TG, AS. M, LJ. M, R. B, et al. Biologics or tofacitinib for people with rheumatoid arthritis unsuccessfully treated with biologics: a systematic review and network meta-analysis. The Cochrane database of systematic reviews. 2017;3:CD012591.

45. JA. S, A. H, AS. M, E. TG, ME. S-A, R. B, et al. Biologics or tofacitinib for people with rheumatoid arthritis naive to methotrexate: a systematic review and network meta-analysis. The Cochrane database of systematic reviews. 2017;5:CD012657.

46. JA. S, A. H, E. TG, AS. M, P. T, GA. W. Biologic or tofacitinib monotherapy for rheumatoid arthritis in people with traditional disease-modifying anti-rheumatic drug (DMARD) failure: a Cochrane Systematic Review and network meta-analysis (NMA). The Cochrane database of systematic reviews. 2016;11:CD012437.

47. Fidahic M, Jelicic Kadic A, Radic M, Puljak L. Celecoxib for rheumatoid arthritis. Cochrane Database Syst Rev. 2017;6:Cd012095.

48. Lawson DO, Eraso M, Mbuagbaw L, Joanes M, Aves T, Leenus A, et al. Tumour necrosis factor inhibitor dose reduction for axial spondyloarthritis: A systematic review and meta-analysis of randomized controlled trials. Arthritis Care Res (Hoboken). 2020.

49. Choy E, McKenna F, Vencovsky J, Valente R, Goel N, Vanlunen B, et al. Certolizumab pegol plus MTX administered every 4 weeks is effective in patients with RA who are partial responders to MTX. Rheumatology (Oxford, England). 2012;51(7):1226-34.

50. Atsumi T, Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, et al. The first double-blind, randomised, parallel-group certolizumab pegol study in methotrexate-naive early rheumatoid arthritis patients with poor prognostic factors, C-OPERA, shows inhibition of radiographic progression. Ann Rheum Dis. 2016;75(1):75-83.

51. Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, Eguchi K, et al. Efficacy and safety of certolizumab pegol plus methotrexate in Japanese rheumatoid arthritis patients with an inadequate response to methotrexate: the J-RAPID randomized, placebo-controlled trial. Mod Rheumatol. 2014;24(5):715-24.

52. Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, Eguchi K, et al. Efficacy and safety of certolizumab pegol without methotrexate co-administration in Japanese patients with active rheumatoid arthritis: the HIKARI randomized, placebo-controlled trial. Mod Rheumatol. 2014;24(4):552-60.

53. Emery P, Burmester GR, Bykerk VP, Combe BG, Furst DE, Barre E, et al. Evaluating drug-free remission with abatacept in early rheumatoid arthritis: results from the phase 3b, multicentre, randomised, active-controlled AVERT study of 24 months, with a 12-month, double-blind treatment period. Ann Rheum Dis. 2015;74(1):19-26.

54. Li Z, Zhang F, Kay J, Fei K, Han C, Zhuang Y, et al. Efficacy and safety results from a Phase 3, randomized, placebo-controlled trial of subcutaneous golimumab in Chinese patients with active rheumatoid arthritis despite methotrexate therapy. Int J Rheum Dis. 2016;19(11):1143-56.

55. van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, Garcia Meijide JA, Wagner S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med. 2012;367(6):508-19.

56. Westhovens R, Yocum D, Han J, Berman A, Strusberg I, Geusens P, et al. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. Arthritis and rheumatism. 2006;54(4):1075-86.

57. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis and rheumatism. 2006;54(1):26-37.

58. Kavanaugh A, Fleischmann RM, Emery P, Kupper H, Redden L, Guerette B, et al. Clinical, functional and radiographic consequences of achieving stable low disease activity and remission with adalimumab plus methotrexate or methotrexate alone in early rheumatoid arthritis: 26-week results from the randomised, controlled OPTIMA study. Ann Rheum Dis. 2013;72(1):64-71.

59. Normand S-LT. Meta-analysis: formulating, evaluating, combining, and reporting. Statistics in Medicine. 1999;18(3):321-59.

60. van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. Stat Med. 2002;21(4):589-624.

61. Sterne JA, Jüni P, Schulz KF, Altman DG, Bartlett C, Egger M. Statistical methods for assessing the influence of study characteristics on treatment effects in 'meta-epidemiological' research. Stat Med. 2002;21(11):1513-24.

62. Cochran WG. The combination of estimates from different experiments. Biometrics. 1954;10(1):101-29.

63. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Bmj. 2003;327(7414):557-60.

64. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? Stat Med. 2002;21(11):1559-73.

65. Sterne JA, Juni P, Schulz KF, Altman DG, Bartlett C, Egger M. Statistical methods for assessing the influence of study characteristics on treatment effects in 'meta-epidemiological' research. Stat Med. 2002;21(11):1513-24.

66. Nielsen SM, Uggen Rasmussen M, Boers M, D AvdW, de Wit M, T GW, et al. Towards consensus in defining and handling contextual factors within rheumatology trials: an initial qualitative study from an OMERACT working group. Ann Rheum Dis. 2020.

67. Nielsen SM, Storgaard H, Ellingsen T, Shea BJ, Wells GA, Welch VA, et al. Population characteristics as important contextual factors in rheumatological trials: an exploratory meta-epidemiological study from an OMERACT Working Group. Ann Rheum Dis. 2020;79(10):1269-76.

68. Finger ME, Boonen A, Woodworth TG, Escorpizo R, Christensen R, Nielsen SM, et al. An OMERACT Initiative Toward Consensus to Identify and Characterize Candidate Contextual Factors: Report from the Contextual Factors Working Group. J Rheumatol. 2017;44(11):1734-9.

BMJ Open

Risk of Harm in Synthetic and Biological Intervention Trials in Patients with Inflammatory Arthritis: Protocol for A Meta-Epidemiological Study Focusing on Contextual Factors

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-049850.R1
Article Type:	Protocol
Date Submitted by the Author:	26-May-2021
Complete List of Authors:	Malm, Esben; SDU, Research Unit of Rheumatology; The Parker Institute, Musculoskeletal Statistics Unit Berg, Johannes; University of Southern Denmark, Research Unit of Rheumatology; Parker Instituttet Nielsen, Sabrina; The Parker Institute Ioannidis, John; Stanford University, USA Furst, Daniel; UCLA Smolen, Josef S Taylor, Peter; University of Oxford, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences Kristensen, Lars Erik; Bispebjerg and Frederiksberg Hospital, The Parker Institute Tarp, Simon; Musculoskeletal Statistics Unit, The Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark. Ellingsen, Torkell; University of Southern Denmark, Rheumatology Christensen, Robin; Parker Instituttet, Musculoskeletal Statistics Unit; University of Southern Denmark
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Epidemiology
Keywords:	RHEUMATOLOGY, Rheumatology < INTERNAL MEDICINE, EPIDEMIOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

META-RESEARCH

Protocol

Risk of Harm in Synthetic and Biological Intervention Trials in Patients with Inflammatory Arthritis: Protocol for A Meta-Epidemiological Study Focusing on Contextual Factors

Esben Malm (medical student); Johannes Berg (medical student); Sabrina M Nielsen, MSc, PhD Student; John PA Ioannidis, MD, DSc; Daniel E Furst, MD; Josef S Smolen, MD; Peter C. Taylor, MD, PhD; Lars Erik Kristensen, MD, PhD; Simon Tarp, MSc, PhD; Torkell Ellingsen, MD, PhD; Robin Christensen, MSc, PhD

Collaborator/Author information

EM: Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, & Section for Biostatistics and Evidence-Based Research, the Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark. esmal14@student.sdu.dk

JB: Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, Denmark & Section for Biostatistics and Evidence-Based Research, the Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark. jober14@student.sdu.dk

SMN: Section for Biostatistics and Evidence-Based Research, the Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark & Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, Denmark. sabrina.mai.nielsen@regionh.dk

JPAI: Department of Medicine, Department of Epidemiology and Population Health, Department of Biomedical Data Science, Department of Statistics, Stanford University, Stanford, CA, USA. jioannid@stanford.edu

DEF: David Geffen School of Medicine, Division of Rheumatology, UCLA, Los Angeles; University of Washington, Seattle; Washington and University of Florence, Florence, Italy. defurst@mednet.ucla.edu

JS: Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, Vienna, Austria.

PCT: Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences and the Kennedy Institute of Rheumatology, University of Oxford, Oxford, UK. peter.taylor@kennedy.ox.ac.uk

LEK: Department of Rheumatology & The Parker Institute, Frederiksberg, Denmark. lars.erik.kristensen@regionh.dk

ST: Section for Biostatistics and Evidence-Based Research, the Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark. simon.tarp@regionh.dk

TE: Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, Denmark. torkell.ellingsen@rsyd.dk

RC: Section for Biostatistics and Evidence-Based Research, the Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark & Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, Denmark. robin.christensen@regionh.dk

Corresponding author

Robin Christensen, BSc, MSc, PhD; biostatistician & professor

Section for Biostatistics and Evidence-Based Research, the Parker Institute, Bispebjerg and Frederiksberg Hospital & Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, Denmark. Mailing address: The Parker Institute, Bispebjerg and Frederiksberg Hospital, Nordre Fasanvej 57, DK-2000 Copenhagen F, Denmark.

e-mail: Robin.Christensen@regionh.dk

Tel: +45 3816 4165/Fax: +45 3816 4159

ORCID iD: 0000-0002-6600-0631/

web: http://www.parkerinst.dk/staff/robin-christensen

Disclaimers

The views expressed in the submitted protocol are the authors' own and not an official position of the institution or funder.

Source(s) of support

The Parker Institute, Bispebjerg and Frederiksberg Hospital is supported by a core grant from the Oak Foundation (OCAY-18-774-OFIL).

Contributions

Study concept and design: EM, JB, SMN, TE, LEK, RC, JPAI, ST, DF, JSS, PCT.
Drafting on the protocol: EM, JB, SMN, TE, LEK, RC, JPAI, ST, DF, JSS, PCT.
Critical revision of the protocol for important intellectual content and final approval before submission: All authors.
Obtained funding: TE & RC.

Competing interests

This study had no financial competing interests.

Funding

The Parker Institute is grateful for the financial support received from public and private foundations, companies, and private individuals over the years. The Parker Institute, Bispebjerg and Frederiksberg Hospital, is supported by a core grant from the Oak Foundation (OCAY-18-774-OFIL); The Oak Foundation is a group of philanthropic organisations that, since its establishment in 1983, has given grants to not-for-profit organisations around the world.

Amendments

Important deviations from the protocol will be reported in the peer-reviewed publication.

ABSTRACT

Introduction: Inflammatory Arthritis (IA) conditions, including rheumatoid arthritis (RA), psoriatic arthritis (PsA), and axial spondyloarthritis (AxSpA), are characterised by inflammatory infiltration of the joints. Biologic and targeted synthetic disease-modifying antirheumatic drugs (bDMARDs and tsDMARDs, respectively) reduce the effects of proinflammatory cytokines and immune cells to ameliorate disease. However, immunosuppression can be associated with high rates of serious adverse events (SAEs), including serious infections, and maybe an increased risk of malignancies and cardiovascular events. Currently, there is no empirical evidence on the extent to which contextual factors and risk of bias (RoB) domains may modify these harm signals in randomised trials.

Method and analysis: We will search MEDLINE (via PubMed) for systematic reviews published since April 2015 and all Cochrane reviews. From these reviews, randomised trials will be eligible if they include patients with an IA condition (RA, PsA, or AxSpA) with at least one group randomly allocated to bDMARD and/or tsDMARD treatments. A predefined form will be used for extracting data on population characteristics (e.g., baseline characteristics or eligibility criteria, such as medication background), and specific harm outcome measures, such as number of withdrawals, numbers of patients discontinuing due to adverse events, and number of patients having SAEs. RoB in individual trials will be assessed using a modified Cochrane RoB tool. We will estimate the potentially causal harm effects related to the experimental intervention compared to control comparator as risk ratios, and heterogeneity across randomised comparisons will be assessed statistically and evaluated as inconsistency using the I^2 Index. Our meta-regression analyses will designate population and trial characteristics, and each RoB domain as independent variables, whereas the three harm domains will serve as dependent variables.

Ethics and dissemination: Ethics approval is not required for this study. Results will be disseminated through publication in international peer-reviewed journals.

Registration: PROSPERO (CRD: 42020171124).

Strengths and limitations of this study

- This will be an extensive and comprehensive risk of harm analysis of bDMARDs and tsDMARDs across multiple IA diagnoses unlike previous assessments that have been more circumscribed.
- A large array of contextual factors and risk of bias items will be assessed.
- The study selection will be done by two independent reviewers.
- Despite the comprehensive nature of the assessment, the study may be limited by poor reporting/lack of data for certain contextual factors and uncommon harms, and some meta-regression assessments may be affected by ecological bias due to the use of aggregated data, and meta-confounding.

INTRODUCTION

Background

Inflammatory Arthritis (IA) is a heterogeneous group of autoimmune diseases that includes rheumatoid arthritis (RA), psoriatic arthritis (PsA), axial spondyloarthritis (axSpA, including ankylosing spondylitis AS) (1, 2). These diseases are characterised by inflammatory infiltration of the joints (3), resulting in pain, swelling, stiffness and restricted movement (4). Ultimately, they can have a detrimental impact on quality of life, cause progressive disability and premature death (5, 6). Not only are the implications severe, also the diseases are a global concern; RA alone affects about 1% of the world's population (7).

Aside from conventional synthetic (cs) DMARDs including methotrexate, targeted therapies, consisting of biological disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) are considered effective for treating IA *per se* (8-10). Notably, bDMARDs work by targeting specific molecules or receptors (11), such as tumour necrosis factor alpha (TNFα), which is a potent inflammatory cytokine produced by T-cells and macrophages (12, 13). In contrast, tsDMARDs target intracellular pathways and reduce the effect of cytokines known to drive the proinflammatory machinery of cellular immune response (14-16). As such, b- and tsDMARDs are Immunomodulatory; although effective in alleviating symptoms of IA, they also carry risk of harm (defined as: "*the totality of possible adverse consequences of an intervention or therapy*" (17)). Indeed, meta-analyses and an observational cohort study have shown that bDMARDs are associated with higher rates of serious infections (18-20) and potentially dose-dependent increased risk of malignancies (21). Some meta-studies and systematic literature reviews suggest that tsDMARD rates of serious infections and malignancies are no different from those of bDMARDs (16, 22, 23). Recent reviews report a possibly increased risk of venous thromboembolism with tsDMARDs (23, 24).

Randomised controlled trials (RCTs) inevitably vary with respect to eligibility criteria, patient characteristics, and internal validity, which may distort their results (i.e., the harm signal) and thus potentially bias their interpretation (25, 26). If evidence were available on which trial characteristics to adjust for when interpreting harm from meta-research, these covariates would be considered important contextual factors. Currently, a contextual factor is broadly defined as a "…*variable that is not an outcome of the study but needs to be recognized (and measured) to understand the study results. This*

includes potential confounders and effect modifiers" (27). However, we currently have no empirical evidence concerning the extent to which contextual factors, such as population and trial characteristics and risk of bias (RoB) domains, modify the harm signals from trials testing targeted therapies (i.e., bDMARDs and tsDMARDs) across IA diseases.

Rationale

Designing, conducting, and reporting RCTs should incorporate methods—such as concealing randomised allocation, blinding participants and personnel, and appropriately engaging the intention-to-treat population—that avoid biases resulting from incompatibilities between the intervention and control groups. Empirical evidence suggests that the absence of rigorous methodology can lead to biased intervention effect estimates (i.e., net benefits) (28). Contextual factors, such as population and trial characteristics, also have been shown to be possible effect modifiers when assessing benefits (8, 29).

The effect on harms of RoB, trial characteristics and contextual factors (e.g., population characteristics) has yet to be investigated, and using meta-epidemiology is the method of choice for doing so (30). Previous meta-epidemiological research within rheumatology has primarily investigated the effect of methodological quality (internal validity) on treatment effects (benefit) (8, 29, 31, 32). To our knowledge, no one has yet investigated the importance in IA therapies of contextual factors (i.e., population and trial characteristics) and RoB when the outcome is harmful effects.

Aims and objectives

This exploratory meta-epidemiological study aims to improve harm reporting by investigating the influence of RoB domains, trial characteristics, and contextual factors on the three harm measures: all withdrawals (WD), withdrawals due to adverse events (WD d/t AEs), and serious adverse events (SAEs) (17), as well as mortality among patients with IA who were treated with bDMARDs and/or tsDMARDs. Our objective is to explore whether specific participant and trial characteristics (i.e., contextual factors including RoB domains) have a quantitative influence in terms of effect modification and/or distortion due to biases on the observed likelihood of harm from an experimental intervention compared to control comparators in randomised trials. If contextual factors have such an influence, we hope to shed light on their importance to future trial reporting and interpretation of harm when reporting

randomised trials (17).

Protocol and registration

This protocol was developed in accordance with the v1.07 2018 Methodological Expectations for Cochrane Intervention Reviews (MECIR) recommendations of the Cochrane Collaboration (33) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Protocols (PRISMA-P) guidelines (34). The study protocol was pre-specified and registered in PROSPERO on 2020-03-27, CRD number: CRD42020171124.

METHODS AND ANALYSIS

This (meta-epidemiological) study combines data from a large representative sample of available trials into a single database by assembling trials already included in published systematic reviews. Generic outcome measures that cover important harm domains (*i:* WD, *ii:* WD d/t AEs and *iii:* SAEs (17)) and mortality will constitute the dependent variable(s) in the database. Harm effects in relation to the use of targeted therapies will be analysed to determine whether they are affected by contextual factors among population and trial characteristics.

Eligibility criteria

We will search MEDLINE (via PubMed) for systematic reviews (published since April 2015) or Cochrane reviews. From these systematic reviews, included randomised trials will (independent of publication year) be eligible if they fulfil our inclusion criteria (see table 1 for PICO framework), with at least one group randomly allocated to bDMARD and/or tsDMARD.

The interventions of interest are targeted therapies (i.e., bDMARDs and tsDMARDs) approved by either EMA or FDA to date, treating IA conditions in adult populations. These therapies will include bDMARDs: abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, guselkumab, infliximab, ixekizumab, rituximab, sarilumab, secukinumab, tocilizumab, ustekinumab, and tsDMARDs: apremilast, baricitinib, filgotinib, tofacitinib and upadacitinib.

Only RCTs included in an existing systematic review of patients with inflammatory arthritis (RA, PsA, and AxSpA [including AS]) will be considered for

eligibility. We will exclude reviews (i.e., not look for trials) that have been withdrawn. Furthermore, only RCTs from the eligible systematic reviews where the full text is available in English will be included. There will be no restriction on publication year of the individual RCTs.

*Table 1. Research objective described using PICO**

Participants	**Adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), axial spondyloarthritis (axSpA) or ankylosing spondylitis (AS).**
Intervention	Targeted therapies (i.e., bDMARDs and tsDMARDs)
Comparison	Placebo, standard care or waiting list/no intervention, active comparator and unclear (i.e. comparison described in insufficient detail to fit within the other categories).
Outcome(s)	Number of withdrawals (WDs), number of WDs due to adverse events (WD d/t AEs), number of serious adverse events (SAEs) and number of patients who died.

*PICO - participants, intervention, comparison, and outcome.

Information sources and search strategy

We will search MEDLINE (via PubMed) for eligible meta-analyses or systematic reviews of trials published since April 2015 and eligible Cochrane reviews using the search algorithm shown in table 2:

Table 2. Search strategy

(arthritis[tiab] OR spondyloarthritis[tiab] OR ankylosing[tiab] OR psoriatic[tiab] OR Spondylarthropathies[tiab] OR rheumatoid[tiab] OR Psoriasis[tiab])

AND

("disease-modifying antirheumatic drugs"[tiab] OR "biological agent*"[tiab] OR biologics*[tiab] OR DMARD[tiab] OR abatacept[tiab] OR adalimumab[tiab] OR anakinra[tiab] OR apremilast[tiab] OR baricitinib[tiab] OR certolizumab[tiab] OR etanercept[tiab] OR filgotinib[tiab] OR golimumab[tiab] OR guselkumab[tiab] OR infliximab[tiab] OR ixekizumab[tiab] OR rituximab[tiab] OR sarilumab[tiab] OR secukinumab[tiab] OR tocilizumab[tiab] OR tofacitinib[tiab] OR upadacitinib[tiab] OR ustekinumab[tiab])

AND

((“Systematic Review”[pt] OR Meta-Analysis[pt] OR meta-analysis[tiab] OR “systematic review”[tiab]

OR meta-analys*[pt] OR meta-analys*[ti] OR metaanalys*[ti] OR meta-regress*[tiab] OR metaregress*[tiab]

AND ("2015/04/01"[Date - Publication]: "3000"[Date - Publication]))

OR “Cochrane Database Syst Rev” [jour])

Study selection

Two independent reviewers (JB and EM, with support from SMN/RC) will screen the systematic reviews based on title and abstract, in accordance with eligibility criteria. The same two reviewers will assess the full systematic review texts for eligibility of the reviews and subsequently select the RCTs from the reviews that are eligible, according to our objectives. We will obtain the full text if at least one of the reviewers considers an RCT to be potentially eligible during the screening process. Disagreements will be resolved by consensus or by consulting a third reviewer (RC). EndNote X9.2 software will be used to manage the reviews and RCT records retrieved from the search.

Data collection process

Two reviewers (JB and EM) will extract data using a predefined, standardised data extraction form, and in case of uncertainty a third reviewer (SMN/RC) will be consulted. If a trial is included in more than one review, the trial will be registered and counted/included once.

Review Level: From the reviews, we will extract data on review registration number, year of publication, first author’s name, number of RCTs eligible for our study, and the condition and intervention studied, according to the review title.

Randomised Trial Level: From the trials, we will extract data on first author’s name, publication ID, trial duration, duration until switch (e.g., relevant for adaptive trial designs), rescue, early escape or cross over, number of participants in each arm, and treatment given in the active and comparator arms (i.e., following the PICO framework). Treatment in the comparator arm will be grouped into the following predefined categories: (*i*) placebo; (*ii*) standard care or waiting list/no intervention; (*iii*) active comparator, or as an ultimate last option; (*iv*) unclear. Outcome measures and data extraction of trial and participant characteristics are specified below and listed in

table 3.

Participant characteristics in individual studies

Data on the following trial eligibility criteria will be extracted:

- Binary indicator (0 or 1) of inflammation scored as 1 with ≥1 of the following criteria: erythrocyte sedimentation rate (ESR) ≥28 mm/hour, CRP level ≥0.3 mg/dL, and/or morning stiffness lasting ≥45 minutes
- minimum AND maximum required number of swollen joint counts (SJC)
- minimum AND maximum required number of tender joint counts (TJC)
- minimum AND maximum allowed disease duration
- rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide antibody (anti-CCP) and/or anti-cyclic citrullinated peptide antibody 2 (CCP2) status

In order to stratify trials according to the DMARD history of their included patients, we will ask the following signalling question: Had the participants, prior to inclusion, potentially exhausted the treatment potential of at least one class of DMARD—either conventional synthetic DMARDs (i.e., [csDMARD], bDMARD, or tsDMARD)?

- csDMARD-naïve (patients were either csDMARD naïve or had not exhausted the treatment potential of at least one csDMARD)
- csDMARD-IR (csDMARD inadequate responders), where patients had exhausted at least one csDMARD option previously
- bDMARD or tsDMARD-IR (bDMARD or tsDMARD inadequate responders), patients had inadequate response to at least one previous bDMARD or tsDMARD. Inclusion in this group entails exclusion from other DMARD history groups.

Patients' concomitant medication (background) of DMARDs during the trial period will be ordered in the following three levels:

- methotrexate (MTX)
- csDMARDs other than MTX
- bDMARDs or tsDMARDs

We will extract information about how the three groups were handled at randomisation, potentially enabling us to cluster the trials into one of the following five levels: (*i*) Naïve (i.e., patients had never used the drug[s] of interest); (*ii*) Not using (i.e., the study included only patients who were currently not using the drug[s] of interest); (*iii*) Discontinued (i.e., patients were not allowed to continue drug[s] of

interest; (iv) Continued (i.e., patients were allowed to continue drug[s] of interest); and (*v*) Not reported (unclear: no information was reported on this matter). In the case of axSpa, NSAID will be extracted equivalent to csDMARDs.

Data on the following aggregate (average/median) patient baseline characteristics will be extracted: age, female (proportion), disease duration (years), ESR (mm/hour), CRP (mg/dL), Disease activity score, RF positive (proportion), anti-CCP positive (proportion), anti-CCP2 positive (proportion), SJC, TJC, health assessment questionnaire—disability index (HAQ-DI), physician global assessment (e.g., Visual Analogue Scale [VAS]), patient global assessment (e.g., VAS), and patient-reported pain on visual analogue scales of 0–100 mm (e.g., VAS).

Risk of bias and trial characteristics in individual studies

Many published reviews include some form of RoB assessment (i.e., at least for the most frequently used RoB domains) for each individual trial; these assessments will be mapped to the best of our ability to correspond to the Cochrane RoB v.1 (35). The RoB will also be assessed by one of the two reviewers (JB or EM) and subsequently compared with the original bias and internal validity assessments' in the review, from which it was sampled.

Within each full-text trial report, we will apply the following domains of the original Cochrane RoB tool (i.e., RoB v.1.0) (35), which comprise methods for:

- sequence generation/maintaining allocation concealment (selection bias)
- blinding both patients and personnel (performance bias)
- management/analysis/reporting of incomplete outcome data (attrition bias)

Each of these three domains will be rated as high risk, low risk, or unclear RoB (35). In case of uncertainty, another reviewer (SMN/RC) will be consulted. Any discrepancy between RoB assessment sources will be resolved by discussion among the authors.

The following additional bias sources will also be assessed, and data will be extracted from them:

- single *vs*. multi-site trials (36)
- small *vs*. large trials (where small will pragmatically be defined as <100 patients per

arm) (37, 38)

- source of funding grouped into one of the following five categories: (*i*) 100% industry (pharmaceutical/device company) funded; (*ii*) mixed funding (e.g., non-industry and industry; (*iii*) provision of drug only; (*iv*) 100% non-profit funded; and (*v*) unclear/undisclosed funding (39)

Outcome measures

Data extraction for each RCT will include the number of patients who died, and the numbers of patients with any of the following "generic events": (*i*) all withdrawals (WDs); (*ii*) WDs due to AEs; and (*iii*) SAEs (17). If the number of individual patients with SAEs is not reported, we will extract the number of reported SAEs instead.

Where reasons are provided to explain the SAEs, they will be categorised according to MedDRA v.23.0 [(*i*) Infections and infestations; (*ii*) Neoplasms benign, malignant and unspecified (including cysts and polyps); (*iii*) Cardiac and vascular disorders; or (*iv*) others]. If patients in the comparison group later are offered the intervention (i.e., switching to the intervention group), the number of events before the switch will be used as the endpoint of choice (i.e., before introducing adaptive trial designs).

Summary measures

For each binary outcome, we will extract data corresponding to the 2×2 table, summarising the number of patients who experienced the outcome in each comparison group as reported in the randomised trial and the total number of patients randomly assigned in each group. For outcomes collected and reported corresponding to different time points, we will select the time point with the longest follow-up while still respecting the primary research design (e.g., before introducing an adaptive trial design, and/or open label extension) (40, 41).

Because all the outcome measures are dichotomous, the relative Risk Ratios (RRs) with 95% confidence intervals (95%CI) will be the preferred measure of relative effect, and these can subsequently be applied to the baseline or control group risks to generate absolute risks (42). When appropriate for the very rare adverse events, we will use a continuity correction (adding to all cells a factor proportional to the reciprocal of the size of the contrasting study group), as suggested by Sweeting and colleagues (43), to take into account zero cell counts in one group only. This continuity correction will be applied when no events are

observed in one study arm of a trial. The correction is inversely proportional to the relative size of the opposite of the study (21, 43). Continuity correction for the experimental intervention arm is 1/(*R*+1); *R* is the ratio of control group to intervention group sizes (i.e., $R = n_C/n_I$). Similarly, the continuity correction for the control comparator arm is *R*/(*R*+1). We expect that most trials will report only a few SAEs and deaths, so the odds ratios and 95%CI's will also (for the purpose of sensitivity analysis) be calculated with the use of the *Peto* method. Because the expected events are sparse and all trials will have similar durations of follow-up for their treatment groups, the use of both risk ratios and odds ratios should represent a valid approach to assessing the risk associated with the use of synthetic or biological intervention in patients with IA. The number of studies to be included will be determined by the number of eligible trials available in the systematic reviews, hence a formal sample size calculation would not be meaningful. However, we expect the search to bring around 175 eligible trials (RA: 117, PsA: 15, AxSpA: 43) based on a few large systematic reviews within the field (44-48).

Synthesis of results

Outcome events will be coded so that an RR direction of more than 1 indicates a potentially harmful effect of the experimental intervention (i.e., $RR = [r_I/n_I]/ [r_C/n_C]$). Mixed effects Restricted Maximum Likelihood (REML) meta-analyses (49) will be used to combine the harm effects across RCTs (based on their log [*RR*]) (50); we will apply the trial ID as a random effect, while applying the review ID (from which the trial was sampled) as a fixed effect in order to model the hierarchical structure of the data sampling (51).

Heterogeneity across randomised comparisons will be assessed by using the Cochrane Q test (52), interpreted based on the I^2 inconsistency index (53), and quantified by the estimate for between-trial variance (τ^2), estimated as T^2 (54). The effect of population and trial characteristics (listed below) on the between-trial variance will be calculated by univariably adding a factor for the specific characteristic in the model. If introducing a specific covariate into the meta-model reduces the observed between-trial variance (T^2), this result will be considered an indication of a potentially important effect modifier (55).

Further analyses might (if possible) include multivariable models (56). Observational by nature, meta-epidemiological studies like the present should be

expected to have some degree of meta-confounding because prognostic factors might be unequally distributed between studies exposed (trial characteristic positive) or not. We will attempt to adjust for possible confounding covariates (i.e. "de-confound") the inference. That is, we will explore the ability to adjust for any important preexposure covariate ' *C* ' (i.e., something that happened before the "*study design variable of interest was generated*") that is potentially unequally distributed between the meta-epidemiological exposure groups (E: Exposed vs. Unexposed), which is ALSO an ancestor (i.e., likely cause) of the trial outcome (i.e., a more exaggerated risk of harm): $M_E \leftarrow C \rightarrow Y_E$ (56).

Table 3. Population and trial characteristics

Trial eligibility criteria:
Minimum and maximum required number of swollen joint counts
Minimum and maximum required number of tender joint counts
Minimum and maximum required C-reactive protein
Minimum and maximum required Erythrocyte sedimentation rate
Minimum and maximum allowed disease duration
Rheumatoid factor
Anti-cyclic citrullinated peptide antibody status
Anti-cyclic citrullinated peptide antibody 2 status
DMARD history:
csDMARD-naïve
csDMARD-IR (csDMARD inadequate responders)
bDMARD or tsDMARD-IR (bDMARD or tsDMARD inadequate responders)
Medication background of DMARDs:
Methotrexate
-Naïve
-Not using
-Discontinued
-Continued
-Not reported
csDMARDs other than methotrexate
-Naïve
-Not using
-Discontinued

-Continued
-Not reported
bDMARDs or tsDMARDs.
-Naïve
-Not using
-Discontinued
-Continued
-Not reported
Aggregate (e.g., average/median) patient baseline characteristics:
Age
Female (%)
Disease duration
Erythrocyte sedimentation rate
C-reactive protein
Disease activity score
RF positive (%)
Anti-CCP positive (%)
CCP2 positive (%)
Swollen joint counts
Tender joint counts
Health assessment questionnaire—disability index
Physician global assessment of disease activity
Patient global assessment of disease activity
Patient-reported pain on visual analogue scales of 0–100 mm

Risk of bias across studies

Stratified meta-analyses will be used for tests of interaction between harms and the trial RoB (listed in Table 4) and trial characteristics collected as described above.

Table 4. Risk of bias

Cochrane risk of bias domains:
· Risk of selection bias
· Risk of performance bias
· Risk of attrition bias
· Overall risk of bias*

Additional bias sources:
· Single vs. multi-site trials
· Small vs. large trials
· Source of funding

*For each trial, the overall RoB will be classified as low (i.e., low RoB for all three domains); high (i.e., high RoB for one or more domains); or unclear (i.e., unclear RoB for one or more domains in the absence of high RoB).

Perspectives

The Outcome Measures in Rheumatology (OMERACT) initiative established the Contextual Factors Working Group to guide the understanding, identification and handling of contextual factors for clinical trials, with most of the current emphasis' being on net benefit inferred from a rheumatology trial (57). This meta-epidemiological study will work from the original definition of what constitutes a contextual factor, as defined in the introduction. We will explore and hope to reveal the possible impact of contextual factors (i.e., population and trial characteristics) and RoB domains of three different (but related) harm measures, as well as deaths (58). Knowing which factors are associated with a causal model for harms—either as effect modifiers or distortions of the outcome due to bias—is important for improving investigation and reporting of harms in future trials (59). If future trials report harms according to important contextual factors, meta-analyses would be able to investigate contextual factors for harms without relying on getting access to individual patient data. Such meta-research might identify subgroups among rheumatic disease patients that are at higher risk of experiencing harms. Such information would provide important evidence for future treatment guideline development. Ultimately the doctor will be able to differentiate the risk of intervention based on the patient's characteristics. This has the potential to enhance informed decision-making and effect therapeutic interventions applied in practice, leading to safer treatment of individual patients and increase efficiency in the health care system.

Patient and public involvement

Patients and/or the public were not involved in designing study concept or drafting of the protocol.

ETHICS AND DISSEMINATION

Because our study does not collect primary data, no formal ethical assessment and informed consent are required. First, second and third author (EM, JB and SMN) will draft the paper

describing this meta-epidemiological study; the study will be disseminated in a peer-reviewed publication.

References

1. Ledingham J, Snowden N, Ide Z. Diagnosis and early management of inflammatory arthritis. BMJ. 2017;358:j3248.
2. Raychaudhuri SP, Deodhar A. The classification and diagnostic criteria of ankylosing spondylitis. J Autoimmun. 2014;48-49:128-33.
3. Miyabe Y, Miyabe C, Luster AD. LTB4 and BLT1 in inflammatory arthritis. Semin Immunol. 2017;33:52-7.
4. McInnes IB, Schett G. The Pathogenesis of Rheumatoid Arthritis. New England Journal of Medicine. 2011;365(23):2205-19.
5. Janke K, Biester K, Krause D, Richter B, Schürmann C, Hirsch K, et al. Comparative effectiveness of biological medicines in rheumatoid arthritis: systematic review and network meta-analysis including aggregate results from reanalysed individual patient data. Bmj. 2020;370:m2288.
6. Schweikert B, Malmberg C, Núñez M, Dilla T, Sapin C, Hartz S. Cost-effectiveness analysis of ixekizumab versus secukinumab in patients with psoriatic arthritis and concomitant moderate-to-severe psoriasis in Spain. BMJ Open. 2020;10(8):e032552.
7. Hartman L, Rasch LA, Klausch T, Bijlsma HWJ, Christensen R, Smulders YM, et al. Harm, benefit and costs associated with low-dose glucocorticoids added to the treatment strategies for rheumatoid arthritis in elderly patients (GLORIA trial): study protocol for a randomised controlled trial. Trials. 2018;19(1):67.
8. Christensen AW, Tarp S, Furst DE, Dossing A, Amris K, Bliddal H, et al. Most Trial Eligibility Criteria and Patient Baseline Characteristics Do Not Modify Treatment Effect in Trials Using Targeted Therapies for Rheumatoid Arthritis: A Meta-Epidemiological Study. PLoS One. 2015;10(9):e0136982.
9. Callhoff J, Sieper J, Weiss A, Zink A, Listing J. Efficacy of TNFalpha blockers in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis: a meta-analysis. Ann Rheum Dis. 2015;74(6):1241-8.
10. Goulabchand R, Mouterde G, Barnetche T, Lukas C, Morel J, Combe B. Effect of tumour necrosis factor blockers on radiographic progression of psoriatic arthritis: a systematic review and meta-analysis of randomised controlled trials. Ann Rheum Dis. 2014;73(2):414-9.
11. Oo C, Kalbag SS. Leveraging the attributes of biologics and small molecules, and releasing the bottlenecks: a new wave of revolution in drug development. Expert review of clinical pharmacology. 2016;9(6):747-9.
12. Komaki Y, Yamada A, Komaki F, Kudaravalli P, Micic D, Ido A, et al. Efficacy, safety and pharmacokinetics of biosimilars of anti-tumor necrosis factor-alpha agents in rheumatic diseases; A systematic review and meta-analysis. J Autoimmun. 2017;79:4-16.
13. So A, Inman RD. An overview of biologic disease-modifying antirheumatic drugs in axial spondyloarthritis and psoriatic arthritis. Best Pract Res Clin Rheumatol. 2018;32(3):453-71.
14. Gadina M, Le MT, Schwartz DM, Silvennoinen O, Nakayamada S, Yamaoka K, et al. Janus kinases to jakinibs: from basic insights to clinical practice. Rheumatology (Oxford, England). 2019;58(Supplement_1):i4-i16.
15. Sarzi-Puttini P, Ceribelli A, Marotto D, Batticciotto A, Atzeni F. Systemic rheumatic diseases: From biological agents to small molecules. Autoimmun Rev. 2019;18(6):583-92.
16. Winthrop KL. The emerging safety profile of JAK inhibitors in rheumatic disease. Nat Rev Rheumatol. 2017;13(4):234-43.
17. Ioannidis JP, Evans SJ, Gøtzsche PC, O'neill RT, Altman DG, Schulz K, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. Annals of internal medicine. 2004;141(10):781-8.

18. Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, Macdonald JK, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database Syst Rev. 2011(2):Cd008794.

19. Minozzi S, Bonovas S, Lytras T, Pecoraro V, Gonzalez-Lorenzo M, Bastiampillai AJ, et al. Risk of infections using anti-TNF agents in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: a systematic review and meta-analysis. Expert Opin Drug Saf. 2016;15(sup1):11-34.

20. Gron KL, Arkema EV, Glintborg B, Mehnert F, Ostergaard M, Dreyer L, et al. Risk of serious infections in patients with rheumatoid arthritis treated in routine care with abatacept, rituximab and tocilizumab in Denmark and Sweden. Ann Rheum Dis. 2019;78(3):320-7.

21. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006;295(19):2275-85.

22. Salgado E, Maneiro JR, Carmona L, Gomez-Reino JJ. Safety profile of protein kinase inhibitors in rheumatoid arthritis: systematic review and meta-analysis. Ann Rheum Dis. 2014;73(5):871-82.

23. Sepriano A, Kerschbaumer A, Smolen JS, van der Heijde D, Dougados M, van Vollenhoven R, et al. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2019 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2020.

24. Mease P, Charles-Schoeman C, Cohen S, Fallon L, Woolcott J, Yun H, et al. Incidence of venous and arterial thromboembolic events reported in the tofacitinib rheumatoid arthritis, psoriasis and psoriatic arthritis development programmes and from real-world data. Ann Rheum Dis. 2020;79(11):1400-13.

25. Rahman MU, Buchanan J, Doyle MK, Hsia EC, Gathany T, Parasuraman S, et al. Changes in patient characteristics in anti-tumour necrosis factor clinical trials for rheumatoid arthritis: results of an analysis of the literature over the past 16 years. Ann Rheum Dis. 2011;70(9):1631-40.

26. Gluud LL. Bias in clinical intervention research. American journal of epidemiology. 2006;163(6):493-501.

27. Boers M, Kirwan JR, Wells G, Beaton D, Gossec L, d'Agostino MA, et al. Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. J Clin Epidemiol. 2014;67(7):745-53.

28. Savović J, Jones HE, Altman DG, Harris RJ, Jüni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. Annals of internal medicine. 2012;157(6):429-38.

29. Ballegaard C, Jorgensen TS, Skougaard M, Strand V, Mease PJ, Kristensen LE, et al. Trial Characteristics as Contextual Factors When Evaluating Targeted Therapies in Patients With Psoriatic Disease: A Meta-Epidemiologic Study. Arthritis Care Res (Hoboken). 2018;70(8):1206-17.

30. Bae JM. Meta-epidemiology. Epidemiology and health. 2014;36:e2014019.

31. Bolvig J, Juhl CB, Boutron I, Tugwell P, Ghogomu EAT, Pardo JP, et al. Some Cochrane risk-of-bias items are not important in osteoarthritis trials: a meta-epidemiological study based on Cochrane reviews. J Clin Epidemiol. 2018;95:128-36.

32. Dossing A, Tarp S, Furst DE, Gluud C, Wells GA, Beyene J, et al. Modified intention-to-treat analysis did not bias trial results. J Clin Epidemiol. 2016;72:66-74.

33. Higgins JPT LT, Chandler J, Tovey D, Churchill R. Methodological Expectations of Cochrane Intervention Reviews. Cochrane: London, Version 1.06. 2018.

34. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;350:g7647.

35. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.

36. Dechartres A, Boutron I, Trinquart L, Charles P, Ravaud P. Single-center trials show larger treatment effects than multicenter trials: evidence from a meta-epidemiologic study. Ann Intern Med. 2011;155(1):39-51.

37. Nüesch E, Trelle S, Reichenbach S, Rutjes AW, Tschannen B, Altman DG, et al. Small study effects in meta-analyses of osteoarthritis trials: meta-epidemiological study. Bmj. 2010;341:c3515.

38. Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. Ann Intern Med. 2001;135(11):982-9.

39. Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. Cochrane Database Syst Rev. 2017;2:Mr000033.

40. Pickles T, Alten R, Boers M, Bykerk V, Christensen J, Christensen R, et al. Adaptive Trial Designs in Rheumatology: Report from the OMERACT Special Interest Group. J Rheumatol. 2019;46(10):1406-8.

41. Buch MH, Silva-Fernandez L, Carmona L, Aletaha D, Christensen R, Combe B, et al. Development of EULAR recommendations for the reporting of clinical trial extension studies in rheumatology. Ann Rheum Dis. 2015;74(6):963-9.

42. Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, et al. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. J Clin Epidemiol. 2013;66(2):158-72.

43. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med. 2004;23(9):1351-75.

44. JA. S, A. H, E. TG, AS. M, LJ. M, R. B, et al. Biologics or tofacitinib for people with rheumatoid arthritis unsuccessfully treated with biologics: a systematic review and network meta-analysis. The Cochrane database of systematic reviews. 2017;3:CD012591.

45. JA. S, A. H, AS. M, E. TG, ME. S-A, R. B, et al. Biologics or tofacitinib for people with rheumatoid arthritis naive to methotrexate: a systematic review and network meta-analysis. The Cochrane database of systematic reviews. 2017;5:CD012657.

46. JA. S, A. H, E. TG, AS. M, P. T, GA. W. Biologic or tofacitinib monotherapy for rheumatoid arthritis in people with traditional disease-modifying anti-rheumatic drug (DMARD) failure: a Cochrane Systematic Review and network meta-analysis (NMA). The Cochrane database of systematic reviews. 2016;11:CD012437.

47. Fidahic M, Jelicic Kadic A, Radic M, Puljak L. Celecoxib for rheumatoid arthritis. Cochrane Database Syst Rev. 2017;6:Cd012095.

48. Lawson DO, Eraso M, Mbuagbaw L, Joanes M, Aves T, Leenus A, et al. Tumour necrosis factor inhibitor dose reduction for axial spondyloarthritis: A systematic review and meta-analysis of randomized controlled trials. Arthritis Care Res (Hoboken). 2020.

49. Normand S-LT. Meta-analysis: formulating, evaluating, combining, and reporting. Statistics in Medicine. 1999;18(3):321-59.

50. van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. Stat Med. 2002;21(4):589-624.

51. Sterne JA, Jüni P, Schulz KF, Altman DG, Bartlett C, Egger M. Statistical methods for assessing the influence of study characteristics on treatment effects in 'meta-epidemiological' research. Stat Med. 2002;21(11):1513-24.

52. Cochran WG. The combination of estimates from different experiments. Biometrics. 1954;10(1):101-29.

53. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Bmj. 2003;327(7414):557-60.

54. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? Stat Med. 2002;21(11):1559-73.

55. Sterne JA, Juni P, Schulz KF, Altman DG, Bartlett C, Egger M. Statistical methods for assessing the influence of study characteristics on treatment effects in 'meta-epidemiological' research. Stat Med. 2002;21(11):1513-24.

56. Christensen R, Berthelsen DB. Controversy and Debate on Meta-epidemiology. Paper 3: Causal inference from meta-epidemiology: a reasonable goal, or wishful thinking? J Clin Epidemiol. 2020;123:131-2.

57. Nielsen SM, Uggen Rasmussen M, Boers M, D AvdW, de Wit M, T GW, et al. Towards consensus in defining and handling contextual factors within rheumatology trials: an initial qualitative study from an OMERACT working group. Ann Rheum Dis. 2020.

58. Nielsen SM, Storgaard H, Ellingsen T, Shea BJ, Wells GA, Welch VA, et al. Population characteristics as important contextual factors in rheumatological trials: an exploratory meta-epidemiological study from an OMERACT Working Group. Ann Rheum Dis. 2020;79(10):1269-76.

59. Finger ME, Boonen A, Woodworth TG, Escorpizo R, Christensen R, Nielsen SM, et al. An OMERACT Initiative Toward Consensus to Identify and Characterize Candidate Contextual Factors: Report from the Contextual Factors Working Group. J Rheumatol. 2017;44(11):1734-9.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Risk of Harm in Synthetic and Biological Intervention Trials in Patients with Inflammatory Arthritis: Protocol for A Meta-Epidemiological Study Focusing on Contextual Factors

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-049850.R2
Article Type:	Protocol
Date Submitted by the Author:	27-Jul-2021
Complete List of Authors:	Malm, Esben; SDU, Research Unit of Rheumatology; The Parker Institute, Musculoskeletal Statistics Unit Nielsen, Sabrina; The Parker Institute Berg, Johannes; University of Southern Denmark, Research Unit of Rheumatology; Parker Instituttet Ioannidis, John; Stanford University, USA Furst, Daniel; UCLA Smolen, Josef S Taylor, Peter; University of Oxford, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences Kristensen, Lars Erik; Bispebjerg and Frederiksberg Hospital, The Parker Institute Tarp, Simon; Musculoskeletal Statistics Unit, The Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark. Ellingsen, Torkell; University of Southern Denmark, Rheumatology Christensen, Robin; Parker Instituttet, Musculoskeletal Statistics Unit; University of Southern Denmark
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Epidemiology
Keywords:	RHEUMATOLOGY, Rheumatology < INTERNAL MEDICINE, EPIDEMIOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

META-RESEARCH

Protocol

Risk of Harm in Synthetic and Biological Intervention Trials in Patients with Inflammatory Arthritis: Protocol for A Meta-Epidemiological Study Focusing on Contextual Factors

Esben Malm, MD; Sabrina M Nielsen, MSc, PhD Student; Johannes Berg (medical student); John PA Ioannidis, MD, DSc; Daniel E Furst, MD; Josef S Smolen, MD; Peter C. Taylor, MD, PhD; Lars Erik Kristensen, MD, PhD; Simon Tarp, MSc, PhD; Torkell Ellingsen, MD, PhD; Robin Christensen, MSc, PhD

Collaborator/Author information

EM: Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, & Section for Biostatistics and Evidence-Based Research, the Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark. esbenmalm@gmail.com

SMN: Section for Biostatistics and Evidence-Based Research, the Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark & Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, Denmark. sabrina.mai.nielsen@regionh.dk

JB: Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, Denmark & Section for Biostatistics and Evidence-Based Research, the Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark. jober14@student.sdu.dk

JPAI: Department of Medicine, Department of Epidemiology and Population Health, Department of Biomedical Data Science, Department of Statistics, Stanford University, Stanford, CA, USA. jioannid@stanford.edu

DEF: David Geffen School of Medicine, Division of Rheumatology, UCLA, Los Angeles; University of Washington, Seattle; Washington and University of Florence, Florence, Italy. defurst@mednet.ucla.edu

JS: Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, Vienna, Austria. josef.smolen@meduniwien.ac.at

PCT: Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences and the Kennedy Institute of Rheumatology, University of Oxford, Oxford, UK. peter.taylor@kennedy.ox.ac.uk

LEK: Department of Rheumatology & The Parker Institute, Frederiksberg, Denmark. lars.erik.kristensen@regionh.dk

ST: Section for Biostatistics and Evidence-Based Research, the Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark. simon.tarp@regionh.dk

TE: Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, Denmark. torkell.ellingsen@rsyd.dk

RC: Section for Biostatistics and Evidence-Based Research, the Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark & Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, Denmark. robin.christensen@regionh.dk

Corresponding author

Robin Christensen, BSc, MSc, PhD; biostatistician & professor

Section for Biostatistics and Evidence-Based Research, the Parker Institute, Bispebjerg and Frederiksberg Hospital & Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, Denmark. Mailing address: The Parker Institute, Bispebjerg and Frederiksberg Hospital, Nordre Fasanvej 57, DK-2000 Copenhagen F, Denmark.

e-mail: Robin.Christensen@regionh.dk

Tel: +45 3816 4165/Fax: +45 3816 4159

ORCID iD: 0000-0002-6600-0631/

web: http://www.parkerinst.dk/staff/robin-christensen

Disclaimers

The views expressed in the submitted protocol are the authors' own and not an official position of the institution or funder.

Source(s) of support

The Parker Institute, Bispebjerg and Frederiksberg Hospital is supported by a core grant from the Oak Foundation (OCAY-18-774-OFIL).

Contributions

Study concept and design: EM, JB, SMN, TE, LEK, RC, JPAI, ST, DF, JSS, PCT.
Drafting on the protocol: EM, JB, SMN, TE, LEK, RC, JPAI, ST, DF, JSS, PCT.
Critical revision of the protocol for important intellectual content and final approval before submission: All authors.
Guarantor of the protocol: RC.
Obtained funding: TE & RC.

Competing interests

This study had no financial competing interests.

Funding

The Parker Institute is grateful for the financial support received from public and private foundations, companies, and private individuals over the years. The Parker Institute, Bispebjerg and Frederiksberg Hospital, is supported by a core grant from the Oak Foundation (OCAY-18-774-OFIL); The Oak Foundation is a group of philanthropic organisations that, since its establishment in 1983, has given grants to not-for-profit organisations around the world.

Amendments

Important deviations from the protocol will be reported in the peer-reviewed publication.

ABSTRACT

Introduction: Inflammatory Arthritis (IA) conditions, including rheumatoid arthritis (RA), psoriatic arthritis (PsA), and axial spondyloarthritis (AxSpA), are characterised by inflammatory infiltration of the joints. Biologic and targeted synthetic disease-modifying antirheumatic drugs (bDMARDs and tsDMARDs, respectively) reduce the effects of proinflammatory cytokines and immune cells to ameliorate disease. However, immunosuppression can be associated with high rates of serious adverse events (SAEs), including serious infections, and maybe an increased risk of malignancies and cardiovascular events. Currently, there is no empirical evidence on the extent to which contextual factors and risk of bias (RoB) domains may modify these harm signals in randomised trials.

Method and analysis: We will search MEDLINE (via PubMed) for systematic reviews published since April 2015 and all Cochrane reviews. From these reviews, randomised trials will be eligible if they include patients with an IA condition with at least one group randomly allocated to bDMARD and/or tsDMARD treatments. A predefined form will be used for extracting data on population characteristics (e.g., baseline characteristics or eligibility criteria, such as medication background), and specific harm outcome measures, such as number of withdrawals, numbers of patients discontinuing due to adverse events, and number of patients having SAEs. RoB in individual trials will be assessed using a modified Cochrane RoB tool. We will estimate the potentially causal harm effects related to the experimental intervention compared to control comparator as risk ratios, and heterogeneity across randomised comparisons will be assessed statistically and evaluated as inconsistency using the I^2 Index. Our meta-regression analyses will designate population and trial characteristics, and each RoB domain as independent variables, whereas the three harm domains will serve as dependent variables.

Ethics and dissemination: Ethics approval is not required for this study. Results will be disseminated through publication in international peer-reviewed journals.

Registration: PROSPERO (CRD: 42020171124).

Strengths and limitations of this study

- This will be an extensive and comprehensive risk of harm analysis of bDMARDs and tsDMARDs across multiple IA diagnoses unlike previous assessments that have been more circumscribed.
- A large array of contextual factors and risk of bias items will be assessed.
- The study selection will be done by two independent reviewers.
- Despite the comprehensive nature of the assessment, the study may be limited by poor reporting (i.e., lack of data/information for certain contextual factors and uncommon harms), and some meta-regression assessments may be affected by ecological bias due to the use of aggregated data, and meta-confounding.

INTRODUCTION

Background

Inflammatory Arthritis (IA) is a heterogeneous group of autoimmune diseases that includes rheumatoid arthritis (RA), psoriatic arthritis (PsA), axial spondyloarthritis (axSpA, including ankylosing spondylitis AS) (1, 2). These diseases are characterised by inflammatory infiltration of the joints (3), resulting in pain, swelling, stiffness and restricted movement (4). Ultimately, they can have a detrimental impact on quality of life, cause progressive disability and premature death (5, 6). Not only are the implications severe, also the diseases are a global concern; RA alone affects about 1% of the world's population (7).

Aside from conventional synthetic (cs) DMARDs including methotrexate, targeted therapies, consisting of biological disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) are considered effective for treating IA *per se* (8-10). Notably, bDMARDs work by targeting specific molecules or receptors (11), such as tumour necrosis factor alpha (TNFα), which is a potent inflammatory cytokine produced by T-cells and macrophages (12, 13). In contrast, tsDMARDs target intracellular pathways and reduce the effect of cytokines known to drive the proinflammatory machinery of cellular immune response (14-16). As such, b- and tsDMARDs are Immunomodulatory; although effective in alleviating symptoms of IA, they also carry risk of harm (defined as: "*the totality of possible adverse consequences of an intervention or therapy*" (17)). Indeed, meta-analyses and an observational cohort study have shown that bDMARDs are associated with higher rates of serious infections (18-20) and potentially dose-dependent increased risk of malignancies (21). Some meta-studies and systematic literature reviews suggest that tsDMARD rates of serious infections and malignancies are no different from those of bDMARDs (16, 22, 23). Recent reviews report a possibly increased risk of venous thromboembolism with tsDMARDs (23, 24).

Randomised controlled trials (RCTs) inevitably vary with respect to eligibility criteria, patient characteristics, and internal validity, which may distort their results (i.e., the harm signal) and thus potentially bias their interpretation (25, 26). If evidence were available on which trial characteristics to adjust for when interpreting harm from meta-research, these covariates would be considered important contextual factors. Currently, a contextual factor is broadly defined as a "…*variable that is not an outcome of the study but needs to be recognized (and measured) to understand the study results. This*

includes potential confounders and effect modifiers" (27). However, we currently have no empirical evidence concerning the extent to which contextual factors, such as population and trial characteristics and risk of bias (RoB) domains, modify the harm signals from trials testing targeted therapies (i.e., bDMARDs and tsDMARDs) across IA diseases.

Rationale

Designing, conducting, and reporting RCTs should incorporate methods—such as concealing randomised allocation, blinding participants and personnel, and appropriately engaging the intention-to-treat population—that avoid biases resulting from incompatibilities between the intervention and control groups. Empirical evidence suggests that the absence of rigorous methodology can lead to biased intervention effect estimates (i.e., net benefits) (28). Contextual factors, such as population and trial characteristics, also have been shown to be possible effect modifiers when assessing benefits (8, 29).

The effect on harms of RoB, trial characteristics and contextual factors (e.g., population characteristics) has yet to be investigated, and using meta-epidemiology is the method of choice for doing so (30). Previous meta-epidemiological research within rheumatology has primarily investigated the effect of methodological quality (internal validity) on treatment effects (benefit) (8, 29, 31, 32). To our knowledge, no one has yet investigated the importance in IA therapies of contextual factors (i.e., population and trial characteristics) and RoB when the outcome is harmful effects.

Aims and objectives

This exploratory meta-epidemiological study aims to improve harm reporting by investigating the influence of RoB domains, trial characteristics, and contextual factors on the three harm measures: all withdrawals (WD), withdrawals due to adverse events (WD d/t AEs), and serious adverse events (SAEs) (17), as well as mortality among patients with IA who were treated with bDMARDs and/or tsDMARDs. Our objective is to explore whether specific participant, drug classes, and trial characteristics (i.e., contextual factors including RoB domains) have a quantitative influence in terms of effect modification and/or distortion due to biases on the observed likelihood of harm from an experimental intervention compared to control comparators in randomised trials. If contextual factors have such an influence, we hope to shed light on their importance to future trial reporting and interpretation of

harm when reporting randomised trials (17).

Protocol and registration

This protocol was developed in accordance with the v1.07 2018 Methodological Expectations for Cochrane Intervention Reviews (MECIR) recommendations of the Cochrane Collaboration (33) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Protocols (PRISMA-P) guidelines (34). The study protocol was pre-specified and registered in PROSPERO on 2020-03-27, CRD number: CRD42020171124.

METHODS AND ANALYSIS

This meta-epidemiological study combines data from a large representative sample of available trials into a single database by assembling trials already included in published systematic reviews. Generic outcome measures that cover important harm domains (*i:* WD, *ii:* WD d/t AEs and *iii:* SAEs (17)) and mortality will constitute the dependent variable(s) in the database. Harm effects in relation to the use of targeted therapies will be analysed to determine whether they are affected by contextual factors among population, drug classes (e.g., biologics vs small molecules) and trial characteristics.

Eligibility criteria

We will search MEDLINE (via PubMed) for systematic reviews (published since April 2015) or Cochrane reviews. From these systematic reviews, included randomised trials will (independent of publication year) be eligible if they fulfil our inclusion criteria (see table 1 for PICO framework), with at least one group randomly allocated to bDMARD and/or tsDMARD.

The interventions of interest are targeted therapies (i.e., bDMARDs and tsDMARDs) approved by either EMA or FDA to date, treating IA conditions in adult populations; this pharmacological distinction will also be used for separate stratified analyses. These therapies will include bDMARDs: abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, guselkumab, infliximab, ixekizumab, rituximab, sarilumab, secukinumab, tocilizumab, ustekinumab, and tsDMARDs: apremilast, baricitinib, filgotinib, tofacitinib and upadacitinib.

Only RCTs included in an existing systematic review of patients with inflammatory arthritis (RA, PsA, and AxSpA [including AS]) will be considered for eligibility. We will exclude reviews (i.e., not look for trials) that have been withdrawn. Furthermore, only RCTs from the eligible systematic reviews where the full text is available in English will be included. There will be no restriction on publication year of the individual RCTs.

*Table 1. Research objective described using PICO**

Participants	**Adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), axial spondyloarthritis (axSpA) or ankylosing spondylitis (AS).**
Intervention	Targeted therapies (i.e., bDMARDs and tsDMARDs)
Comparison	Placebo, standard care or waiting list/no intervention, active comparator and unclear (i.e. comparison described in insufficient detail to fit within the other categories).
Outcome(s)	Number of withdrawals (WDs), number of WDs due to adverse events (WD d/t AEs), number of serious adverse events (SAEs) and number of patients who died.

*PICO - participants, intervention, comparison, and outcome.

Information sources and search strategy

We will search MEDLINE (via PubMed) for eligible meta-analyses or systematic reviews of trials published since April 2015 and eligible Cochrane reviews using the search algorithm shown in table 2:

Table 2. Search strategy

(arthritis[tiab] OR spondyloarthritis[tiab] OR ankylosing[tiab] OR psoriatic[tiab] OR Spondylarthropathies[tiab] OR rheumatoid[tiab] OR Psoriasis[tiab])

AND

("disease-modifying antirheumatic drugs"[tiab] OR "biological agent*"[tiab] OR biologics*[tiab] OR DMARD[tiab] OR abatacept[tiab] OR adalimumab[tiab] OR anakinra[tiab] OR apremilast[tiab] OR baricitinib[tiab] OR certolizumab[tiab] OR etanercept[tiab] OR filgotinib[tiab] OR golimumab[tiab] OR guselkumab[tiab] OR infliximab[tiab] OR ixekizumab[tiab] OR rituximab[tiab] OR sarilumab[tiab] OR secukinumab[tiab] OR tocilizumab[tiab] OR tofacitinib[tiab] OR upadacitinib[tiab] OR ustekinumab[tiab])

AND

((“Systematic Review”[pt] OR Meta-Analysis[pt] OR meta-analysis[tiab] OR “systematic review”[tiab] OR meta-analys*[pt] OR meta-analys*[ti] OR metaanalys*[ti] OR meta-regress*[tiab] OR metaregress*[tiab]

AND ("2015/04/01"[Date - Publication]: "3000"[Date - Publication]))

OR “Cochrane Database Syst Rev” [jour])

Study selection

Two independent reviewers (JB and EM, with support from SMN/RC) will screen the systematic reviews based on title and abstract, in accordance with eligibility criteria. The same two reviewers will assess the full systematic review texts for eligibility of the reviews and subsequently select the RCTs from the reviews that are eligible, according to our objectives. We will obtain the full text if at least one of the reviewers considers an RCT to be potentially eligible during the screening process. Disagreements will be resolved by consensus or by consulting a third reviewer (RC). EndNote X9.2 software will be used to manage the reviews and RCT records retrieved from the search.

Data collection process

Two reviewers (JB and EM) will extract data using a predefined, standardised data extraction form, and in case of uncertainty a third reviewer (SMN/RC) will be consulted. If a trial is included in more than one review, the trial will be registered and counted/included once.

Review Level: From the reviews, we will extract data on review registration number, year of publication, first author’s name, number of RCTs eligible for our study, and the condition and intervention studied, according to the review title.

Randomised Trial Level: From the trials, we will extract data on first author’s name, publication ID, trial duration, duration until switch (e.g., relevant for adaptive trial designs), rescue, early escape or cross over, number of participants in each arm, and treatment given in the active and comparator arms (i.e., following the PICO framework). Treatment in the comparator arm will be grouped into the following predefined categories: (*i*) placebo; (*ii*) standard care or waiting list/no intervention; (*iii*)

active comparator, or as an ultimate last option (*iv*) unclear. Outcome measures and data extraction of trial and participant characteristics are specified below and listed in table 3.

Participant characteristics in individual studies

Data on the following trial eligibility criteria will be extracted:

- Binary indicator (0 or 1) of inflammation scored as 1 with ≥1 of the following criteria: erythrocyte sedimentation rate (ESR) ≥28 mm/hour, CRP level ≥0.3 mg/dL, and/or morning stiffness lasting ≥45 minutes
- minimum AND maximum required number of swollen joint counts (SJC)
- minimum AND maximum required number of tender joint counts (TJC)
- minimum AND maximum allowed disease duration
- rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide antibody (anti-CCP) and/or anti-cyclic citrullinated peptide antibody 2 (CCP2) status

In order to stratify trials according to the DMARD history of their included patients, we will ask the following signalling question: Had the participants, prior to inclusion, potentially exhausted the treatment potential of at least one class of DMARD—either conventional synthetic DMARDs (i.e., [csDMARD], bDMARD, or tsDMARD)?

- csDMARD-naïve (patients were either csDMARD naïve or had not exhausted the treatment potential of at least one csDMARD)
- csDMARD-IR (csDMARD inadequate responders), where patients had exhausted at least one csDMARD option previously
- bDMARD or tsDMARD-IR (bDMARD or tsDMARD inadequate responders), patients had inadequate response to at least one previous bDMARD or tsDMARD. Inclusion in this group entails exclusion from other DMARD history groups.

Patients' concomitant medication (background) of DMARDs during the trial period will be ordered in the following three levels:

- methotrexate (MTX)
- csDMARDs other than MTX
- bDMARDs or tsDMARDs

We will extract information about how the three groups were handled at randomisation, potentially enabling us to cluster the trials into one of the following five levels: (*i*) Naïve (i.e., patients had never used the drug[s] of interest); (*ii*) Not using

(i.e., the study included only patients who were currently not using the drug[s] of interest); (*iii*) Discontinued (i.e., patients were not allowed to continue drug[s] of interest; (iv) Continued (i.e., patients were allowed to continue drug[s] of interest); and (*v*) Not reported (unclear: no information was reported on this matter). In the case of axSpa, NSAID will be extracted and considered equivalent to csDMARDs.

Data on the following aggregate (average/median) patient baseline characteristics will be extracted: age, female (proportion), disease duration (years), ESR (mm/hour), CRP (mg/dL), Disease activity score, RF positive (proportion), anti-CCP positive (proportion), anti-CCP2 positive (proportion), SJC, TJC, health assessment questionnaire—disability index (HAQ-DI), physician global assessment (e.g., Visual Analogue Scale [VAS]), patient global assessment (e.g., VAS), and patient-reported pain on visual analogue scales of 0–100 mm (e.g., VAS).

Risk of bias and trial characteristics in individual studies

Many published reviews include some form of RoB assessment (i.e., at least for the most frequently used RoB domains) for each individual trial; these assessments will be mapped to the best of our ability to correspond to the Cochrane RoB v.1 (35). The RoB will also be assessed by one of the two reviewers (JB or EM) and subsequently compared with the original bias and internal validity assessments' in the review, from which it was sampled.

Within each full-text trial report, we will apply the following domains of the original Cochrane RoB tool (i.e., RoB v.1.0) (35), which comprise methods for:

- sequence generation/maintaining allocation concealment (selection bias)
- blinding both patients and personnel (performance bias)
- management/analysis/reporting of incomplete outcome data (attrition bias)

Each of these three domains will be rated as high risk, low risk, or unclear RoB (35). In case of uncertainty, another reviewer (SMN/RC) will be consulted. Any discrepancy between RoB assessment sources will be resolved by discussion among the authors.

The following additional bias sources will also be assessed, and data will be extracted from them:

- single *vs*. multi-site trials (36)
- small *vs*. large trials (where small will pragmatically be defined as <100 patients per arm) (37, 38)
- source of funding grouped into one of the following five categories: (*i*) 100% industry (pharmaceutical/device company) funded; (*ii*) mixed funding (e.g., non-industry and industry; (*iii*) provision of drug only; (*iv*) 100% non-profit funded; and (*v*) unclear/undisclosed funding (39)

Outcome measures

Data extraction for each RCT will include the number of patients who died, and the numbers of patients with any of the following "generic events": (*i*) all withdrawals (WDs); (*ii*) WDs due to AEs; and (*iii*) SAEs (17). If the number of individual patients with SAEs is not reported, we will extract the number of reported SAEs instead.

Where reasons are provided to explain the SAEs, they will be categorised according to MedDRA v.23.0 [(*i*) Infections and infestations; (*ii*) Neoplasms benign, malignant and unspecified (including cysts and polyps); (*iii*) Cardiac and vascular disorders; or (*iv*) others]. If patients in the comparison group later are offered the intervention (i.e., switching to the intervention group), the number of events before the switch will be used as the endpoint of choice (i.e., before introducing adaptive trial designs).

Summary measures

For each binary outcome, we will extract data corresponding to the 2×2 table, summarising the number of patients who experienced the outcome in each comparison group as reported in the randomised trial and the total number of patients randomly assigned in each group. For outcomes collected and reported corresponding to different time points, we will select the time point with the longest follow-up while still respecting the primary research design (e.g., before introducing an adaptive trial design, and/or open label extension) (40, 41).

Because all the outcome measures are dichotomous, the relative Risk Ratios (RRs) with 95% confidence intervals (95%CI) will be the preferred measure of relative effect, and these can subsequently be applied to the baseline or control group risks to generate absolute risks (42). When appropriate for the very rare adverse events, we will use a continuity correction (adding to all cells a factor proportional to the reciprocal of the size of the contrasting study group), as

suggested by Sweeting and colleagues (43), to take into account zero cell counts in one group only. This continuity correction will be applied when no events are observed in one study arm of a trial. The correction is inversely proportional to the relative size of the opposite of the study (21, 43). Continuity correction for the experimental intervention arm is 1/(*R*+1); *R* is the ratio of control group to intervention group sizes (i.e., $R = n_C/n_I$). Similarly, the continuity correction for the control comparator arm is *R*/(*R*+1). We expect that most trials will report only a few SAEs and deaths, so the odds ratios and 95%CI's will also (for the purpose of sensitivity analysis) be calculated with the use of the *Peto* method. Because the expected events are sparse and all trials will have similar durations of follow-up for their treatment groups, the use of both risk ratios and odds ratios should represent a valid approach to assessing the "*risk*" associated with the use of synthetic or biological intervention in patients with IA. The number of studies to be included will be determined by the number of eligible trials available in the systematic reviews, hence a formal sample size calculation would not be meaningful. However, we expect the search to bring around 175 eligible trials (RA: 117, PsA: 15, AxSpA: 43) based on a few large systematic reviews within the field (44-48).

Synthesis of results

Outcome events will be coded so that an RR direction of more than 1 indicates a potentially harmful effect of the experimental intervention (i.e., $RR = [r_I/n_I]/ [r_C/n_C]$). Mixed effects Restricted Maximum Likelihood (REML) meta-analyses (49) will be used to combine the harm effects across RCTs (based on their log [*RR*]) (50); we will apply the trial ID as a random effect, while applying the review ID (from which the trial was sampled) as a fixed effect in order to model the hierarchical structure of the data sampling (51).

Heterogeneity across randomised comparisons will be assessed by using the Cochrane Q test (52), interpreted based on the I^2 inconsistency index (53), and quantified by the estimate for between-trial variance (τ^2), estimated as T^2 (54). The effect of population and trial characteristics (listed below) on the between-trial variance will be calculated by univariably adding a fixed factor for the specific characteristic in the model. If introducing a specific covariate into the meta-model reduces the observed between-trial variance (T^2), this result will be considered an indication of a potentially important effect modifier (55).

Further analyses might (if possible) include multivariable models (56). Observational by nature, meta-epidemiological studies like the present should be expected to have some degree of meta-confounding because prognostic factors might be unequally distributed between studies exposed (trial characteristic positive) or not. We will attempt to adjust for possible confounding covariates (i.e. "de-confound") the inference. That is, we will explore the ability to adjust for any important preexposure covariate ' *C* ' (i.e., something that happened before the "*study design variable of interest was generated*") that is potentially unequally distributed between the meta-epidemiological exposure groups (E: Exposed vs. Unexposed), which is ALSO an ancestor (i.e., likely cause) of the trial outcome (i.e., a more exaggerated risk of harm): $M_E \leftarrow C \rightarrow Y_E$ (56).

Power and sample size considerations

Although the number of trials being eligible in the synthesis is fixed based on the premises, there are several factors that can influence the statistical power in meta-analyses, such as the total number of eligible RCTs (k), their individual sample sizes (N_1, N_2, ….., N_k), and the number of harm events observed in each of the trials (e_1, e_2, …., e_k). Since we want to study harmful effects of various experimental interventions, even very small effect sizes would be informative. Substantial heterogeneity – between exposed vs unexposed subgroups will affect the precision of our meta-analytic estimates, and thus our potential to find significant differences between strata. Thus, on an *ad hoc* basis, we performed some analyses exploring how large the difference between two strata had to be in order for us to be able to detect it, given the expected number of studies at our disposal (say, at least 200 trials across conditions) (8, 29, 57, 58). An *ad hoc* subgroup power analysis was conducted in R using the `power.analysis.subgroup` function, based on the approach described by Hedges and Pigott (59, 60): Assuming that we want to compare two independent Odds Ratios, $OR_1 = 2$ *vs* $OR_2 = 1$, with a conservative guestimate of the standard error of the log(OR) values of 0.15 (61), we would have a good statistical power to detect a difference between strata (90.4%). The output also tells us that, all else being equal, the effect size difference ($\log[OR_1]$ *vs* $\log[OR_2]$) needs to be at least 0.595 in order to reach sufficient power.

Table 3. Population and trial characteristics

Trial eligibility criteria:
Minimum and maximum required number of swollen joint counts
Minimum and maximum required number of tender joint counts
Minimum and maximum required C-reactive protein
Minimum and maximum required Erythrocyte sedimentation rate
Minimum and maximum allowed disease duration
Rheumatoid factor
Anti-cyclic citrullinated peptide antibody status
Anti-cyclic citrullinated peptide antibody 2 status
DMARD history:
csDMARD-naïve
csDMARD-IR (csDMARD inadequate responders)
bDMARD or tsDMARD-IR (bDMARD or tsDMARD inadequate responders)
Medication background of DMARDs:
Methotrexate
-Naïve
-Not using
-Discontinued
-Continued
-Not reported
csDMARDs other than methotrexate
-Naïve
-Not using
-Discontinued
-Continued
-Not reported
bDMARDs or tsDMARDs.
-Naïve
-Not using
-Discontinued
-Continued
-Not reported
Aggregate (e.g., average/median) patient baseline characteristics:
Age

Female (%)
Disease duration
Erythrocyte sedimentation rate
C-reactive protein
Disease activity score
RF positive (%)
Anti-CCP positive (%)
CCP2 positive (%)
Swollen joint counts
Tender joint counts
Health assessment questionnaire—disability index
Physician global assessment of disease activity
Patient global assessment of disease activity
Patient-reported pain on visual analogue scales of 0–100 mm

Risk of bias across studies

Stratified meta-analyses will be used for tests of interaction between harms and the trial RoB (listed in Table 4) and trial characteristics collected as described above.

Table 4. Risk of bias

Cochrane risk of bias domains:
· Risk of selection bias
· Risk of performance bias
· Risk of attrition bias
· Overall risk of bias*
Additional bias sources:
· Single vs. multi-site trials
· Small vs. large trials
· Source of funding

*For each trial, the overall RoB will be classified as low (i.e., low RoB for all three domains); high (i.e., high RoB for one or more domains); or unclear (i.e., unclear RoB for one or more domains in the absence of high RoB).

DISCUSSION

The Outcome Measures in Rheumatology (OMERACT) initiative established the Contextual Factors Working Group to guide the understanding, identification and handling of contextual factors for clinical trials, with most of the current emphasis' being on net benefit inferred from a rheumatology trial (62). This meta-epidemiological study will work from the original definition of what constitutes a contextual factor, as defined in the introduction. We will explore and hope to reveal the possible impact of contextual factors (i.e., population and trial characteristics) and RoB domains of three different (but related) harm measures, as well as deaths (63). Knowing which factors are associated with a causal model for harms—either as effect modifiers or distortions of the outcome due to bias—is important for improving investigation and reporting of harms in future trials (64). If future trials report harms according to important contextual factors, meta-analyses would be able to investigate contextual factors for harms without relying on getting access to individual patient data. Such meta-research might identify subgroups among rheumatic disease patients that are at higher risk of experiencing harms. Such information would provide important evidence for future treatment guideline development. Ultimately the doctor will be able to differentiate the risk of intervention based on the patient's characteristics. This has the potential to enhance informed decision-making and effect therapeutic interventions applied in practice, leading to safer treatment of individual patients and increase efficiency in the health care system.

This study has several strengths. This will be a comprehensive risk of harm analysis of bDMARDs and tsDMARDs across multiple IA diagnoses unlike previous assessments. The study selection, data extraction and RoB assessment will be done by two independent reviewers, the data extraction will be extensive as it will include data on many different contextual factors and risk of bias items. Finally, we will only include RCTs to avoid inherent problems when investigating potential effect modifiers from non-RCT evidence.

Nevertheless, several limitations should be considered. First, the analyses may be limited by poor reporting, and data is likely to be lacking for certain contextual factors (i.e., exposures) and uncommon harms (i.e. outcomes). Second, by relying on the search results of published reviews, we assume that we retrieve a representative sample for our analysis, however, it is possible that potentially useful trials may be omitted, e.g. due to very specific eligibility criteria in the reviews or very recent trials that has not yet been included in a systematic review, which could theoretically influence our results. Third, other characteristics that we do not consider may be relevant. Fourth, meta-regression assessments, despite including only RCTs, are observational by nature and their results may by themselves be confounded by other factors(65). Finally, the meta-regression assessments involving aggregated data may be affected by ecological fallacy and could potentially be misleading(66).

Patient and public involvement

Patients and/or the public were not involved in designing study concept or drafting of the protocol.

ETHICS AND DISSEMINATION

Because our study does not collect primary data, no formal ethical assessment and informed consent are required. The study will be disseminated in a peer-reviewed publication.

References

1. Ledingham J, Snowden N, Ide Z. Diagnosis and early management of inflammatory arthritis. BMJ. 2017;358:j3248.
2. Raychaudhuri SP, Deodhar A. The classification and diagnostic criteria of ankylosing spondylitis. J Autoimmun. 2014;48-49:128-33.
3. Miyabe Y, Miyabe C, Luster AD. LTB4 and BLT1 in inflammatory arthritis. Semin Immunol. 2017;33:52-7.
4. McInnes IB, Schett G. The Pathogenesis of Rheumatoid Arthritis. New England Journal of Medicine. 2011;365(23):2205-19.
5. Janke K, Biester K, Krause D, Richter B, Schürmann C, Hirsch K, et al. Comparative effectiveness of biological medicines in rheumatoid arthritis: systematic review and network meta-analysis including aggregate results from reanalysed individual patient data. Bmj. 2020;370:m2288.
6. Schweikert B, Malmberg C, Núñez M, Dilla T, Sapin C, Hartz S. Cost-effectiveness analysis of ixekizumab versus secukinumab in patients with psoriatic arthritis and concomitant moderate-to-severe psoriasis in Spain. BMJ Open. 2020;10(8):e032552.
7. Hartman L, Rasch LA, Klausch T, Bijlsma HWJ, Christensen R, Smulders YM, et al. Harm, benefit and costs associated with low-dose glucocorticoids added to the treatment strategies for rheumatoid arthritis in elderly patients (GLORIA trial): study protocol for a randomised controlled trial. Trials. 2018;19(1):67.
8. Christensen AW, Tarp S, Furst DE, Dossing A, Amris K, Bliddal H, et al. Most Trial Eligibility Criteria and Patient Baseline Characteristics Do Not Modify Treatment Effect in Trials Using Targeted Therapies for Rheumatoid Arthritis: A Meta-Epidemiological Study. PLoS One. 2015;10(9):e0136982.
9. Callhoff J, Sieper J, Weiss A, Zink A, Listing J. Efficacy of TNFalpha blockers in patients with ankylosing spondylitis and non-radiographic axial spondyloarthritis: a meta-analysis. Ann Rheum Dis. 2015;74(6):1241-8.
10. Goulabchand R, Mouterde G, Barnetche T, Lukas C, Morel J, Combe B. Effect of tumour necrosis factor blockers on radiographic progression of psoriatic arthritis: a systematic review and meta-analysis of randomised controlled trials. Ann Rheum Dis. 2014;73(2):414-9.
11. Oo C, Kalbag SS. Leveraging the attributes of biologics and small molecules, and releasing the bottlenecks: a new wave of revolution in drug development. Expert review of clinical pharmacology. 2016;9(6):747-9.
12. Komaki Y, Yamada A, Komaki F, Kudaravalli P, Micic D, Ido A, et al. Efficacy, safety and pharmacokinetics of biosimilars of anti-tumor necrosis factor-alpha agents in rheumatic diseases; A systematic review and meta-analysis. J Autoimmun. 2017;79:4-16.
13. So A, Inman RD. An overview of biologic disease-modifying antirheumatic drugs in axial spondyloarthritis and psoriatic arthritis. Best Pract Res Clin Rheumatol. 2018;32(3):453-71.
14. Gadina M, Le MT, Schwartz DM, Silvennoinen O, Nakayamada S, Yamaoka K, et al. Janus kinases to jakinibs: from basic insights to clinical practice. Rheumatology (Oxford, England). 2019;58(Supplement_1):i4-i16.

15. Sarzi-Puttini P, Ceribelli A, Marotto D, Batticciotto A, Atzeni F. Systemic rheumatic diseases: From biological agents to small molecules. Autoimmun Rev. 2019;18(6):583-92.

16. Winthrop KL. The emerging safety profile of JAK inhibitors in rheumatic disease. Nat Rev Rheumatol. 2017;13(4):234-43.

17. Ioannidis JP, Evans SJ, Gøtzsche PC, O'neill RT, Altman DG, Schulz K, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. Annals of internal medicine. 2004;141(10):781-8.

18. Singh JA, Wells GA, Christensen R, Tanjong Ghogomu E, Maxwell L, Macdonald JK, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database Syst Rev. 2011(2):Cd008794.

19. Minozzi S, Bonovas S, Lytras T, Pecoraro V, Gonzalez-Lorenzo M, Bastiampillai AJ, et al. Risk of infections using anti-TNF agents in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: a systematic review and meta-analysis. Expert Opin Drug Saf. 2016;15(sup1):11-34.

20. Gron KL, Arkema EV, Glintborg B, Mehnert F, Ostergaard M, Dreyer L, et al. Risk of serious infections in patients with rheumatoid arthritis treated in routine care with abatacept, rituximab and tocilizumab in Denmark and Sweden. Ann Rheum Dis. 2019;78(3):320-7.

21. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006;295(19):2275-85.

22. Salgado E, Maneiro JR, Carmona L, Gomez-Reino JJ. Safety profile of protein kinase inhibitors in rheumatoid arthritis: systematic review and meta-analysis. Ann Rheum Dis. 2014;73(5):871-82.

23. Sepriano A, Kerschbaumer A, Smolen JS, van der Heijde D, Dougados M, van Vollenhoven R, et al. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2019 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2020.

24. Mease P, Charles-Schoeman C, Cohen S, Fallon L, Woolcott J, Yun H, et al. Incidence of venous and arterial thromboembolic events reported in the tofacitinib rheumatoid arthritis, psoriasis and psoriatic arthritis development programmes and from real-world data. Ann Rheum Dis. 2020;79(11):1400-13.

25. Rahman MU, Buchanan J, Doyle MK, Hsia EC, Gathany T, Parasuraman S, et al. Changes in patient characteristics in anti-tumour necrosis factor clinical trials for rheumatoid arthritis: results of an analysis of the literature over the past 16 years. Ann Rheum Dis. 2011;70(9):1631-40.

26. Gluud LL. Bias in clinical intervention research. American journal of epidemiology. 2006;163(6):493-501.

27. Boers M, Kirwan JR, Wells G, Beaton D, Gossec L, d'Agostino MA, et al. Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. J Clin Epidemiol. 2014;67(7):745-53.

28. Savović J, Jones HE, Altman DG, Harris RJ, Jüni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. Annals of internal medicine. 2012;157(6):429-38.

29. Ballegaard C, Jorgensen TS, Skougaard M, Strand V, Mease PJ, Kristensen LE, et al. Trial Characteristics as Contextual Factors When Evaluating Targeted Therapies in Patients With Psoriatic Disease: A Meta-Epidemiologic Study. Arthritis Care Res (Hoboken). 2018;70(8):1206-17.

30. Bae JM. Meta-epidemiology. Epidemiology and health. 2014;36:e2014019.

31. Bolvig J, Juhl CB, Boutron I, Tugwell P, Ghogomu EAT, Pardo JP, et al. Some Cochrane risk-of-bias items are not important in osteoarthritis trials: a meta-epidemiological study based on Cochrane reviews. J Clin Epidemiol. 2018;95:128-36.

32. Dossing A, Tarp S, Furst DE, Gluud C, Wells GA, Beyene J, et al. Modified intention-to-treat analysis did not bias trial results. J Clin Epidemiol. 2016;72:66-74.

33. Higgins JPT LT, Chandler J, Tovey D, Churchill R. Methodological Expectations of Cochrane Intervention Reviews. Cochrane: London, Version 1.06. 2018.

34. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;350:g7647.

35. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.

36. Dechartres A, Boutron I, Trinquart L, Charles P, Ravaud P. Single-center trials show larger treatment effects than multicenter trials: evidence from a meta-epidemiologic study. Ann Intern Med. 2011;155(1):39-51.

37. Nüesch E, Trelle S, Reichenbach S, Rutjes AW, Tschannen B, Altman DG, et al. Small study effects in meta-analyses of osteoarthritis trials: meta-epidemiological study. Bmj. 2010;341:c3515.

38. Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. Ann Intern Med. 2001;135(11):982-9.

39. Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. Cochrane Database Syst Rev. 2017;2:Mr000033.

40. Pickles T, Alten R, Boers M, Bykerk V, Christensen J, Christensen R, et al. Adaptive Trial Designs in Rheumatology: Report from the OMERACT Special Interest Group. J Rheumatol. 2019;46(10):1406-8.

41. Buch MH, Silva-Fernandez L, Carmona L, Aletaha D, Christensen R, Combe B, et al. Development of EULAR recommendations for the reporting of clinical trial extension studies in rheumatology. Ann Rheum Dis. 2015;74(6):963-9.

42. Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, et al. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. J Clin Epidemiol. 2013;66(2):158-72.

43. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med. 2004;23(9):1351-75.

44. JA. S, A. H, E. TG, AS. M, LJ. M, R. B, et al. Biologics or tofacitinib for people with rheumatoid arthritis unsuccessfully treated with biologics: a systematic review and network meta-analysis. The Cochrane database of systematic reviews. 2017;3:CD012591.

45. JA. S, A. H, AS. M, E. TG, ME. S-A, R. B, et al. Biologics or tofacitinib for people with rheumatoid arthritis naive to methotrexate: a systematic review and network meta-analysis. The Cochrane database of systematic reviews. 2017;5:CD012657.

46. JA. S, A. H, E. TG, AS. M, P. T, GA. W. Biologic or tofacitinib monotherapy for rheumatoid arthritis in people with traditional disease-modifying anti-rheumatic drug (DMARD) failure: a Cochrane Systematic Review and network meta-analysis (NMA). The Cochrane database of systematic reviews. 2016;11:CD012437.

47. Fidahic M, Jelicic Kadic A, Radic M, Puljak L. Celecoxib for rheumatoid arthritis. Cochrane Database Syst Rev. 2017;6:Cd012095.

48. Lawson DO, Eraso M, Mbuagbaw L, Joanes M, Aves T, Leenus A, et al. Tumour necrosis factor inhibitor dose reduction for axial spondyloarthritis: A systematic review and meta-analysis of randomized controlled trials. Arthritis Care Res (Hoboken). 2020.

49. Normand S-LT. Meta-analysis: formulating, evaluating, combining, and reporting. Statistics in Medicine. 1999;18(3):321-59.

50. van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. Stat Med. 2002;21(4):589-624.

51. Sterne JA, Jüni P, Schulz KF, Altman DG, Bartlett C, Egger M. Statistical methods for assessing the influence of study characteristics on treatment effects in 'meta-epidemiological' research. Stat Med. 2002;21(11):1513-24.

52. Cochran WG. The combination of estimates from different experiments. Biometrics. 1954;10(1):101-29.

53. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Bmj. 2003;327(7414):557-60.

54. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? Stat Med. 2002;21(11):1559-73.

55. Sterne JA, Juni P, Schulz KF, Altman DG, Bartlett C, Egger M. Statistical methods for assessing the influence of study characteristics on treatment effects in 'meta-epidemiological' research. Stat Med. 2002;21(11):1513-24.

56. Christensen R, Berthelsen DB. Controversy and Debate on Meta-epidemiology. Paper 3: Causal inference from meta-epidemiology: a reasonable goal, or wishful thinking? J Clin Epidemiol. 2020;123:131-2.

57. S. T, D. EF, M. B, G. L, H. B, U. T, et al. Risk of serious adverse effects of biological and targeted drugs in patients with rheumatoid arthritis: a systematic review meta-analysis. Rheumatology (Oxford, England). 2017;56(3):417-25.

58. Andreasen RA, Kristensen LE, Baraliakos X, Strand V, Mease PJ, de Wit M, et al. Assessing the effect of interventions for axial spondyloarthritis according to the endorsed ASAS/OMERACT core outcome set: a meta-research study of trials included in Cochrane reviews. Arthritis Res Ther. 2020;22(1):177.

59. Hedges LV, Pigott TD. The power of statistical tests for moderators in meta-analysis. Psychol Methods. 2004;9(4):426-45.

60. Hedges LV, Pigott TD. The power of statistical tests in meta-analysis. Psychol Methods. 2001;6(3):203-17.

61. JA. S, C. C, S. N, T. C, M. T, R. C, et al. Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis. Lancet (London, England). 2015;386(9990):258-65.

62. Nielsen SM, Uggen Rasmussen M, Boers M, D AvdW, de Wit M, T GW, et al. Towards consensus in defining and handling contextual factors within rheumatology trials: an initial qualitative study from an OMERACT working group. Ann Rheum Dis. 2020.

63. Nielsen SM, Storgaard H, Ellingsen T, Shea BJ, Wells GA, Welch VA, et al. Population characteristics as important contextual factors in rheumatological trials: an exploratory meta-epidemiological study from an OMERACT Working Group. Ann Rheum Dis. 2020;79(10):1269-76.

64. Finger ME, Boonen A, Woodworth TG, Escorpizo R, Christensen R, Nielsen SM, et al. An OMERACT Initiative Toward Consensus to Identify and Characterize Candidate Contextual Factors: Report from the Contextual Factors Working Group. J Rheumatol. 2017;44(11):1734-9.

65. Thompson SG, Higgins JP. Treating individuals 4: can meta-analysis help target interventions at individuals most likely to benefit? Lancet. 2005;365(9456):341-6.

66. Berlin JA, Santanna J, Schmid CH, Szczech LA, Feldman HI. Individual patient- versus group-level data meta-regressions for the investigation of treatment effect modifiers: ecological bias rears its ugly head. Stat Med. 2002;21(3):371-87.

PRISMA-P (preferred reporting items for systematic review and meta-analysis protocols) 2015 checklist: recommended items to address in a systematic review protocol

Section and topic	Item No	Checklist item
Administrative information		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review (Line 3)
Update	1b	If the protocol is for an update of a previous systematic review, identify as such (n/a)
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number (Line 111)
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author (Line 11-55)
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review (Line 65-70)
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments (n/a)
Support:		
Sources	5a	Indicate sources of financial or other support for the review (Line 73)
Sponsor	5b	Provide name for the review funder and/or sponsor (Line 76-79)
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol (n/a)
Introduction		
Rationale	6	Describe the rationale for the review in the context of what is already known (Line 166-181)
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) (Table 1, line 235)
Methods		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review (Line 215-233)
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage (238-241)
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated (Table 2, Line 243)
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review (Line 253)
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) (Line 245-254)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators (Line 257-260)
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications (Line 262-358)
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale (Line 262-358)
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis (Line 321-346)
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesized (Line 392-418 and line 443-450)
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) (Line 360-407)

	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) (Line 408-418)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned (n/a)
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) (n/a)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) (n/a)