Concise protocol

Outcome Influencing Contextual Factors in Rheumatoid Arthritis: Protocol for a Scoping Review

Authors/collaborators

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Abstract

Background: The Outcome Measures in Rheumatology (OMERACT) Contextual Factor Working Group defines Outcome Influencing Contextual Factors (OI-CFs) as prognostic factors of relevance to longitudinal observational studies (LOS) and hence, potential confounders. The working group aims to select these potential confounders to be collected in all studies to improve interpretation of study results in rheumatology.

Objectives: To identify baseline variables commonly adjusted for in LOS in rheumatoid arthritis (RA).

Design: Scoping review.

Eligibility criteria: Longitudinal observational studies (e.g., based on data from registries) in RA that investigate the association between any exposures or interventions and clinical or patient-centered outcomes, and published in English.

Sources of evidence: Studies included in a previously conducted systematic review, which in turn was based on searches in Medline, Embase, Google Scholar, the Agency for Healthcare Research and Quality (AHRQ) Registry of Patient Registries (RoPR), and ClinicalTrials.gov.

Charting methods: Various study characteristics, as well as data on all variables adjusted for in the studies' analyses including the domain and measure.

Perspectives and dissemination: This study may provide insights into candidate OI-CFs and may support the development of a consensus-based set of important OI-CFs to be considered in LOS of RA and possibly other rheumatic conditions. The results will be disseminated in a peer-reviewed journal and within OMERACT.

Background

The Outcome Measures in Rheumatology (OMERACT) initiative initially defined a Contextual Factor (CF) as a "*variable that is not an outcome of the study but needs to be recognized (and measured) to understand the study results*."[1] Since then, the OMERACT CF Working Group has achieved consensus on an operational definition of CF's, including three types: (*i*) Effect Modifying CFs (EM-CFs), (*ii*) Outcome Influencing CFs (OI-CFs), and (*iii*) Measurement Affecting CFs (MA-CFs)[2]. The working group defines an OI-CF as a variable that is prognostically important as it influences the outcome and, hence, such variables may confound the results of longitudinal observational studies (LOS) or quasi-controlled trials if they lead to the exposure and thus are important to take into account in the analyses (i.e. in order to *de-confound* the inferential analyses). Hence, variables commonly adjusted for in LOS are likely to be potentially important OI-CFs. For this review, we will focus on rheumatoid arthritis (RA) as it is one of the most commonly investigated diseases in rheumatology.

Objective

To identify baseline variables frequently adjusted for in LOS in RA (i.e. potential OI-CFs).

Design

Scoping review based on the search and study selection by the systematic review conducted by Lopez-Olivo et al[3]. Their systematic review aimed to identify outcome domains and measures, whereas we are looking for baseline variables used for de-confounding.

Protocol and registration

This protocol was uploaded on the Parker Institute's website (http://www.parkerinst.dk/research) and registered at Open Science Framework (OSF; https://osf.io/registries) prior to initiating the work.

Eligibility criteria

We will initially use the search and study selection results from the systematic review by Lopez-Olivo et al[3], which were based on the following eligibility criteria: LOS (e.g., based on data from registries) including individuals with RA, assessing clinical or patient-centered outcomes (as defined by the Patient Centered Outcomes Research Institute [PCORI][4]), and reported in at least one published article written in English since 2013. Studies were excluded if they could be considered an open-label extension of a clinical trial or if the registry only included individuals having specific manifestations or belonging to a specific sub-sample of the overall study.

For the current review, we will additionally require that the publications have a specific research question and that they investigate the association between any exposures or interventions and

clinical or patient-centered outcomes in individuals with RA. We will exclude cross-sectional studies, i.e., eligible studies need to include at least two time points regardless of timeframe. Furthermore, the publication needs to be available as a full-text version, and, hence, conference abstracts will be excluded. Conference abstracts are unlikely to report detailed information on baseline variables used for adjustment in the models due to word limitations. The focus of this study is on the information reported in full texts.

Information sources, search, and study selection

The systematic review by Lopez-Olivo et al.[3] searched Google Scholar, the Agency for Healthcare Research and Quality (AHRQ) Registry of Patient Registries (RoPR) and ClinicalTrials.gov, and subsequently MEDLINE (via Ovid) and Embase (via Ovid).

Lopez-Olivo et al.[3] initially identified URLs for registries/LOS by searching each of the names of the 193 United Nations member states combined with the keywords 'rheumatoid' and 'registry'. The AHRQ RoPR and ClinicalTrials.gov were searched using RA and registry-related terms, and hand-searching was used when URLs were missing. Study selection was conducted by two independent pairs of reviewers, and in case of disagreement, a third party was involved. Subsequently, an expert health science librarian used the registry/LOS names, acronyms, and ClinicalTrial.gov identifiers, as well as keywords related to RA and registry or cohort, for searching the MEDLINE and Embase for retrieving articles published until August 2018. For more details (including the specific search terms), see the publication by Lopez-Olivo et al.[3]

For this study, the 1,623 publications included in the systematic review by Lopez-Olivo et al.[3] will be screened based on title and abstract and subsequently assessed based on full text.

The study selection will be conducted by two independent reviewers (MM and AGC/SS), supported by a third reviewer (SMN). In case of disagreement, a senior researcher will be consulted (RC or RA).

Data charting process

The data extraction and initial classification of variables (i.e. matching measures with domains) will be conducted by one reviewer (MM) using a predefined, standardized data extraction form, and validated by a second reviewer (SMN/AGC/SS/AJ). A summary of the data extraction and classifications will be reviewed and discussed among the co-authors.

Data items

The data extraction will be conducted for individual studies, i.e. publications with distinct research questions, regardless of whether they originate from the same registry. This is in contrast to the study by Lopez-Olivo et al.[3], in which data was extracted on the level of registries/overall LOS.

For each study, we will extract the following basic information:

- Last name of the first author
- Publication year
  (earliest publication in case of multiple study reports)
- Registry or LOS acronym and/or registration number
- Number of participants included
- Study population
- Primary exposure or intervention (as applicable)
- Primary comparator (as applicable)
- The primary (or most emphasized) outcome
- Study duration
  (from baseline to latest follow-up)
- Country/-ies where the study was conducted
- Continent/-s where the study was conducted

Primary exposure or intervention and primary outcome will be those explicitly reported as primary or main. Exposure or intervention is anticipated to be categorized according to the following categories: pharmacological, physical/physiotherapeutic, surgical, psychological, dietary, other, unclear/not explicitly reported.

Importantly, we will extract data on ***all*** baseline variables explicitly reported to be adjusted for in the analyses. For each variable, we will extract:

- The variable name used in the publication
- The domain
  (i.e. *what* was measured, such as disease severity)
- The measure
  (i.e., *how* the domain was measured, such as Disease Activity Score-28 for Rheumatoid Arthritis with C-reactive protein (CRP) [DAS28-CRP])
- Potential categories used for categoric variables or cutoffs used for dichotomizing/ categorizing continuous variables
  (e.g., DAS28-CRP [in remission] <2.6 vs DAS28-CRP ≥2.6 [not in remission])
- Whether it is also reported as an outcome of the trial and not only as a confounding variable/covariate.

The measures will be classified within domains (e.g., the DAS28-CRP measure will be matched with the disease severity domain).

Synthesis of results

The study characteristics (i.e. all basic information collected on the studies) will be summarized using descriptive statistics including means (SDs) or medians (range), depending on the distribution of the data, and numbers (percentage). The domains for the adjustment variables (potential OI-CFs) will be summarized using descriptive statistics such as frequencies and percentages, i.e. describing how many of the included studies report each domain. The domains will be ordered according to the contextual factor categories, personal factors (such as age, sex, and race), disease-related factors (such as disease severity, disease duration), and environmental factors (such as healthcare system, place of residence). The measure and categories/cutoffs used will be listed for each domain.

Perspectives and dissemination

The results of this study will provide important insights into variables considered essential to adjust for in RA studies, hence, candidate OI-CFs, and could be an important step towards the development of a consensus-based set of important OI-CFs that should always be considered in RA and possibly rheumatologic non-randomized studies. The results will be reported according to guidelines from the Equator Network (www.equator-network.org), i.e., *Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews* (PRISMA-ScR)[5]. The results will be disseminated in a peer-reviewed article and at OMERACT meetings and possibly other relevant rheumatology congresses/meetings.

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Competing interests

This study has no financial competing interests.

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