Protocol

Patient characteristics and stratification factors reported within rheumatology: A scoping review of randomized trials included in Cochrane reviews

Authors/collaborators

Midhat Kamal[1,2,4]*, Farwa Asim[1,2,3]*, Maria A. Lopez-Olivo[1], Maria E. Suarez-Almazor[1], Maarten de Wit[5], Marieke Voshaar[6], Danielle A van der Windt[7], Maarten Boers[8], Jennifer Petkovic[9], Lars Erik Kristensen[2], Lyn March[10], Peter Tugwell[11], Robin Christensen[2,12], Sabrina M. Nielsen[2,12]

** MK and FA contributed equally. MK and FA are joint first authors.*

1: Department of Health Services Research and Section of Rheumatology and Clinical Immunology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA.
2: The Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark.
3: Shifa College of Medicine, Islamabad, Pakistan.
4: Dow University of Health Sciences (D.U.H.S.), Karachi, Pakistan.
5: OMERACT Patient Research Partner, Amsterdam, the Netherlands.
6: Department of Pharmacy, Sint Maartenskliniek, The Netherlands. Department of Pharmacy, Radboudumc, Nijmegen, the Netherlands.
7: School of Medicine, Keele University, Staffordshire, United Kingdom.
8: Department of Epidemiology & Data Science, and Amsterdam Rheumatology and Immunology Center, Amsterdam University Medical Centers, Vrije Universiteit, Amsterdam, the Netherlands.
9: Bruyère Research Institute, University of Ottawa, Ottawa, Canada.
10: Florance and Cope Professorial Department of Rheumatology, Royal North Shore Hospital and Institute of Bone and Joint Research, Faculty of Medicine and Health, University of Sydney, Sydney, New South Wales, Australia.
11: Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada.
12: Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, Odense, Denmark.

Date: April 25, 2022

ABSTRACT

Background: Contextual factors (CFs) are important for interpreting the results of trials. The so-called 'effect modifying contextual factors' (EM-CFs) are factors modifying the treatment effect in a trial. To ensure consistent reporting and stratification of trial results, allowing for future evidence synthesis, a consensus-based set of important EM-CFs is needed. A first step involves collecting candidate EM-CFs.

Objectives: We will identify and summarize baseline patient characteristics and stratification factors (i.e. potential EM-CFs) reported in trial reports of randomized controlled trials (RCTs) across rheumatology.

Methods: In this scoping review, we will include RCTs published from 2000 onwards, examining any type of intervention versus any comparator in patients with rheumatic and musculoskeletal conditions. The RCTs will be collected by two independent reviewers from the existing systematic reviews by the Cochrane Musculoskeletal Group listed in the Cochrane Database of Systematic Reviews (via the Cochrane Library). Two independent reviewers will extract basic information on the trial, as well as data on all reported baseline and stratification factors in terms of domain (i.e. *what* was measured), measure (i.e., *how* was it measured), and any cutoffs used for making subgroups for subgroup analyses in the trial reports. The data will be summarized using descriptive statistics. Additionally, we will investigate whether some characteristics are more commonly reported for certain diseases and/or intervention types.

Perspectives and dissemination: This scoping review will provide an important overview by mapping potential EM-CFs candidates across rheumatology. This will provide the basis for the next study seeking consensus on important candidate EM-CFs. The results will be disseminated in a peer-reviewed article and at relevant OMERACT meeting activities.

Systematic review registration: *[OSF registration here when closing the protocol]*

BACKGROUND

Evidence-based medicine is essential for developing clinical guidelines, and, hence, shapes clinical practice. However, an average treatment effect estimate from a clinical trial may not be valid for deciding what treatment is best for an individual patient [1-3]. Using the treatment that on average is the most effective will likely do more good than harm, but it is not necessarily cost-effective [1] and it may prevent the use of alternatives that could be more effective for individual patients [4]. In fact, most common drugs have incomplete efficacy, and it has been estimated that the top ten grossing drugs in the United States improve the conditions of only 4-25% of the patients who take them [5]. This leaves a potential for exploring what characterizes the patients who benefit from a treatment and those who do not, and subsequently match patient subgroups with the treatment that best suits them. Key stakeholder organizations, such as regulatory authorities approving new medical treatments, are increasingly focusing on the issue of variation of treatment response among patients [6], and the *European Medicines Agency* (EMA) states "It is not acceptable to assume consistent effects across important subgroups without further investigation or discussion"[7]. Designing interventions to target treatment to those who are most likely to benefit by identifying effect modifiers, is termed stratified medicine (when considering subgroups) [8] or personalized medicine (when individualizing treatment decisions). In addition, such effort may reveal optimal treatment options for certain social groups and thereby reduce health inequity, defined as the presence of unfair and avoidable differences in health between populations [9].

Individual randomized controlled trials (RCTs) are usually designed to have adequate power to detect a difference greater than or equal to a prespecified target difference between intervention and control groups. Such trials will not have the adequate power to detect the same target difference between the effect of the treatment and control in people in a subgroup compared to people in another subgroup (e.g. males vs females), as a four-fold greater sample size is usually needed for an interaction to be statistically significant [4]. Designing RCTs with such large sample sizes is both costly and likely not feasible in practice. Instead, estimating subgroup effects by pooling individual RCTs in a meta-analysis can help to achieve satisfactory power [10 11]. This method relies on sufficient and consistent reporting of data on treatment effects stratified by suspected effect modifiers from each trial. However, such detailed data is currently not available from most trial reports [12-16] – even baseline data for many suspected important effect modifiers [17 18] are often lacking [19]. The lack of sufficient reporting in trial reports prevents any future evidence synthesis exploring possible subgroup effects. Therefore, efforts are needed to improve the reporting of subgroup analyses in trial reports – preferably, the reporting should be consistent and based on a consensus-based list of potentially important effect modifiers of high priority.

The *Outcome Measures in Rheumatology* (OMERACT; omeract.org) initiative is known for establishing consensus on core outcome sets for trials within rheumatology. In 2018, OMERACT established the *Contextual Factors Working Group* (CFWG) to guide the understanding, identification, and handling of so-called 'contextual factors' (CFs) for RCTs in rheumatology [17 20]. Recent work has dealt with developing an operational definition of CFs for trials [21 22], and exploring the evidence for so-called 'effect modifying CFs' across trials [19]. Effect modifying CFs are equal to effect modifiers, but they are limited to factors related to the person (e.g. age), disease (e.g. disease duration), or environment (e.g. healthcare system) [21]. There is an urgent need for establishing a generic list of important effect modifying CFs to always be taken into account in clinical trials within rheumatology. A first step involves collecting candidate EM-CFs. The baseline patient characteristics and stratification factors reported in trial reports (typically reported in 'table 1' or as subgroup variables) likely reflect what the triallists consider important for interpreting the trial results, such as suspected prognostic factors or effect modifiers, so summarizing such from RCTs across rheumatology could provide a list of EM-CFs candidates within rheumatology.

OBJECTIVES

We will identify and summarize baseline patient characteristics and stratification factors (i.e. potential EM-CFs) reported in trial reports of RCTs across rheumatology.

METHODS

Design

We will conduct a scoping review of baseline characteristics and stratification factors (i.e. potential EM-CFs) reported in RCTs within rheumatology. The reporting will be guided by the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews* (PRISMA-ScR)[23].

A scoping review focuses on identifying key characteristics or factors related to a concept that may help fill knowledge gaps in future research and may sometimes be considered as a precursor to systematic review[24]. Based on the recommendations by Levac et al[25], a scoping review may be relevant when gathering literature on emerging topics, like rehabilitation science, where very small number of randomized controlled trials have been done. Our study will identify candidates for a generic set of patient characteristics (incl. personal -, disease-related, and environmental factors), that need to be considered in rheumatology trials, using a scoping review, as this approach is especially suitable for relatively new and broader concepts[26], and helps in reviewing literature that has not been extensively reviewed[27], as compared to a systematic review.

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 include RCTs examining any type of intervention versus any comparator in patients with rheumatic and musculoskeletal conditions (i.e., conditions studied by the Cochrane Musculoskeletal Group). The trial reports for the RCTs need to be published from 2000 onwards; the year 2000 is chosen because the 'Consolidated Standards of Reporting Trials' (CONSORT)[28] has led to more transparent and complete reporting since the beginning of the 21st century[29]. The trial reports need to be published as a full-text written in English.

Sources of evidence and search

We will apply a meta-epidemiological approach, obtaining all the RCTs included in the published systematic reviews by the Cochrane Musculoskeletal Group (CMSG).

We will search the Cochrane Database of Systematic Reviews (via the Cochrane Library; https://www.cochranelibrary.com/). To identify all current systematic reviews from the CMSG, we will use the Cochrane Library's tool 'Advanced Search', with the search limits 'Cochrane Reviews' (Content Type) and 'Musculoskeletal' (Cochrane Group).

Selection of sources of evidence

Two reviewers (MK and FA) will independently identify eligible trial reports from the systematic reviews. Disagreements will be resolved by discussion or by consulting a third reviewer (SMN). First, the reference lists of included studies in the systematic reviews will be screened, and, subsequently, the full-texts will be obtained and assessed for eligibility.

Data charting process and data items

The data extraction will be done by two reviewers (MK and FA); the data from each study will be extracted by one reviewer and verified by the other reviewer using a predefined, standardized data extraction form. Disagreements will be resolved by discussion or by consulting a third reviewer (SMN).

For each trial, we will extract basic information on:

- Name of first author
- Publication year
  (earliest publication in case of more trial reports)
- Number of trial reports
- Trial registration number
  (e.g. the NCT number from ClinicalTrials.gov)
- Trial acronym
- Number of patients randomized
  (total number and numbers randomized to each arm)
- Patient population
  (categorized as rheumatic/musculoskeletal conditions)
- Intervention
  (categorized as pharmacological, physical/physiotherapeutic, surgical, psychological, or other)
- Comparator
  (categorized as placebo/sham, other intervention/active comparator, standard care, waiting list, no intervention, unclear)
- Trial duration
  (from baseline to latest reported follow-up time)
- Country where the trial was conducted
- Continent where the trial was conducted

The basic trial information will mainly be based on information reported by the systematic reviews.

Furthermore, we will extract the following data on each potential EM-CF candidate:

- The domain
  (i.e. *what* was measured, such as disease severity)
- The measures
  (i.e., *how* was it measured, such as Disease Activity Score-28 for Rheumatoid Arthritis with CRP [DAS28-CRP])
- Potential cutoffs used for continuous variables to make subgroups
  (e.g. DAS28-CRP >4.5 vs DAS28-CRP ≥4.5)

- Whether the variable is a baseline patient characteristic, stratification factor (potentially with a test for interaction), or both, in the trial report
  (coded as 'baseline', 'stratification', 'both')
- Whether the variable is also reported as an outcome of the trial

Data on baseline patient characteristics and stratification factors will be sought for in the result section and appendixes (if readily available) of the trial reports. Data on baseline patient characteristics will likely be reported in a usual 'Table 1' and/or in the beginning of the result section, whereas stratified analyses are likely reported in the end of the result section or in an appendix. For baseline characteristics, we will accept both binary, nominal, ordinal, and continuous data, whereas data for stratification factors cannot be continuous. In case of more eligible trial reports for one RCT, we will extract all available information from the reports.

The domains will initially be ordered according to the contextual factor categories, personal factors (such as age and sex), disease-related factors (such as disease severity), and environmental factors (such as healthcare system, place of residence).

The matching between domains and measures, as well as ordering according to the contextual factor categories will initially be done by two reviewers (MK and FA), supported by a third reviewer (SMN), and verified by a group of experts involving rheumatologists, researchers, methodologists, patient research partners, etc.

Synthesis of results

The data available for each domain will be summarized with a barplot for patient characteristics and stratification factors separately.

The measurement instruments and cutoffs used will be listed for each domain, and summarized using descriptive statistics such as frequencies and percentages.

Additionally, we will investigate whether some domains and/or instruments are more commonly reported for certain rheumatic/musculoskeletal conditions and/or intervention types. Subgroups will include:

Disease category, inspired by a previous paper on a similar trial sample [19]:

- OA
- RA
- OA and RA (i.e., mixed patient population in the trials)
- Fibromyalgia
- Osteoporosis
- Etc.

Disease type

- Inflammatory arthritis (including rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis [including ankylosing spondylitis])
- Non-inflammatory conditions (such as osteoarthritis, fibromyalgia, etc.)
- Autoimmune (i.e, systemic lupus erythematosus)
- Other (such as rotator cuff injury, adhesive capsulitis, and patellofemoral syndrome)

Intervention types

- Pharmacological
- Physical/physiotherapeutic
- Surgical
- Psychological
- Other

If a category includes less than 5 trials, that particular category will not be investigated.

PERSPECTIVES AND DISSEMINATION

This scoping review will provide an important overview by mapping the reporting of baseline patient characteristics and stratification factors across rheumatology. This will provide the basis for the next study seeking consensus on important candidate EM-CFs, like it has been attempted in the field of metastatic colorectal cancer [30 31], but across the field of rheumatology. The results will be disseminated in a peer-reviewed article and at relevant OMERACT meeting activities.

OTHER ASPECTS

Contributions

Study concept and design: MK, FA, SMN, RC
Drafting on the protocol: MK, FA, SMN, RC
Critical revision of the protocol for important intellectual content and final approval before submission: All authors.
Obtained funding: LEK

Funding

This research was not supported by any specific grant. The Parker Institute, Bispebjerg and Frederiksberg Hospital is supported by a core grant from the Oak Foundation (OCAY-13-309). The Oak Foundation is a group of philanthropic organizations that, since its establishment in 1983, has given grants to not-for-profit organizations around the world. The Parker Institute is grateful for the financial support received from public and private foundations, companies, and private individuals over the years.

Competing interests

This study had no financial competing interests.

REFERENCES

1. Rothwell PM. Can overall results of clinical trials be applied to all patients? *Lancet (London, England)* 1995;345(8965):1616-9. doi: 10.1016/s0140-6736(95)90120-5 [published Online First: 1995/06/24]
2. Kravitz RL, Duan N, Braslow J. Evidence-based medicine, heterogeneity of treatment effects, and the trouble with averages. *The Milbank quarterly* 2004;82(4):661-87. doi: 10.1111/j.0887-378X.2004.00327.x [published Online First: 2004/12/15]

3. Kent DM, Hayward RA. Limitations of applying summary results of clinical trials to individual patients: the need for risk stratification. *Jama* 2007;298(10):1209-12. doi: 10.1001/jama.298.10.1209 [published Online First: 2007/09/13]
4. Rothwell PM. Treating individuals 2. Subgroup analysis in randomised controlled trials: importance, indications, and interpretation. *Lancet (London, England)* 2005;365(9454):176-86. doi: 10.1016/s0140-6736(05)17709-5 [published Online First: 2005/01/11]
5. Schork NJ. Personalized medicine: Time for one-person trials. *Nature* 2015;520(7549):609-11. doi: 10.1038/520609a [published Online First: 2015/05/01]
6. Wijn SRW, Rovers MM, Le LH, et al. Guidance from key organisations on exploring, confirming and interpreting subgroup effects of medical treatments: a scoping review. *BMJ open* 2019;9(8):e028751. doi: 10.1136/bmjopen-2018-028751 [published Online First: 2019/08/26]
7. European Medicines Agency (EMA). Guideline on the investigation of subgroups in confirmatory clinical trials. London, United Kingdom: European Medicines Agency (EMA), 2019.
8. Hingorani AD, Windt DA, Riley RD, et al. Prognosis research strategy (PROGRESS) 4: stratified medicine research. *BMJ (Clinical research ed)* 2013;346:e5793. doi: 10.1136/bmj.e5793 [published Online First: 2013/02/07]
9. Whitehead M. The concepts and principles of equity and health. *International journal of health services : planning, administration, evaluation* 1992;22(3):429-45. [published Online First: 1992/01/01]
10. Thompson SG, Higgins JP. Treating individuals 4: can meta-analysis help target interventions at individuals most likely to benefit? *Lancet (London, England)* 2005;365(9456):341-6. doi: 10.1016/s0140-6736(05)17790-3 [published Online First: 2005/01/25]
11. Fisher DJ, Carpenter JR, Morris TP, et al. Meta-analytical methods to identify who benefits most from treatments: daft, deluded, or deft approach? *BMJ (Clinical research ed)* 2017;356:j573. doi: 10.1136/bmj.j573 [published Online First: 2017/03/05]
12. Attwood S, van Sluijs E, Sutton S. Exploring equity in primary-care-based physical activity interventions using PROGRESS-Plus: a systematic review and evidence synthesis. *The international journal of behavioral nutrition and physical activity* 2016;13(1):60. doi: 10.1186/s12966-016-0384-8 [published Online First: 2016/05/22]
13. Frampton GK, Shepherd J, Dorne JL. Demographic data in asthma clinical trials: a systematic review with implications for generalizing trial findings and tackling health disparities. *Social science & medicine (1982)* 2009;69(8):1147-54. doi: 10.1016/j.socscimed.2009.06.012 [published Online First: 2009/07/14]
14. Welch V, Petticrew M, Ueffing E, et al. Does consideration and assessment of effects on health equity affect the conclusions of systematic reviews? A methodology study. *PloS one* 2012;7(3):e31360. doi: 10.1371/journal.pone.0031360 [published Online First: 2012/03/20]
15. Wang R, Lagakos SW, Ware JH, et al. Statistics in medicine--reporting of subgroup analyses in clinical trials. *The New England journal of medicine* 2007;357(21):2189-94. doi: 10.1056/NEJMsr077003 [published Online First: 2007/11/23]
16. Gabler NB, Duan N, Raneses E, et al. No improvement in the reporting of clinical trial subgroup effects in high-impact general medical journals. *Trials* 2016;17(1):320. doi: 10.1186/s13063-016-1447-5 [published Online First: 2016/07/18]
17. Nielsen SM, Tugwell P, de Wit MPT, et al. Identifying Provisional Generic Contextual Factor Domains for Clinical Trials in Rheumatology: Results from an OMERACT Initiative. *The Journal of rheumatology* 2019;46(9):1159-63. doi: 10.3899/jrheum.181081 [published Online First: 2019/01/17]
18. Welch VA, Norheim OF, Jull J, et al. CONSORT-Equity 2017 extension and elaboration for better reporting of health equity in randomised trials. *BMJ (Clinical research ed)* 2017;359:j5085. doi: 10.1136/bmj.j5085 [published Online First: 2017/11/25]
19. Nielsen SM, Storgaard H, Ellingsen T, et al. Population characteristics as important contextual factors in rheumatological trials: an exploratory meta-epidemiological study from an OMERACT Working Group. *Annals of the rheumatic diseases* 2020 doi: 10.1136/annrheumdis-2020-217237 [published Online First: 2020/07/02]
20. Finger ME, Boonen A, Woodworth TG, et al. An OMERACT Initiative Toward Consensus to Identify and Characterize Candidate Contextual Factors: Report from the Contextual Factors Working Group.

The Journal of rheumatology 2017;44(11):1734-39. doi: 10.3899/jrheum.161200 [published Online First: 2017/05/04]
21. Nielsen SM, Boers M, de Wit M, et al. OMERACT consensus-based operational definition of contextual factors in rheumatology clinical trials: A mixed methods study. *Seminars in arthritis and rheumatism* 2021;51(3):601-06. doi: 10.1016/j.semarthrit.2021.03.013 [published Online First: 2021/04/21]
22. Nielsen SM, Uggen Rasmussen M, Boers M, et al. Towards consensus in defining and handling contextual factors within rheumatology trials: an initial qualitative study from an OMERACT working group. *Annals of the rheumatic diseases* 2021;80(2):242-49. doi: 10.1136/annrheumdis-2020-217895 [published Online First: 2020/10/16]
23. Tricco AC, Lillie E, Zarin W, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Annals of internal medicine* 2018;169(7):467-73. doi: 10.7326/m18-0850 [published Online First: 2018/09/05]
24. Munn Z, Peters MDJ, Stern C, et al. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC medical research methodology* 2018;18(1):143. doi: 10.1186/s12874-018-0611-x [published Online First: 2018/11/21]
25. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. *Implementation science : IS* 2010;5:69. doi: 10.1186/1748-5908-5-69 [published Online First: 2010/09/22]
26. Tricco AC, Lillie E, Zarin W, et al. A scoping review on the conduct and reporting of scoping reviews. *BMC medical research methodology* 2016;16:15. doi: 10.1186/s12874-016-0116-4 [published Online First: 2016/02/10]
27. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *International Journal of Social Research Methodology* 2005;8(1):19-32. doi: 10.1080/1364557032000119616
28. Moher D, Jones A, Lepage L. Use of the CONSORT statement and quality of reports of randomized trials: a comparative before-and-after evaluation. *Jama* 2001;285(15):1992-5. [published Online First: 2001/04/20]
29. CONSORT. Impact of CONSORT. [Internet. Accessed 14 May 2019] [Available from: http://www.consort-statement.org/about-consort/impact-of-consort.
30. Goey KKH, Mahmoud R, Sørbye H, et al. Reporting of patient characteristics and stratification factors in phase 3 trials investigating first-line systemic treatment of metastatic colorectal cancer: A systematic review. *European journal of cancer (Oxford, England : 1990)* 2018;96:115-24. doi: 10.1016/j.ejca.2018.03.026 [published Online First: 2018/05/08]
31. Goey KKH, Sørbye H, Glimelius B, et al. Consensus statement on essential patient characteristics in systemic treatment trials for metastatic colorectal cancer: Supported by the ARCAD Group. *European journal of cancer (Oxford, England : 1990)* 2018;100:35-45. doi: 10.1016/j.ejca.2018.05.010 [published Online First: 2018/06/25]