Association between trial retention and the proportion of included elderly individuals: Protocol for a meta-research project

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ABSTRACT

Importance

Recently, we showed that the elderly are significantly underrepresented in randomized controlled trials (RCT) in rheumatoid arthritis (RA) and osteoarthritis (OA). While this phenomenon has been detected in other fields as well, efforts by various international institutions to tackle the issue were without decisive success. Researchers might be cautious about including more elderly people because they fear reduced trial retention rates.

Objective

To evaluate whether the proportion of included elderly individuals (defined by an age of ≥65 years) is independently associated with trials' retention rates.

Data Source

MEDLINE (via PubMed).

Eligibility

RCT on any intervention in RA or OA published in 2016 or 2017.

Outcome

Retention rate.

Critical Appraisal

We will not address any conclusion made by included RCT. Thus, we will not perform a formal risk of bias assessment.

Synthesis Methods

The proportion of elderly people is either directly abstracted from the research manuscript or estimated from an assumed truncated normal distribution. Multivariable meta-regression will explore whether the proportion of included elderly people is independently associated with trials' retention rates, even after adjusting for trial duration. The model will include as covariates – apart from the proportion of elderly people and study duration - disease, type of intervention, region, sample size at enrollment, and the proportion of women. Additional models will explore whether the proportion of included elderly people is independently associated with trial retention rates when only drop-outs due to adverse events, resp. lack of efficacy are counted.

TAGS

Meta-analysis

elderly

Show tags

PROTOCOL STATUS

Working

GUIDELINES

PRISMA

Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* 2009;151(4):W65-94.

PRISMA-P

Preferred reporting items for systematic review and meta-analysis protocols

Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349:g7647. doi: 10.1136/bmj.g7647.

INTRODUCTION

1 The elderly – commonly defined by an age of 65 or more years – are significantly underrepresented in clinical trials as has been shown for a wide variety of diseases and throughout various medical specialties.[1-18] This poses a potentially serious problem as older people differ from younger adults in multiple aspects including pharmaco-dynamics and -kinetics, comorbidity, polypharmacy and physical performance, all of which affect the potential for benefit and usually increase the overall chance of drug-related adverse events.[19-22] In addition, the number of elderly is expected to rise dramatically in countries all over the world, leading to higher numbers of elderly.[23, 24]

Barriers impeding recruitment and retention of elderly people have been identified as well as strategies to overcome these.[25-31] Since underrepresentation of the elderly was first systematically proven in the 1990s, various international institutions have put forth efforts to overcome this issue – without decisive success. Excluding specific patients from randomized controlled trials (RCT) by installing arbitrary upper age limits has even increased in osteoarthritis (OA) trials over the last ten years. One reason for researchers being reluctant to include more elderly people might be the fear of diminished trial retention rates. Attrition may introduce bias (e.g., by differential/selective attrition or nonresponse bias), decrease statistical power, complicate statistical analysis, and lead to higher overall expenses.

RATIONALE

2 Potential factors predicting retention rates have been analyzed, but studies doing so have come to conflicting results concerning age. A rheumatoid arthritis (RA) registry found no significant association between age and attrition,[32] while a review of population-based studies in the elderly and a longitudinal study on aging found higher age to be predictive.[33, 34] Other studies found age not to be significantly associated with retention.[35, 36] Quite the contrary, in some studies, age was inversely correlated with attrition.[37, 38]

Recently, we showed that the elderly are still underrepresented in RA and OA trials by studying 265 RCT (51,240 patients) in a systematic review and comparing these (exact number of RCT varying by outcome [mean age, standard deviation, proportion being elderly]) with data from population-based studies.[39] For the study at hand, our objective is to analyze whether the proportion of elderly people is independently associated with trials' retention rates in these previously selected trials. Sensitivity analyses will assess whether a potential association is connected to a specific type of attrition, i.e., dropping out due to adverse events (AE) or lack of efficacy (LoE).

METHODS

3 **Protocol**

This protocol conforms to the *Preferred Reporting Items for Systematic Review and Meta-analysis protocols* (PRISMA-P) guidelines for reporting a protocol for a systematic review and meta-analysis.[40]

Eligibility

Formal screening of search results against eligibility criteria has already been performed (see above) and yielded 265 RCT.[39] We included therapeutic RCT on OA and RA that report at least participant's mean (or median) age, excluding those on pediatric patients. To assess current developments and explore recent trends, and also for reasons of feasibility, we decided to limit our search to RCT published within the last two years; i.e., the period from January 1st, 2016 to Dec 31st, 2017. Corresponding to participating GLORIA collaborators and their language skills, publications must be in English, German, French, Spanish, Portuguese, Dutch, Slovakian, Italian, Romanian or Hungarian.

If multiple reports were derived from the same data set, we attempted to include the latest published findings. We excluded prevention and phase I clinical trials as well as secondary analyses and (ancillary) reports of multiple studies and of studies already included. We did not include studies reporting age data from study completers only as we suspect younger patients might have a higher probability for completing a study.

Information Sources

Our information source is the full publication referenced by the online biomedical and life science database MEDLINE (via PubMed). If necessary, we will consult trial registries specified in respective manuscripts to get full data on retention. Note that of the five domains addressed by the PICOS-mnemonic (Patient/Population; Intervention; Comparison; Outcome; Study design) recommended by the Cochrane Musculoskeletal Group, only the respective first and last sections of the acronym are applicable parts of our search strategies.[41]

Search Strategy

We constructed search strategies for RCT in RA and OA with researchers experienced in systematic reviews of the literature (see below). Additionally, we performed a hand search for relevant publications including a scan of the references of major guidelines and reviews of the two diseases we address.

RA ("Arthritis, Rheumatoid"[Mesh] OR "Rheumatoid Arthritis"[Title/Abstract] OR (Rheumatoid Arthr[Title/Abstract]) OR "rheumatic arthritis"[Title/Abstract] OR "arthritis deformans"[Title/Abstract] OR "arthritis, rheumatoid"[Title/Abstract] OR "arthrosis deformans"[Title/Abstract] OR "chronic polyarthritis"[Title/Abstract] OR "chronic progressive polyarthritis"[Title/Abstract] OR "inflammatory arthritis"[Title/abstract] OR "rheumatic polyarthritis"[Title/Abstract] OR "Felty Syndrome"[Title/Abstract])*

AND

RCT (("Randomized Controlled Trial"[Publication Type]) OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract])) NOT (Review[Title]) NOT (Meta-analysis[Title]) NOT (Letter[Publication Type]) NOT (Case Report[Title]) AND ("2016/01/01"[PDAT] : "2017/12/31"[PDAT]) AND (Species: Humans)

and

OA (("Osteoarthritis"[Mesh]) OR osteoarthritis[Title/Abstract] OR (osteoarthr[Title/Abstract]) OR osteoarthrosis[Title/Abstract] OR "degenerative joint disease"[Title/Abstract] OR "noninflammatory arthritis"[Title/Abstract] OR arthrosis[Title/Abstract] OR "degenerative arthritis"[Title/Abstract] OR "osteo-arthritis"[Title/Abstract] OR "osteo-arthrosis"[Title/Abstract] OR "primary osteoarthritis"[Title/Abstract])*

AND

RCT (see above)

Data Collection and Management

We will use R version 3.3.3 or newer (R Foundation for Statistical Computing, Vienna, Austria) with packages *meta* and *metafor* and Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA) software for data extraction, management, and analysis. We have and will continue to extract data using predefined data extraction sheets which are derived from the Cochrane Collaboration's recommendations for data extraction and modified for our purposes.[42] The variable "study duration" will be defined as the time from randomization to the study's last follow-up. Intervention types will be categorized as "pharmacological", "surgical", "psychological", and "physical/physiotherapeutic".

Study Selection

We imported retrieved articles into EndNote X8 software (Clarivate Analytics, Philadelphia, PA, USA). Two Authors (AP and TB) independently screened the articles for inclusion or exclusion. They eliminated duplicates with the help of EndNote X8 software, screened the articles by title and abstract, and then assessed the remaining articles in full text. Afterwards, consensus on study inclusion was achieved between the two reviewers by discussion. We will provide a flow diagram of the study selection process as proposed in the *PRISMA* statement.[43]

Outcomes

Our endpoint is the observed retention rate at follow up, which we define as the number of participants completing a trial (to the last follow-up; or, if reported only that way, the number of participants "completing the treatment") divided by the number of randomized participants. We will calculate overall retention as well as retention when counting drop-outs due to AE only, and drop-outs due to LoE only. Additionally, we will screen the included publications' methods sections to assess whether they applied strategies to include higher numbers of elderly people or improve retention of these.

Risk of bias in individual studies

We will not infer from conclusions made by included RCT and do not include RCT outcomes in our synthesis of results. Thus, we consider a formal risk of bias assessment not to be applicable. This improves feasibility and allows for including a high number of trials in our study.

Data Synthesis

We have estimated the proportion of people aged ≥65 years under the assumption that age is normally distributed.[39] However, we considered all age distributions of all studies to be singly truncated at a lower age level of 18 years, even if this was not reported. Studies that also employed an upper age limit were assumed to have a doubly truncated age distribution. For each study, we derived individual cumulative distribution functions $F_a(x)$ from study mean ages and their standard deviations in order to obtain the cumulative integral of individual probability density functions $f_a(x)$, to obtain the proportion of patients at or below the age of x. This allowed for the calculation of the proportion of people aged 65 or more years (x equals the participant's age; a is the respective study ID) by employing the following formula:

$(1 - F_a(64)) \times 100 = \text{Percentage of people aged 65 years or more in Study } a$

We followed the guidance available from the Cochrane Collaboration's Handbook on how to combine the results of multiple study arms into one single group per trial.[42] If studies reported median age and interquartile range (IQR) instead of mean age and standard deviation (SD), we followed the Cochrane Collaboration's guidelines and assumed equality of the median and the mean, and equality of the IQR and 1.35 SDs.[42] If it was the case that studies report median age and the range thereof (maximum and minimum), we followed the method proposed by Hozo et al. to estimate mean age and standard deviation,[44] which includes the following:

Say x is the mean, a the minimum, b the maximum, R the range (i.e., maximum – minimum), m the median, SD the standard deviation, and n the sample size, then:

if n ≤ 15, then

$$x = (a + 2m + b)/4$$

$$SD = \sqrt{(1/12((a - 2m + b)^2/4 + (b - a)^2))}$$

if 15 < n ≤ 25, then

$$x = (a + 2m + b)/4$$

$$SD = R/4$$

if 25 < n ≤ 70, then

$$x = m$$

$$SD = R/4$$

and if n > 70, then

$$x = m$$

$$SD = R/6.$$

If studies reported mean or median age only, we did not use these data for calculation and comparison of proportions of people aged 65 years or more.

We will apply a mixed effects meta-regression model with trial retention rate as the dependent variable abstracted from each RCT; Handling RCT as random effects assumes the true treatment effect differs from study to study and provides an estimate of the average retention rate,[45] whereas study level covariates will be included as fixed effects.

We will evaluate heterogeneity across included studies with Cochran's Q-statistic and interpret heterogeneity based on the I^2 value; I^2 measures the total percentage of variance across studies due to clinical heterogeneity rather than statistical error.[42, 46] Subsequently, we will perform meta-regression to evaluate whether the proportion of included elderly individuals is independently associated with trials' retention rates.

Meta-regression will be restricted to investigation of suspected differences between trials, which vary substantially across trials. Therefore, all the following trial-level features collected will be considered potential covariates. Among the variables tested as predictors of study heterogeneity, we will include (apart from the proportion of elderly people):

a) study duration (in weeks),

b) disease (categorical variable),

c) type of intervention (categorical variable),

d) region (categorical variable),

e) sample size, and

f) the proportion of women.

This regression/stratifying will be assessed fitting multiple restricted maximum likelihood–based meta-regression models.[47] A priori, we define a relevant study level covariate as one that will decrease the between-study variance, estimated as tau squared [T^2 or τ^2]), as a consequence of inclusion in the (mixed-effects) statistical model.[48]

Additional sensitivity analyses will assess whether a potential association between the proportion of included elderly people and trial retention is connected to a specific type of attrition. I.e., we will conduct regression analyses with retention rates that are calculated counting only drop-outs due to

a) AE and

b) LoE.

Meta-bias

We will not assess the strength of the body of evidence (e.g., GRADE) as we are neither investigating a specific intervention nor synthesizing information from a homogenous set of trials on such an intervention. However, we will attempt to explore systematic errors. E.g., trials with low retention might generally be less likely to get published.

ETHICS AND DISSEMINATION

4 We do not collect any primary data. Thus, no additional formal ethics approval is necessary. Our systematic review will be the first to systematically analyze the adequacy of the representation of elderly people in osteoarthritis and rheumatoid arthritis trials. The results of this review will be published in a peer-reviewed journal according to the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines.

COMPETING INTERESTS

5 All authors declare that they have no competing interests.

FUNDING

6 This project is part of the *GLORIA* project and trial (Glucocorticoid low-dose outcome in rheumatoid arthritis study; http://www.gloriatrial.org/; registered on https://clinicaltrials.gov/; identifier NCT02585258) and has received funding from the European Union's Horizon 2020 Framework Programme for Research and Innovation under grant agreement No. 634886. Musculoskeletal Statistics Unit, The Parker Institute, (SMN and RC) is supported by grants from The Oak Foundation. Funders had no role in design and conduct of the protocol; preparation, review, or approval of the protocol; and decision to submit the protocol for publication.

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