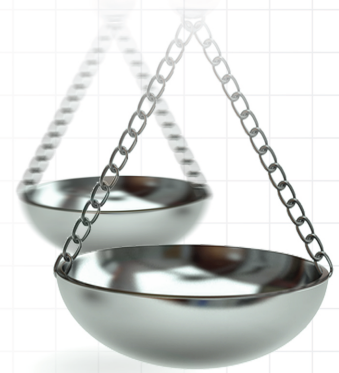




Selective reporting bias due to discrepancies between registered and published outcomes in osteoarthritis trials

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Aim: Outcome reporting bias (ORB) occurs when outcomes planned in a study protocol are subsequently not reported or are partially reported. Our aim was to analyze ORB in randomized controlled trials (RCTs) about conservative interventions for osteoarthritis (OA) by comparing registered protocols and published manuscripts, as well as association between study funding type and intervention type, and ORB in those RCTs. **Materials & methods:** We analyzed RCTs that were published in a peer-review journal and analyzed any type of conservative intervention for treatment of OA in humans that reported in the manuscript registration in a public clinical trial registry and provided unique registration identifier. We extracted data indicating ORB by comparing outcomes in protocol and published article, and characteristics of trials. **Results:** In 190 (57%) of 334 included RCTs, it was indicated in the manuscript that a trial was registered. In 48% of trials we found discrepancies in number, type or time point of primary efficacy outcome between protocol and manuscript. Significantly less discrepancies in primary efficacy outcomes between protocols and published articles were found in trials funded by a commercial sponsor ($p = 0.0062$) and trials of pharmacological interventions ($p = 0.0016$). **Conclusion:** Trials about conservative therapies for OA have high prevalence of discrepancies between protocol and publication, and frequent ORB. This may mislead readers of published results because it has been shown that ORB can lead to both overestimation and underestimation of effects of interventions, depending on the intervention and outcome. Efforts to prevent nonregistration of protocols and selective reporting are needed.

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Selective reporting refers to a publication practice where study authors preferentially publish interesting or positive research findings, while ignoring less interesting results and those that do not confirm their hypothesis. Unfortunately, many clinical trials are affected by selective reporting, which introduces bias [1,2]. Ultimately, selective reporting will most likely lead to trials claiming to be more effective and safer than they might otherwise.

There are several types of selective reporting bias such as publication bias, time lag bias, location bias, language bias and outcome reporting bias (ORB) [3]. ORB occurs when some outcomes that were planned in a registered study protocol are subsequently not reported or are partially reported based on their perceived importance or attractiveness [4]. Hutton and Williamson first defined ORB in 2000 as: 'the selection on the basis of the results of a subset of the original variables recorded for inclusion in a publication' [5].

Empirical research provides strong evidence that outcomes that are statistically significant have higher odds of being fully reported than nonsignificant outcomes (odds ratios ranging from 2.2 to 4.7) [1,2], and also suggests that ORB is a threat to the validity of the evidence base and contributes to research waste. Kirkham *et al.* have highlighted up-to-date approaches and recommendations for detecting this problem and adjusting the results when performing sensitivity analyses in systematic reviews and also anticipate continued application of these methods and methodological research into the assessment and adjustment of ORB in the years to come [6]. A systematic review analyzed cohort studies that have assessed publication bias or ORB in randomized controlled trials (RCTs) [2], and found that only two empirical studies explored different types of discrepancies that may arise between protocol and subsequent publication. As many as 40–62% of analyzed trials had major discrepancies between primary outcomes that were listed in registered protocols and primary outcomes indicated in the published manuscripts. Up to a third of primary outcomes defined in a trial protocol were omitted from a subsequently published manuscript and up to a fifth of trials reported primary outcomes that were not listed in a protocol. Incomplete reporting was more common for harm outcomes [2]. Their systematic review pointed out to scarcity of studies that analyzed ORB.

The primary aim of this study was to analyze ORB in RCTs about conservative interventions for osteoarthritis (OA) by comparing registered protocols and published manuscripts. The secondary aim was to analyze association between study funding type, intervention type and ORB in those RCTs.

Materials & methods

Study design

This was a research-on-research (methodological) study. Since we analyzed published articles, that were publicly available, there was no need for requiring approval of research ethics committee for conducting this study.

Inclusion criteria

We included RCTs that were published in a peer-review journal and analyzed any type of conservative (nonsurgical) intervention for treatment of OA in humans that reported in the manuscript registration in a public clinical trial registry and provided unique registration identifier. We excluded interventions of pharmacological therapies and interventions such as injections of corticosteroids or platelet-rich plasma, except studies that mentioned that participants received pharmacological treatment for breakthrough pain. We also excluded studies with diagnostic arthroscopy considering it as surgical treatment. Only studies published in the English language were included. We included all studies which were self-described by their authors as RCTs.

Search

We searched PubMed to find eligible OA trials published as a journal article from June 2012 to June 2017. Manuscripts published in any journal indexed on PubMed were eligible. For the purpose of the search we used keywords ‘osteoarthritis’, filter for ‘RCTs’ and filter for ‘chosen dates’, as well as filter for ‘humans’. The flow diagram of study inclusion is shown in Figure 1.

Study screening

One pair of authors screened titles and abstracts of retrieved records and the second pair of authors verified the screening results on all records. Full texts were analyzed if it was not clear from the title and/or abstract that a study was eligible for inclusion. A third pair of authors was consulted, if necessary, for resolving discrepancies. All eligible studies were obtained in full text for subsequent data extraction. We analyzed in detail only manuscripts that indicated that a trial was registered.

Data extraction

We created a data extraction sheet in Microsoft Excel (Microsoft Corp, WA, USA) and piloted the data extraction on ten studies. Authors extracting data had a calibration exercise until consistency of data extraction was achieved. One author extracted data, and the second author verified the extractions.

We extracted the following data: bibliographic details (first author, year), trial registration number, whether there were changes in the registered protocol and if yes, did the changes include outcomes; number and list of primary and secondary outcomes, outcome measures and outcome time points in the manuscript and in the registered protocol, funding (industry or nonprofit) and type of intervention (pharmacotherapy, alternative medicine or other). If secondary outcomes were not specifically indicated, all outcomes that were not defined as primary were

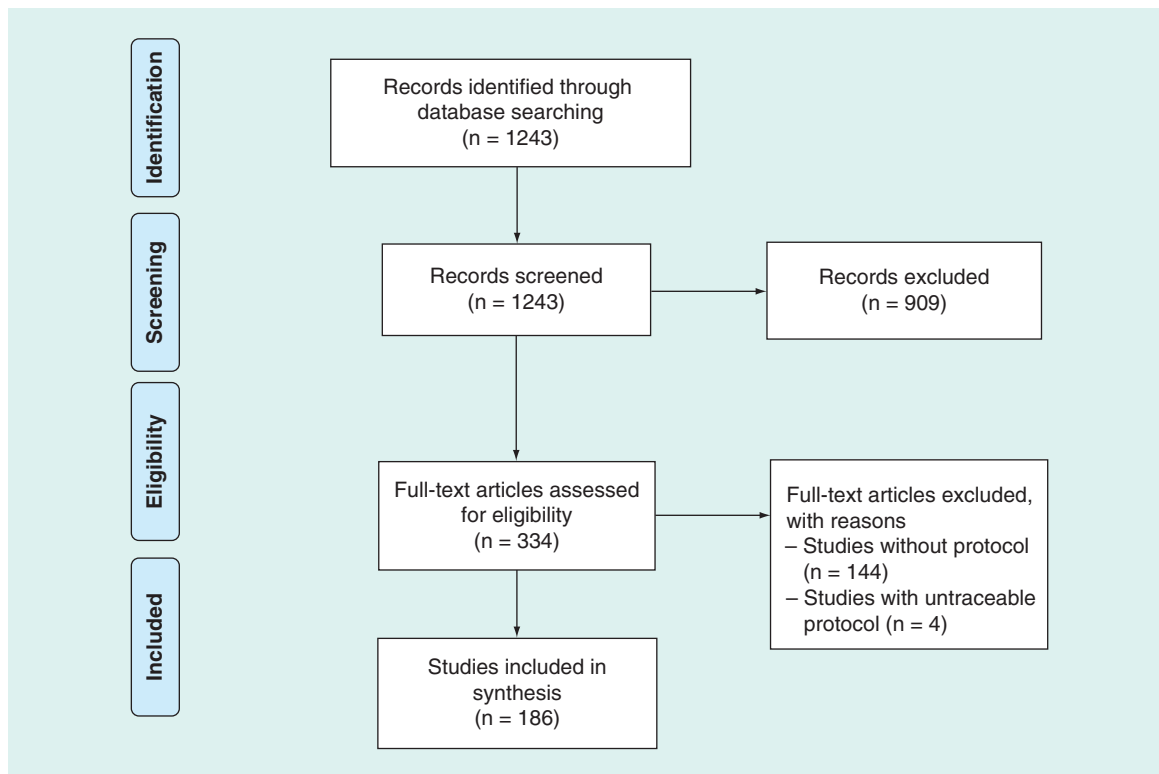


Figure 1. Study flow diagram.

considered to be secondary outcomes. According to importance, we classified outcomes as primary or secondary. Primary and secondary outcomes were defined in protocol or in the study. We defined discrepancies as differences between registered protocol and publication, in other words, differences in number, type or timing in outcomes and outcome measures. Outcome measures are instruments used to measure outcomes, for example, visual analog scale is an outcome measure for the outcome pain. If the registered protocol did not provide planned outcome time point, this was just noted, but it was not considered a discrepancy.

Data analysis

We analyzed discrepancies between outcomes reported in a registered protocol and in journal publication in terms of outcome importance (primary vs secondary), type (efficacy vs safety), discrepancies in number and type of outcomes and time points when outcomes were measured. We did not assign different weight to studies based on number of discrepancies found in certain parts of analysis. For example, if there was a change in one or more primary outcomes, we considered this a discrepant unit of analysis. We presented descriptive data as frequencies and percentages. We used Fisher's test to calculate differences in frequencies between two groups. We used MedCalc statistical software, v 15.2.1 (MedCalc Software bvba, Ostend, Belgium) for data analysis. Statistical significance was set at $p < 0.05$.

Results

Studies eligible for inclusion

We found 334 RCTs about conservative interventions for OA indexed in PubMed between June 2012 and June 2017. Characteristics of those 334 RCTs are shown in [Supplementary Table 1](#). A third of those 334 studies had duration of 7–12 weeks ($N = 103$; 31%); only two trials lasted less than a week. Median duration of patient follow-up was 3 months (range: 1 day–7 years). Five (1.5%) trials did not specify duration; 70 (21%) trials had duration of 1 year or longer. The majority of trials had two study arms ($N = 247$; 74%). In those 334 trials, 55,877 participants were randomized, and 39,607 participants completed the study, indicating that overall attrition in

Table 1. Clinical trial registries where protocols of analyzed trials were registered.

Name of registry	N (%)
ClinicalTrials.gov	116 (62)
Australian New Zealand Clinical Trials Registry	19 (10)
ISRCTN Registry	17 (9.1)
Netherlands Trial Register	8 (4.3)
Clinical Trials Registry – India	7 (3.8)
Iranian Registry of Clinical Trials	7 (3.8)
EU Clinical Trials Register	5 (2.7)
Chinese Clinical Trial Registry	2 (1.1)
Brazilian Registry of Clinical Trials	2 (1.1)
Research Information Service (CRiS) Republic of Korea	1 (0.5)
JAPIC Clinical Trials Information	1 (0.5)
UMIN Clinical Trials Registry	1 (0.5)

CRiS: Clinical Record Interactive Search; ISRCTN: International Standard Randomized Controlled Trials Number; JAPIC: Japan Pharmaceutical Information Center; UMIN: University hospital Medical Information Network.

those trials was 29%. Median number of randomized participants per study arm was 37 (range: 2–588 per study arm); 195 (58%) studies had less than 50 participants per study arm.

Funding was reported in 298 (89%) of the 334 trials. There were 152 (46%) trials with nonprofit funding, 85 (25%) trials with commercial funding, 61 (18%) indicated that no funding was received and 36 (11%) trials did not report information regarding funding.

Trial registration

In 190 (57%) of the 334 analyzed RCTs, it was indicated in the manuscript that the trial was registered. When we tried to retrieve the registered protocols on internet by using the reported protocol registration number, registered protocols for four (2.1%) RCTs were untraceable. After excluding those, we were left with 186 RCTs that we analyzed in more detail.

Protocols of the 186 RCTs were registered in 12 different clinical trials registries; the majority (62%) of those RCTs were registered on ClinicalTrials.gov (Table 1).

Most of the trials (N = 144; 77%) changed the study protocol at least once. Among them, there were 12 (8.3%) trials that changed outcomes, while 8 (5.6%) added and deleted some outcomes. In 44 (31%) trials, the authors made changes in outcomes measures.

Efficacy outcomes

Primary outcomes were defined in 180 (97%) of registered protocols and 159 (85%) of publications. Most of the analyzed registered protocols (N = 113; 63%) and publications (N = 97; 61%) had one primary outcome. Among 159 trials that had primary outcomes reported both in the registered protocol and in publication, there were 45 (28%) trials that had discrepancy in the number of primary efficacy outcomes between registered protocol and publication. Discrepancy in type of primary efficacy outcomes between registered protocol and publication was found in 51 (32%) trials. In 52 (33%) trials, we found discrepancy in primary outcome time points. Only eight trials with discrepancy in number or type of primary efficacy outcomes between registered protocol and publication reported those outcomes in a manuscript as secondary outcomes.

Overall, 77 of 159 trials (48%) had at least one of those discrepancies (in number, type, time point), or their combination. Among trials with discrepancies in primary efficacy outcomes between registered protocol and manuscript, there were significantly less pharmacological interventions ($p = 0.0016$) than other interventions and significantly less conflict of interest related to financial ties with a study sponsor (authors as employees or consultants; grants, fees, honoraria, royalties, etc.; $p = 0.0062$) compared with trials with no such conflict of interest reported. Detailed characteristics of trials with and without discrepancies in primary efficacy outcomes are shown in Table 2.

Most of the analyzed trials (N = 161; 87%) defined secondary efficacy outcomes in registered protocol, and 141 (76%) in a publication. Discrepancy in number of secondary efficacy outcomes was found in 109 trials (59%). Discrepancy in type of secondary efficacy outcomes between registered protocol and publication was found in 108 trials (58%). Discrepancy in secondary efficacy outcome time points was found in 60 (32%) trials.

Table 2. Characteristics of studies with and without discrepancies in primary efficacy outcome between protocol and publication, in terms of type of intervention, funding and reported conflict of interest.

Characteristics	Discrepancies (N = 77), n (%)	Without discrepancies (N = 82), n (%)
Type of intervention		
– Pharmacological	26 (34)	47 (57)
– Other	51 (66)	35 (43)
Type of funding		
– Nonprofit	41 (77)	31 (38)
– Industry and combined nonprofit/industry	27 (35)	36 (44)
– Not reported	8 (10)	15 (18)
– No funding	1 (1.3)	0 (0)
Conflict of interest		
– None	45 (58)	32 (39)
– Not reported	9 (12)	14 (27)
– Unclear	7 (9)	2 (2.4)
– Financial ties with sponsor	16 (21)	34 (41)

Table 3. Characteristics of trials for which protocol was available and those for which protocol registration was not reported.

Characteristics	Trials for which protocol was available (N = 186)	Trials for which protocol registration was not reported (N = 144)
Type of intervention, N (%)		
– Alternative	49 (26)	48 (33)
– Physical	48 (26)	45 (31)
– Pharmacological	41 (22)	14 (10)
– Combined	27 (15)	24 (17)
– Behavioral	9 (5)	2 (1)
– Assistive devices	7 (4)	8 (6)
– Psychologic	3 (2)	2 (1)
– Genetic engineering	2 (1)	1 (1)
Type of joint, N (%)		
– Knee	140 (75)	116 (81)
– Other	46 (25)	28 (19)
Type of funding, N (%)		
– Not-for-profit	96 (52)	54 (38)
– Commercial	62 (33)	22 (15)
– No funding	20 (11)	40 (28)
– Not reported	8 (4)	28 (19)
Median number of participants (range)	76 (11–1256)	73 (6–1371)
Study duration, N (%)		
– Under 1 month	21 (11)	22 (15)
– 1–2 months	30 (16)	18 (13)
– 3–6 months	68 (37)	50 (35)
– 6–12 months	47 (25)	42 (29)
– More than 1 year	16 (9)	10 (7)
– Not reported	3 (2)	2 (1)

Safety outcomes

Only six of 186 (3.2%) trials defined primary safety outcomes in registered protocol and five (2.7%) in publication in journal. There was one discrepancy in primary safety outcomes between those manuscripts and registered protocols in time point, but there were no discrepancies in number or type of primary safety outcomes between registered protocol and publications. Secondary safety outcomes were defined in 37 (20%) registered protocols and 135 (73%) publications. Discrepancies in the number of secondary outcomes between registered protocol and publication were found in five (2.7%) trials, in the type of secondary safety outcomes in 15 (8.1%) trials and in time points for secondary efficacy outcomes in 13 (7%) trials.

Differences between trials with available protocol & those that did not report protocol registration

Comparison of descriptive variables between trials that had reported protocol registration and for which trial protocol was available (N = 186) and trial articles that did not report protocol registration is shown in Table 3. As can be seen from the Table 3, there were no major differences between the two groups in trial characteristics.

Discussion

We found that 55% of the analyzed OA trials had reported information about traceable publicly-available registered protocol, and 77% of those protocols were changed at least once. Among trials that reported primary outcomes both in registered protocols and in publications, 48% of trials changed type, number or time point of primary efficacy outcome, indicating that only 24% of analyzed 334 OA trials were both registered and had outcomes/outcomes measures reported as planned. We did not find that prevalence of changes in primary efficacy outcomes were more common in trials of pharmacological interventions, or in trials sponsored by industry, or with authors having reported financial conflict of interest related to a sponsor. These changes were more common in trials funded by nonprofit sources. This result indicates that more effort is needed into investigating why trial authors embark on changing primary efficacy outcomes, if they do not have financial interest in doing so. Also, it could be argued that not all discrepancies between registered protocols and publications are the same, and that some changes may be justified. However, in that case the authors should elaborate in their publication why they made changes, and we did not find such explanations in our study.

To our best knowledge, this is the first such study in this research field. In the field of orthopedics, we were able to find only one prior study that addressed ORB; the study of Rongen and Hannik, published in 2016, compared registered and published outcomes in trials about orthopedic surgical interventions. They found that few orthopedic surgical trials reported registration of the trial, and even fewer of these trials were adequately registered. Additionally, they found high inconsistency between registered primary outcome measures and those reported in the published manuscripts [7].

In 2017, Zhang *et al.* published a report about selection bias in Phase III RCTs published in the four leading biomedical journals that had available registered protocols [8]. Out of 299 eligible RCTs, 8.4% had certain discrepancy in primary outcome between registered protocol and publication. They identified the following discrepancies: primary outcomes from registered protocol reported as secondary outcomes in publication, completely new primary outcome reported in publication and different time of primary outcome assessment in publication compared with registered protocol. When trials with discrepancy in primary outcome were analyzed in more detail, it was found that 60% of them had discrepancies that favored statistically significant results [8].

The study by Zhang *et al.* specifically targeted trials with published protocols, but they did report that out of 447 eligible Phase III RCTs there were 299 with available registered protocols; of those 299 trials, 244 had appended protocols, 49 had protocols that were previously published and six had protocol that was available via links included in the text. This leaves 148 (33%) trials that were excluded because registered protocol was not appended, trial had nonaccessible or expired links to registered protocol or in two cases, there was no registered protocol in the English language [8]. These results indicate that even in the four top general medical journals, for a third of trials published relatively recently, from January 2012 to June 2015, it was not possible to analyze potential selection bias due to nonavailability of a study protocol.

Trial registration is very important for transparency and tracking potential publication bias and selection bias and ORB. Therefore, since 2005, International Committee of Medical Journal Editors (ICMJE) requires trialists to prospectively register trial protocols in a publicly available register as a prerequisite for publishing a trial [9]. However, there are still many trials being published in biomedical journals without mentioning protocol registration, and even when protocol is published, outcomes may not be reported as registered [10,11]. Despite standards put in place to improve prospective registration of clinical trials and their transparency, less than 15% of psychiatry trials were registered prospectively and without subsequent changes in primary outcomes [12]. Our study contributes further evidence that ICMJE requirements for protocol registration are not being enforced, since we found that 190 (57%) out of 334 analyzed trials reported trial registration in the published manuscript, and for four out of those 190 trials, we were unable to trace the protocol by using the information reported in the manuscript.

One of the conclusions of the Zhang *et al.* manuscript was that their results may not reflect trials published elsewhere, as they focused on general biomedical journals. Targeted analyses of ORB were conducted in several different specialty fields. Rankin *et al.* analyzed trials from obesity journals published from 2013 to 2015 and reported 15% of major outcome discrepancies between registered protocol and publication [13]. In 2017, Bradley *et al.* found that 60% of psychotherapy trials published between 2010 and 2014 were registered, of which 24% were prospectively registered; only 12% were correctly registered and reported and of those more than half showed evidence of selective outcome reporting [11].

Rhagav *et al.* analyzed oncology trials published in high-ranking journals in 2012, and found that 12% of analyzed trials had discrepancies between planned and published primary end points [14].

Analysis of our group of studies, as a secondary result, indicated that only a fifth of interventions for OA lasted 1 year or longer. OA is a chronic disease, and it is troublesome that some studies follow patients only during 1 day, in other words, immediately before and after an intervention. With short-term studies, there is a question of how long can a treatment effect last, and when will it wear off. For this reason, trialists should make an effort to design OA trials that will follow participants longer.

Most of the trials that were assessed for eligibility in our analysis were small, with a median of 37 participants in each study arm. The smallest trial had a total of six participants; two in each of three study arms. Making judgments about the sample size without making formal power analysis may be overarching, but it is difficult to believe that most of the hypotheses about treatment effect can be achieved with such small number of participants.

Although trials should be prospectively registered in publicly available clinical trial registries in order to be considered for publication [9], our findings indicate poor adherence of authors and journals with this requirement. We found that just over half of analyzed trials mentioned protocol registration. Nonreporting may not be synonymous with lack of registration; in theory, these trials might have been registered, but authors failed to report it, but we have not investigated this. While authors may not be aware of the need for trial registration, it is unclear why journal editors allow publication of trials that do not follow this rule.

Our study was conducted in a specific field of conservative therapies for OA, but it has confirmed previous findings from other biomedical fields: almost half of the identified trials either did not mention protocol registration or the mentioned protocol was not traceable. In almost half of the trials, primary outcome was changed in publication compared with registered protocol. Trialists need to be aware that these findings may negatively impact confidence in reported outcomes. Selective outcome reporting distorts clinical findings, and will limit available outcomes for evidence syntheses such as systematic reviews. Using consistent outcomes, and reporting them, is very important to ensure comparability of trials [15–19]. Over-representation of positive findings, in other words, results that the sponsors and authors wanted to obtain, is irresponsible and potentially dangerous.

Clinical implications of ORB are that selective outcome reporting may bias the field to positive findings and provide erroneous picture about efficacy and safety of tested therapies. In 2012, Hart *et al.* have reported results of reanalysis of meta-analysis for data about new drugs that were approved by the US Food and Drug Administration (FDA) [20]. They hypothesized that nonpublication of unfavorable results of drug trials can lead to overestimation of the efficacy of drugs in meta-analyses and systematic reviews that are based on published data only. They compared results of meta-analyses in published systematic reviews with their re-analysis of meta-analyses based on unpublished trial data submitted to FDA and found that adding unpublished trial outcome data to published meta-analyses had changed their results. After conducting 42 new meta-analyses for nine drugs belonging to six drug classes, they found that addition of unpublished trial data that were submitted to FDA caused 46% of summary estimates to show lower efficacy of the drug, 7% showed the same efficacy and 46% showed higher efficacy. Summary estimates of meta-analyses for single harm outcome showed more harm after including unpublished trial data. This analysis indicates that ORB can lead to both overestimation and underestimation of effects of interventions, depending on the intervention and outcome [20].

Nonpublication of conducted trials is a serious drawback in research community. Protocol registration is one way of tracking whether registered protocols were marked as completed, and subsequently not published. Additionally, some trials are presented in research conferences, and their subsequent tracking shows that many of those RCT conference presentations are not subsequently published as full text, and that those that are published often have major discrepancies compared with abstracts, including both qualitative and quantitative differences [21].

Highly prevalent publication bias and selection bias, including ORB, could be remedied by interventions at different levels. Studies we analyzed were all published by peer-reviewed journals, indicating that editors and/or peer-reviewers have failed to notice that the study did not mention protocol registration, and that results were not compared with the published protocol. Research ethics committees (institutional review boards) and funders should require mandatory protocol registration when making decisions about approving and funding clinical trials.

Limitation of our study is search limited only to RCTs indexed in PubMed; some published RCTs about interventions for OA may not be indexed on PubMed and therefore we may have missed some relevant trials. Additionally, we analyzed discrepancies based on primary and secondary outcomes, and we did not attempt to conduct further analyses regarding statistical significance of changed outcomes. The strength of this study is analysis of the large number of OA trials that were published in recent 5-year period.

In conclusion, trials about conservative therapies for OA often fail to report protocol registration, have high prevalence of discrepancies between registered protocol and publication and frequent ORB. These findings are reducing confidence in reported outcomes and validity of such trials in this field. Research community should make more effort to prevent nonregistration of protocols and selective reporting.

Summary points

- We analyzed outcome reporting bias in randomized controlled trials about conservative interventions for osteoarthritis that had reported details about protocol registration.
- Only 56% of analyzed trials had reported details about accessible registered protocol.
- A total of 77% of randomized controlled trial protocols were changed at least once.
- A total of 48% of trials changed type, number or time point of primary efficacy outcome.
- Discrepancy in number of secondary efficacy outcomes was found in 109 trials (59%), in type of secondary efficacy outcomes in 108 trials (58%) and in outcome time points was in 60 (32%) trials.
- Only six of 186 (3.2%) trials defined primary safety outcomes in registered protocol and five (2.7%) in publication in journal.
- Prevalence of changes in primary efficacy outcomes were less common in trials of pharmacological interventions, in trials sponsored by industry, and trials with authors having reported financial conflict of interest related to a sponsor.

Author contributions

L Puljak designed the study. M Krsticevic, D Saric, F Saric, E Slapnicar, K Boric and M Jeric Kegalj extracted data. M Krsticevic, S Dosenovic, L Puljak and A Jelacic Kadic were involved in data analysis. All authors participated in interpretation of the data. All authors revised manuscript critically and did final approval of the submitted version.

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