Prospective registration was associated with a reduced risk of bias for randomized controlled trials: A meta-research study

Yuan Tian[1], Haofei Lu[2], Wenxuan Zhou[3], Suhail A. R. Doi[4], Luis Furuya-Kanamori[5], Lifeng Lin[6], Yoon Loke[7], Sunita Vohra[8], Chang Xu[1], Zheqi Xu[9]✉

1. Proof of Concept Center, Eastern Hepatobiliary Surgery Hospital, Third Affiliated Hospital, Second Military Medical University, Naval Medical University, Shanghai, China
2. The First School of Clinical Medicine, Anhui Medical University, Hefei, China
3. The Third Department of Hepatic Surgery, Eastern Hepatobiliary Surgery Hospital, Third Affiliated Hospital, Second Military Medical University, Naval Medical University, Shanghai, China
4. Department of Population Medicine, College of Medicine, QU Health, Qatar University, Doha, Qatar
5. UQ Center for Clinical Research, The University of Queensland, Herston, Australia
6. Department of Epidemiology and Biostatistics, University of Arizona, Tucson, AZ, USA.
7. Norwich Medical School, University of East Anglia, Norwich, UK
8. Departments of Pediatrics & Psychiatry, Faculty of Medicine & Dentistry, University of Alberta, Edmonton, Alberta, Canada
9. The Third Department of Hepatic Surgery, Eastern Hepatobiliary Surgery Hospital, Third Affiliated Hospital, Second Military Medical University, Naval Medical University, Shanghai, China

Running title: Prospective registration associated with a reduced risk of bias

Correspondence to:

Zheqi Xu, The Third Department of Hepatic Surgery, Eastern Hepatobiliary Surgery Hospital, Third Affiliated Hospital, Second Military Medical University, Naval Medical University, Shanghai, China; Email: zheqixu@smmu.edu.cn

Abstract

Objectives: To investigate the association between trial registration and the risk of bias.

Study design and settings: Randomized controlled trials (RCTs) from systematic reviews of medication-harm published between January 1, 2015, and January 1, 2020 were used, assessing first post and start dates on open registries along with risk of bias. Multivariable logistic regression analyses for both individual safeguards and overall risk of bias (RoB) by registration status (i.e., not registered, retrospectively registered, prospectively registered) were conducted.

Results: A total of 2,030 RCTs were identified from 151 systematic reviews; 65.46% (851/1,300) were registered prospectively and 34.54% (449/1,300) retrospectively among 64.04% (1,300/2,030) registered RCTs. Regression analysis indicated that when compared to no registration, prospective registration was associated with safeguards against bias using randomization sequence generation (OR = 1.51, 95% CI: 1.09 to 2.07), allocation concealment (OR = 1.69, 95% CI: 1.22 to 2.36), blinding of outcome assessors (OR = 1.65, 95% CI: 1.14 to 2.38), as well as lower overall RoB (OR = 2.04, 95% CI: 1.19 to 3.50). When comparing prospectively and retrospectively registered trials, prospective registration was more likely to have lower overall and individual RoB, but this was not statistically significant. Prospective registration was associated with blinding of participants (OR = 1.70, 95% CI: 1.26 to 2.30) and outcome assessors (OR = 1.68, 95% CI: 1.25 to 2.28), but not lower overall RoB as compared to retrospective registration.

Conclusion: Prospectively registered trials were more likely than non-registered trials to implement adequate procedures against bias. Prospectively registered trials may also serve as an indicator of lower overall RoB in RCTs.

Keywords: randomized controlled trial, risk of bias, prospective registration, harms, adverse events,

Word counts: 2,945

Conflicts of interest: None

Introduction

In evidence-based medicine, randomized controlled trials (RCTs) are considered the trusted gold standard for the generation of high-quality evidence about the effectiveness of interventions [1]. In RCTs, participants are randomly assigned to intervention groups, ensuring that the subjects among groups are comparable to minimize potential confounding bias [2]. However, RCTs are not completely free from biases that can arise from other design weaknesses or poor implementation of the recommended methodology. For example, allocation bias may arise from weaknesses in the randomization procedure [3], whereas performance and measurement biases can crop up if concealment and blinding are not well implemented [4]. All these biases can potentially cause effect estimates to deviate from the true value [5].

Substantial efforts have been made to promote methods that safeguard against the threat of bias in RCTs. These include, but are not limited to, standardization of the trial procedures [6], the development of the risk of bias instruments to explicitly highlight problematic areas [7], and the promotion of the transparency of the trial life cycle [8]. Trial registration is a key initiative aimed at improving transparency through facilitating the detection of selective reporting bias [9] and subsequent reduction in publication bias [10]. Published empirical research has suggested that prospective trial registration is associated with a reduction in outcome reporting bias [11-13].

The potential benefits of trial registration may extend beyond the reduction in reporting biases. Several empirical studies have noticed that registration may also be associated with methodological improvements in trial design and implementation [14]. Nevertheless, there have been divergent findings regarding the extent of this association. For example, in the study by Lindsley et al., registered trials were more often judged as having low risk of bias [15]. However, Farquhar et al. did not consistently observe such associations in some of the bias components of registered and non-registered trials [16]. There is a clear need for further empirical studies to better define whether trial registration is truly associated with lower risk of bias, particularly in studies reporting medication-harms such as that harms were reported inconsistently and critical methodological elements diverged in registry and published studies [17, 18], thus serving as a strong foundation for

robust evidence to inform healthcare decision-making. Therefore, in this study, we have used a large-scale empirical dataset to evaluate any potential association between prospective trial registration and specific implementation of safeguards as well as overall risk of bias.

Methods

This meta-research, as a part of a large research project, aimed to examine bias safeguards implemented in RCTs by registration status, thereby evaluating the association between registration and risk of bias. For the reporting of this study, we accorded to related guidelines whenever possible [19].

Data source

Key features of our study design and protocol have been reported previously [20]; our work was conducted based on a comprehensive empirical dataset, the SMART Safety [21]. Briefly, we conducted a literature search of systematic reviews focused on adverse events via PubMed from January 1, 2015 to January 1, 2020. We included systematic reviews and meta-analyses for healthcare interventions, with safety as the exclusive outcome, and pairwise meta-analyses that reported two-by-two data for each trial. We defined adverse events as *"any untoward medical occurrence in a patient or subject in clinical practice,"* which consists of adverse effects, adverse reactions, harms, complications, and toxicity in pharmaceutical interventions [22]. The sensitivity of the search was verified, and it ranged from 93.85% to 99.30% [23].

Two reviewers screened the records independently. In step one, titles and abstracts were screened; reasons for inclusion and exclusion were documented in detail using Rayyan (https://www.rayyan.ai/) [24]. Subsequently, the full-text records were retrieved and assessed for eligibility. Any disagreements were resolved through discussion.

Data collection

Data collection was conducted through independent duplicate extraction (CX, YT, XY, RZ, YZ); see Table S2. Three types of information regarding the included trials were collected: baseline characteristics, registration status, and risk of bias assessment. For baseline information, we extracted the year of publication, number of participants, regions where the studies were conducted (e.g., Asia), funding (e.g., industry, academic), and age groups (e.g., children). For each trial, we retrieved the number of publications by the first author via Scopus. A triple-checking process was implemented to verify information to minimize errors [21]. The detailed procedure for collecting registration status and assessing the risk of bias is described below.

Registration information

We classified the trial registration status into three exclusive categories: prospectively registered, retrospectively registered, and not registered [25]. We used a two-step process to define the registration status for each trial. First, we reviewed the full texts of the included trials to access any reported registration information. Second, if such information was not reported, we conducted reverse searches in three registries and a search portal: ClinicalTrials.gov, European Clinical Trials Register, International Standard Randomized Controlled Trial Number, and WHO's International Clinical Trials Registry Platform—based on the principal author's name, intervention, control, and sample size. We took this step because around 10% of published reports do not explicitly report their registration status [26]. To more precisely define the registration category (prospective or retrospective), we recorded the exact dates when the trials were posted to the public registry, when they started, and when the primary trial was completed. Those trials registered before or within one month of the first participant enrollment were categorized as prospectively registered (Supplementary Box 1), while all others were considered retrospectively registered [27].

Risk of bias (RoB) assessment

In terms of the Cochrane risk-of-bias tool (RoB [7]), the risk of bias was mainly evaluated across 7 safeguards: 1) random sequence generation, 2) allocation concealment, 3) blinding of participants and personnel, 4) blinding of outcome assessors, 5) incomplete outcome data, 6) selective reporting, and 7) other bias. However, our evaluation focused on the first four safeguards due to their relatively objective characteristics [28]. These four safeguards were used to assess the overall risk of bias in

the included trials. Five authors conducted the RoB assessment (XY, RZ, TQ, FY, YY); to minimize potential measurement bias, pilot training was employed prior to the start of the risk of bias assessment, using five trials randomly selected from the dataset. After the training, the authors were divided into two groups to independently assess the RoB (Group 1: FY, TQ, YY; Group 2: XY, RZ).

We aimed to use the response options: 'Yes', 'Probably Yes' (PY), 'No', 'Probably No' (PN), and 'No information' (NI). However, in our pilot training, we found that the negatively worded phrasing for the assessment of the implementation of safeguards created some confusion in interpretations. Therefore, to avoid confusion, we took the options of 'Yes' or 'Probably Yes' as studies that implemented or probably implemented the safeguards, and 'No' and anything else as did not or probably did not implement the safeguards, in contrast to the original responses of RoB 2.

The overall risk of bias was decided based on the Cochrane risk-of-bias tool [29], as follows: 1) low risk: a trial, if all four safeguards implemented (PY or Y); 2) unclear: at least 1 safeguard out of four was assessed unclear, and no safeguards were assessed as high; 3) high risk: any one or more of the safeguards were assessed as not implemented (N or PN). Any disagreements were resolved through discussion and consensus.

Outcomes

Our primary interest was to examine the odds of implementation of each of the four safeguards by category of trial registration status. A secondary outcome was the odds of a trial having low overall risk of bias (by the scheme outlined above) according to the category of trial registration, namely prospective, retrospective, and not registered.

Statistical analysis

Baseline characteristics were summarized using counts and proportions for categorical variables. For the main analysis, we employed a multivariable logistic regression with the implementation status of RoB as the response variable and registration status as the explanatory variable, taking potential confounders into account. To model the regression, we indexed the implemented category

as 1 (e.g., prospective registration) and the not-implemented as 0 (e.g., not registered), with registration implementation status as defined in the methods. Similarly, for RoB, we indexed low risk of bias as 1 and high/unclear risk of bias as 0, using the categories defined in the methods.

To identify potential confounders, a directed acyclic graph (DAG) (http://dagitty.net/) was used. This method allowed us to establish the directed relationship of related variables between registration status and either implementation or RoB [30]. To this end, the following variables were found to be potential confounders and were further adjusted in the regression model: year of publication, region, funding sources, and trial experience of the first author. We stratified the year of publication into three categories (before 2004, 2005 to 2010, after 2011) based on the time of release of two important registration and reporting policies, specifically, the ICMJE (2004) and CONSORT 2010 (2010) [31]. We stratified the region into four categories based on the economic levels and geography, such as multi-region, North America or Europe, other regions, and no information. We stratified funding sources into three categories based on the nature of the sponsors: academic funding, industry funding, and others. The trialists' prior experience with RCTs was measured by determining whether the first author of included trials had previously been a co-author on a preceding RCT. We stratified the number of published studies into four parts (Q1, Q2, Q3, Q4, and no information) as a proxy for trialists' experience; see Figures S2 and S3.

We reported our results as the odds ratio (OR) and its 95% confidence interval (CI) [33]. To avoid potentially misleading results, we defined a minimal important difference (MID) for the covariates, where "effects" larger than 1.05 or lower than 0.95 were interpreted as associations. All statistical analyses were conducted using Stata/SE 16.0 (Stata Corp LCC, College Station, TX), with a significance level of alpha=0.05.

Results

Of the 18,636 records from PubMed, 1,976 duplicates were identified, and 15,339 were further

removed after screening titles and abstracts. The full-text versions of the remaining 1,330 were reviewed, leading to the initial inclusion of 151 systematic reviews, which consisted of 629 meta-analyses involving 2,305 trials. Among these 2,305 trials, 156 duplicate trials, 78 ongoing trials, and 41 trials with inaccurate registration numbers that could not be verified on registry platforms were subsequently excluded. Finally, 2,030 trials were included and underwent risk of bias assessment and statistical analysis (Figure 1).

The baseline characteristics of the 2,030 included trials are shown in Table 1. There were 1,300 (64.04%) registered trials, compared to 730 (35.96%) trials that were not registered. Of the 1,300 registered trials, 851 (65.46%) were deemed to have been prospectively registered. The distribution of our judgements (high, low, or unclear risk of bias) regarding specific bias safeguards as well as the overall risk for prospectively, retrospectively, and not registered trials are depicted in Figure 2.

Impact of registration status

Four confounding factors—regions, years, funding, and the first authors' trial experience, were adjusted based on the DAG (*Supplementary Figure S4)***.** Our regression analysis suggested higher odds of low RoB (OR = 2.04, 95% CI: 1.19 to 3.50) for prospectively registered trials compared to those that were not registered (Figure 3).

With regard to the specific safeguards, trials that had been registered prospectively showed higher odds of implementing adequate randomization sequence generation (OR = 1.51, 95% CI: 1.09 to 2.07), allocation concealment (OR = 1.69, 95% CI: 1.22 to 2.36), blinding procedure for participants (OR = 1.47, 95% CI: 1.02 to 2.13), blinding procedure for health care providers (OR = 1.50, 95% CI: 1.04 to 2.16), and blinding procedure for outcome assessors (OR = 1.65, 95% CI: 1.14 to 2.38) compared to trials that were not registered.

Our regression analysis showed higher odds of low RoB (OR = 1.32, 95% CI: 0.88 to 1.98), which was not statistically significant, for prospectively registered trials compared to those that were retrospectively registered (Figure 3).

With regard to the individual safeguards, trials that had been registered prospectively showed higher odds of implementation of blinding procedures for participants (OR = 1.70, 95% CI: 1.26 to 2.30) and health care providers (OR = 1.68, 95% CI: 1.25 to 2.28) compared to trials that were registered retrospectively. We found a similar effect for the safeguards pertaining to adequate randomization sequence generation (OR = 1.02, 95% CI: 0.78 to 1.33), allocation concealment (OR = 1.14, 95% CI: 0.86 to 1.52), and blinding procedures for outcome assessors (OR = 1.34, 95% CI: 1.00 to 1.80) compared to retrospectively registered trials.

Trials that were registered before the first participant enrollment showed higher odds of low RoB (OR = 2.06, 95% CI: 1.19 to 3.57) than trials that were not registered. With regard to retrospectively registered trials, no association (OR = 1.25, 95% CI: 0.89 to 1.76) was observed for overall and individual risk of bias (Figure 3).

Discussion

In this study, we used a large-scale empirical dataset to compare the risk of bias between prospectively registered, retrospectively registered, and not registered trials. Prospective registration, when compared to trials that had no registration, was associated with a lower overall risk of bias as well as individual safeguards against bias pertaining to adequate randomization sequence generation, allocation concealment, and blinding of outcome assessors. In contrast, retrospective registration was less likely to implement blinding of participants, healthcare providers, and outcome assessors. There was a trend that prospective registration was associated with a higher likelihood of lower risk of bias than retrospectively registered trials.

Our current findings are different in some aspects from those of previous studies. In the study by Tan et al., prospectively registered trials had similar risk of bias across four out of six items compared to retrospective registration, but this study was based on relatively narrow empirical data

in 2017 [34]. Conversely, Dechartres et al. suggested that not registered trials or retrospectively registered trials may contribute to inflated or larger effect estimates, and that trial registration status may represent another form of meta-bias [35]. In our study, evidence of prospective registration (compared to non-registration) was associated with a lower risk of bias. This may be due to the fact that trials registered prospectively tend to have better reporting than those not registered ones — in our dataset, there was a large proportion (85.21%) of non-registered trials with missing methodological information (i.e., no information), and thus were more likely to be judged to have high/unclear risk of bias. It is also possible that the principal authors of retrospective/not registered trials may have limited experience in trial design and implementation, potentially leading to a higher risk of bias [36]. Plausibly, both high risk of bias and retrospectively/not registered could be features of poorly designed RCTs due to the limited experience of trial initiators.

Implications for future practice

It has been 20 years since the ICMJE recommended that journals should only publish trials if they are listed on a public registry. Although prospective registration has increased rapidly, retrospective registration remains widespread. This is not unexpected; there are many diverse reasons why retrospective registration still occurs , one for instance, delay arising frommiscommunication between trialists and ethics/administrative staff [37]. Given that more RCTs have been published recently, we advocate that trialists should be fully aware of the policies of RCTs, draft detailed protocols, and more importantly, proactively prepare submissions of trial protocols to public registries. In addition, in the study of Hunter et al. [38], 74% of retrospective registrations were linked to non-academic issues, which could be addressed by expediting ethics, administrative, and registry services. Due to a potential lack of awareness amongst researchers about registering trials prospectively [37], there is an urgent need to further promote the importance of prospective registration in driving forward better reporting for harms.

Strengths and limitations

Our study is based on what we consider to be the largest empirical databank of adverse events, ensuring sufficient breadth and representativeness. The data collection process was closely

supervised, including triple-checking to reduce human errors. In data analysis, we utilized the DAG plot to identify potential confounders when assessing the association between registration status and risk of bias. These steps are designed to enhance the reliability of the findings of the current study.

However, several limitations should be highlighted. First, in our study, we only considered the first four safeguards of the RoB checklist, whilst the remaining safeguards (e.g., selective reporting) were not considered. This would have some impact on the ranking of the overall risk of bias. However, those safeguards were more likely to be influenced by subjective judgment, and thus were prone to measurement error. Second, we acknowledge that incomplete reporting on specific bias safeguards (such as sequence generation) had to be classified as 'No Information' during our assessment, thereby hindering a complete assessment of all relevant aspects of bias. Third, the findings of this study stem from systematic reviews of medication-related harms; it is possible that these may differ from the findings from medication-related benefits or other non-pharmaceutical interventions (e.g., surgery and education). Therefore, a further investigation of the relationship between prospective registration and risk of bias is warranted for systematic reviews of other types of interventions.

Conclusions

The empirical evidence from this study suggested that prospectively registered trials may serve as an indicator of lower overall bias in RCTs, especially in performance bias and measurement bias. Conversely, systematic reviewers should proceed more cautiously if their evidence synthesis is largely based on non-registered or retrospectively registered trials that are potentially more prone to methodological weaknesses. Whenever possible, prospective registration should always be the primary consideration for the incoming trials.

Contributors

Yuan Tian: Conceptualization, Data analysis and result interpretation, Manuscript drafting, Data collection and Manuscript editing. Haofei Lu: Data collection, Data analysis and result interpretation, Manuscript editing. Wenxuan Zhou: Statistical guidance, Methodology guidance, Manuscript editing. Suhail A. R. Doi: Statistical guidance, Methodology guidance, Manuscript editing. Luis Furuya-Kanamori: Methodology guidance, Manuscript editing. Yoon Loke: Statistical guidance, Methodology guidance, Manuscript editing. Sunita Vohra: Statistical guidance, Methodology guidance, Manuscript editing. Chang Xu: Methodology guidance, Result interpretation, Manuscript editing. Zheqi Xu: Data collection, Manuscript editing, and Funding support.

Funding

The current study was supported by the Postdoctoral Fellowship Program of CPSF (Number: GZC20242282) and National Natural Science Foundation of China (Number: 82204379)

Acknowledgments

We thank Mr. Lu Cuncun from Lanzhou University for developing the search strategy for the whole project. We also thank Rui Zhang, Xi Yang, Yi Zhu, Zhangnan Ye, Sicheng Jin, Zhengyang Pan from Anhui Medical University, Xiaoqin Zhou, Tianqi Yu from Sichuan University of West China Hospital for helping for the data collection data checking of the whole project.

Data sharing:

Data can be found at https://osf.io/g3mdu/.

References

1. Naidoo N, Nguyen VT, Ravaud P, Young B, Amiel P, Schanté D, et al. The research burden of randomized controlled trial participation: a systematic thematic synthesis of qualitative evidence. BMC Med. 2020;18(1):6.
2. Fonarow GC. Randomization-There Is No Substitute. JAMA Cardiol. 2016; 1(6):633-5.
3. Herbison P, Hay-Smith J, Gillespie WJ. Different methods of allocation to groups in randomized trials are associated with different levels of bias. A meta-epidemiological study. J Clin Epidemiol. 2011; 64(10):1070-5.
4. Barcot O, Boric M, Dosenovic S, Puljak L. Assessing the risk of performance and detection bias in Cochrane reviews as a joint domain is less accurate compared to two separate domains. BMC Med Res Methodol. 2021;21(1):149.
5. Savovic J, Turner RM, Mawdsley D, Jones HE, Beynon R, Higgins JPT, et al. Association Between Risk-of-Bias Assessments and Results of Randomized Trials in Cochrane Reviews: The ROBES Meta-Epidemiologic Study. Am J Epidemiol. 2018;187(5):1113-1122.
6. Butcher NJ, Monsour A, Mew EJ, Chan AW, Moher D, Mayo-Wilson E, et al. Guidelines for Reporting Outcomes in Trial Reports: The CONSORT-Outcomes 2022 Extension. JAMA. 2022;328(22):2252-2264.
7. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011 Oct 18;343:d5928.
8. Sotgiu G, Humbert M, Dinh-Xuan AT, Migliori GB. Clinical trials: registration and transparency. Eur Respir J. 2016; 47(5):1342-4.
9. Mitra-Majumdar M, Kesselheim AS. Reporting bias in clinical trials: Progress toward transparency and next steps. PLoS Med. 2022;19(1):e1003894.
10. Bax L, Moons KG. Beyond publication bias. J Clin Epidemiol. 2011;64(5):459-62.
11. Won J, Kim S, Bae I, Lee H. Trial registration as a safeguard against outcome reporting bias and spin? A case study of randomized controlled trials of acupuncture. PLoS One. 2019; 14(10):e0223305.
12. Innocenti T, Giagio S, Salvioli S, Feller D, Minnucci S, Brindisino F, et al. Completeness of Reporting Is Suboptimal in Randomized Controlled Trials Published in Rehabilitation Journals,

With Trials With Low Risk of Bias Displaying Better Reporting: A Meta-research Study. Arch Phys Med Rehabil. 2022;103(9):1839-1847.

13. Xu C, Zhang F, Doi SAR, Furuya-Kanamori L, Lin L, Chu H, et al. Influence of lack of blinding on the estimation of medication-related harms: a retrospective cohort study of randomized controlled trials. BMC Med. 2024 Mar 7;22(1):83.
14. Dickersin K, Mayo-Wilson E. Standards for design and measurement would make clinical research reproducible and usable. Proc Natl Acad Sci U S A. 2018;115(11):2590-2594.
15. Lindsley K, Fusco N, Li T, Scholten R, Hooft L. Clinical trial registration was associated with lower risk of bias compared with non-registered trials among trials included in systematic reviews. J Clin Epidemiol. 2022; 145:164-173.
16. Farquhar CM, Showell MG, Showell EAE, Beetham P, Baak N, Mourad S, et al. Clinical trial registration was not an indicator for low risk of bias. J Clin Epidemiol. 2017; 84:47-53.
17. Zhang F, Zhu Y, Zhao S, Zhang Q, Tao H, Wu Y, et al. Discordant Information on Blinding in Trial Registries and Published Research: A Systematic Review. JAMA Netw Open. 2024 Dec 2;7(12):e2452274
18. Hartung DM, Zarin DA, Guise JM, McDonagh M, Paynter R, Helfand M. Reporting discrepancies between the ClinicalTrials.gov results database and peer-reviewed publications. Ann Intern Med. 2014 Apr 1;160(7):477-83.
19. Murad MH, Wang Z. Guidelines for reporting meta-epidemiological methodology research. Evid Based Med. 2017;22(4):139–42.
20. Fan S, Yu T, Yang X, Zhang R, Furuya-Kanamori L, Xu C. The SMART Safety: An empirical dataset for evidence synthesis of adverse events. Data Brief. 2023; 51:109639.
21. Xu C, Zhou X, Zorzela L, Ju K, Furuya-Kanamori L, Lin L, et al. Utilization of the evidence from studies with no events in meta-analyses of adverse events: an empirical investigation. BMC Med. 2021;19(1):141.
22. Zorzela L, Loke YK, Ioannidis JP, Golder S, Santaguida P, Altman DG, et al. PRISMA harms checklist: improving harms reporting in systematic reviews. BMJ. 2016; 352:i157.
23. Xu C, Yu T, Furuya-Kanamori L, Lin L, Zorzela L, Zhou X, et al. Validity of data extraction in evidence synthesis practice of adverse events: reproducibility study. BMJ. 2022; 377:e069155.
24. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for

systematic reviews. Syst Rev. 2016 Dec 5;5(1):210.

25. Al-Durra M, Nolan RP, Seto E, Cafazzo JA. Prospective registration and reporting of trial number in randomised clinical trials: global cross sectional study of the adoption of ICMJE and Declaration of Helsinki recommendations. BMJ. 2020; 369:m982.
26. van de Wetering FT, Scholten RJ, Haring T, Clarke M, Hooft L. Trial registration numbers are underreported in biomedical publications. PLoS One. 2012;7(11):e49599.
27. International Committee of Medical Journal Editors (ICMJE). Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. https://www.icmje.org/icmje-recommendations.pdf. Accessed Sept. 29, 2024.
28. Wang Y, Ghadimi M, Wang Q, Hou L, Zeraatkar D, Iqbal A, et al. Instruments assessing risk of bias of randomized trials frequently included items that are not addressing risk of bias issues. J Clin Epidemiol. 2022; 152:218-225.
29. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). Cochrane, 2022. Available from www.training.cochrane.org/handbook.
30. Tennant PWG, Murray EJ, Arnold KF, Berrie L, Fox MP, Gadd SC, et al. Use of directed acyclic graphs (DAGs) to identify confounders in applied health research: review and recommendations. Int J Epidemiol. 2021; 50(2):620-632.
31. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010 Mar 23;340:c332.
32. Odutayo A, Emdin CA, Hsiao AJ, et al. Association between trial registration and positive study findings: cross sectional study (Epidemiological Study of Randomized Trials-ESORT). BMJ. 2017 Mar 14;356:j917.
33. Doi SA, Furuya-Kanamori L, Xu C, Chivese T, Lin L, Musa OAH, et al. The Odds Ratio is "portable" across baseline risk but not the Relative Risk: Time to do away with the log link in binomial regression. J Clin Epidemiol. 2022; 142:288-293.
34. Tan AC, Jiang I, Askie L, Hunter K, Simes RJ, Seidler AL. Prevalence of trial registration varies by study characteristics and risk of bias. J Clin Epidemiol. 2019; 113:64-74.
35. Dechartres A, Ravaud P, Atal I, Riveros C, Boutron I. Association between trial registration and treatment effect estimates: a meta-epidemiological study. BMC Med. 2016; 14(1):100.

36. Haslberger M, Gestrich S, Strech D. Reporting of retrospective registration in clinical trial publications: a cross-sectional study of German trials. BMJ Open. 2023; 13(4):e069553.
37. Harriman SL, Patel J. When are clinical trials registered? An analysis of prospective versus retrospective registration. Trials. 2016; 17:187.
38. Hunter KE, Seidler AL, Askie LM. Prospective registration trends, reasons for retrospective registration and mechanisms to increase prospective registration compliance: descriptive analysis and survey. BMJ Open. 2018; 8(3): e019983.

Figure 1. Flowchart for screening eligible randomized controlled trials.

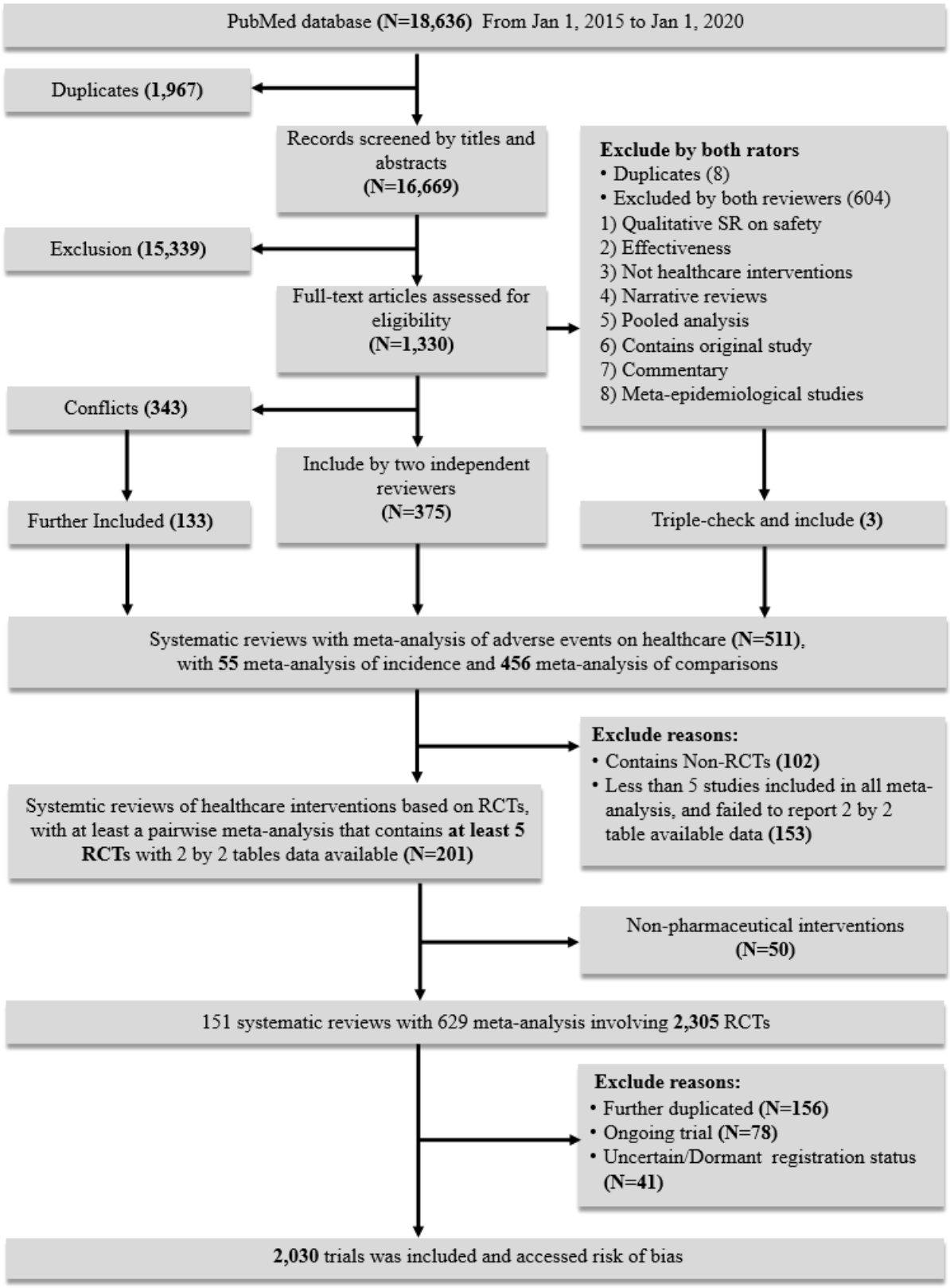


Table 1. Baseline information of clinical trials included in systematic reviews.

Basic characteristics	Total trials n=2030	Registered trials n=1300	Not registered trials n=730
Publication year, number (%)			
< 2004	417 (20.54)	10 (0.77)	407 (55.75)
2005 to 2010	503 (24.78)	291 (22.38)	212 (29.04)
>2011	1110 (54.68)	999 (76.85)	109 (14.93)
Trial participants, number (%)			
<100 participants	445 (21.92)	201 (15.46)	244 (33.42)
100-300 participants	711 (35.02)	429 (33.00)	282 (38.63)
>300 participants	874 (43.05)	670 (51.54)	204 (27.95)
Geographic region, number (%)			
Multiple regions	904 (44.53)	762 (58.62)	142 (19.45)
Northern America/Europe	552 (27.19)	342 (26.31)	210 (28.77)
Asia/Africa/Australia/Southern America	212 (10.44)	149 (11.46)	63 (8.63)
No information	362 (17.83)	47 (3.62)	315 (43.15)
Funding, number (%)			
Industry	1578 (77.73)	1131 (87.00)	447 (61.23)
Academic	242 (11.92)	131 (10.08)	111 (15.21)
No funding or missing	210 (10.34)	38 (2.92)	172 (23.56)
Age, number (%) *			
Children	93 (4.58)	36 (2.77)	57 (7.81)
Adults	1245 (61.33)	806 (62.00)	439 (60.14)
Seniors	594 (29.26)	412 (31.69)	182 (24.93)
Household	1 (0.05)	-	1 (0.14)
No information	97 (4.78)	46 (3.54)	51 (6.99)
Number of publications (quartiles), number (%)			
Q1	504 (24.83)	246 (18.92)	258 (35.34)
Q2	501 (24.68)	321 (24.69)	180 (24.66)
Q3	505 (24.88)	356 (27.38)	149 (20.41)
Q4	500 (24.63)	372 (28.62)	128 (17.53)
No information	20 (0.99)	5 (0.38)	15 (2.05)

***Note**: Population age was defined following WHO in 2013; children are defined as under 18 years of age, adults as between 18 and 59 years of age, and seniors as 60 and over;

Figure 2. Summary of risk of bias in prospectively, retrospectively, and not registered clinical trials.

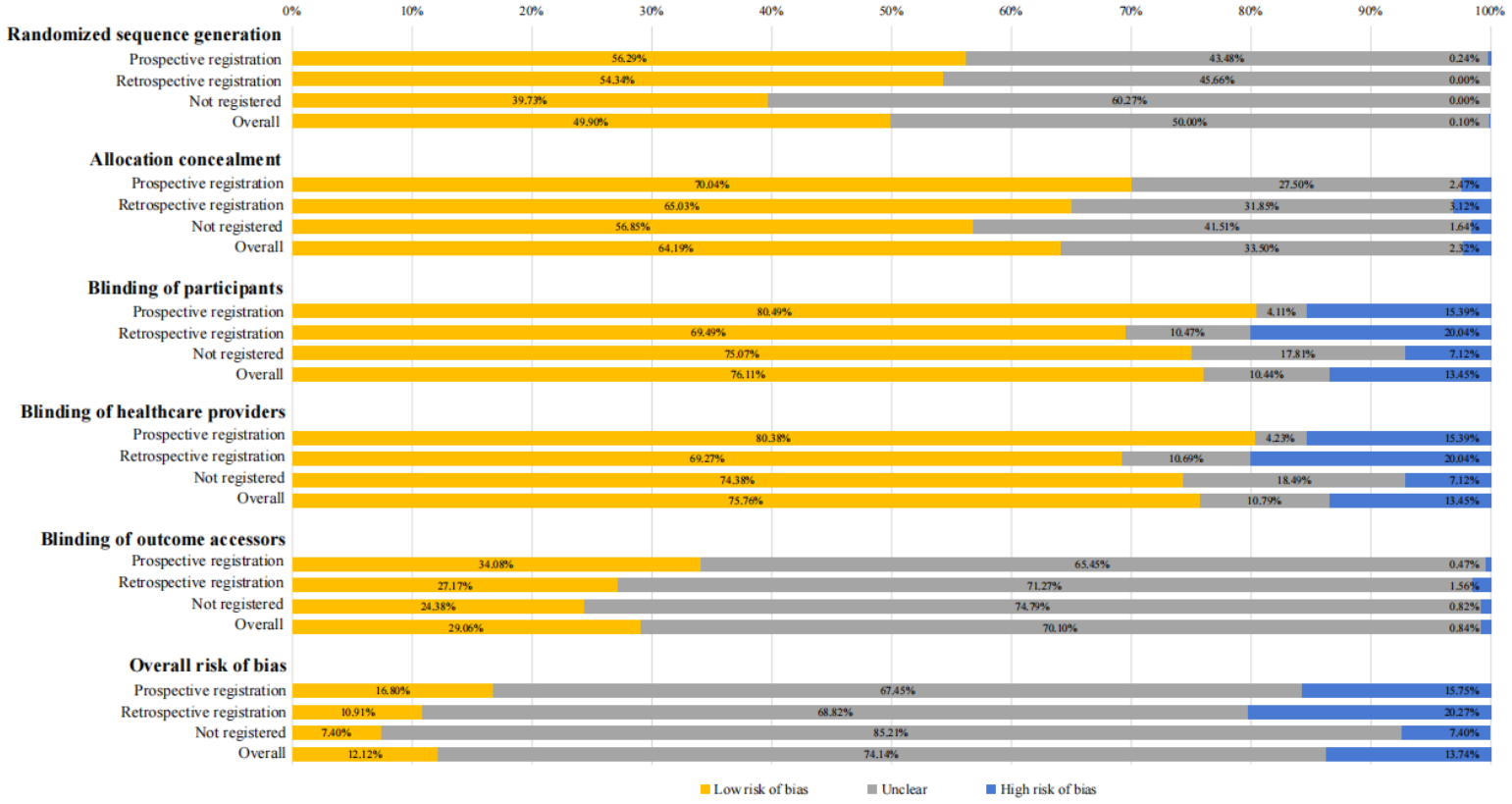
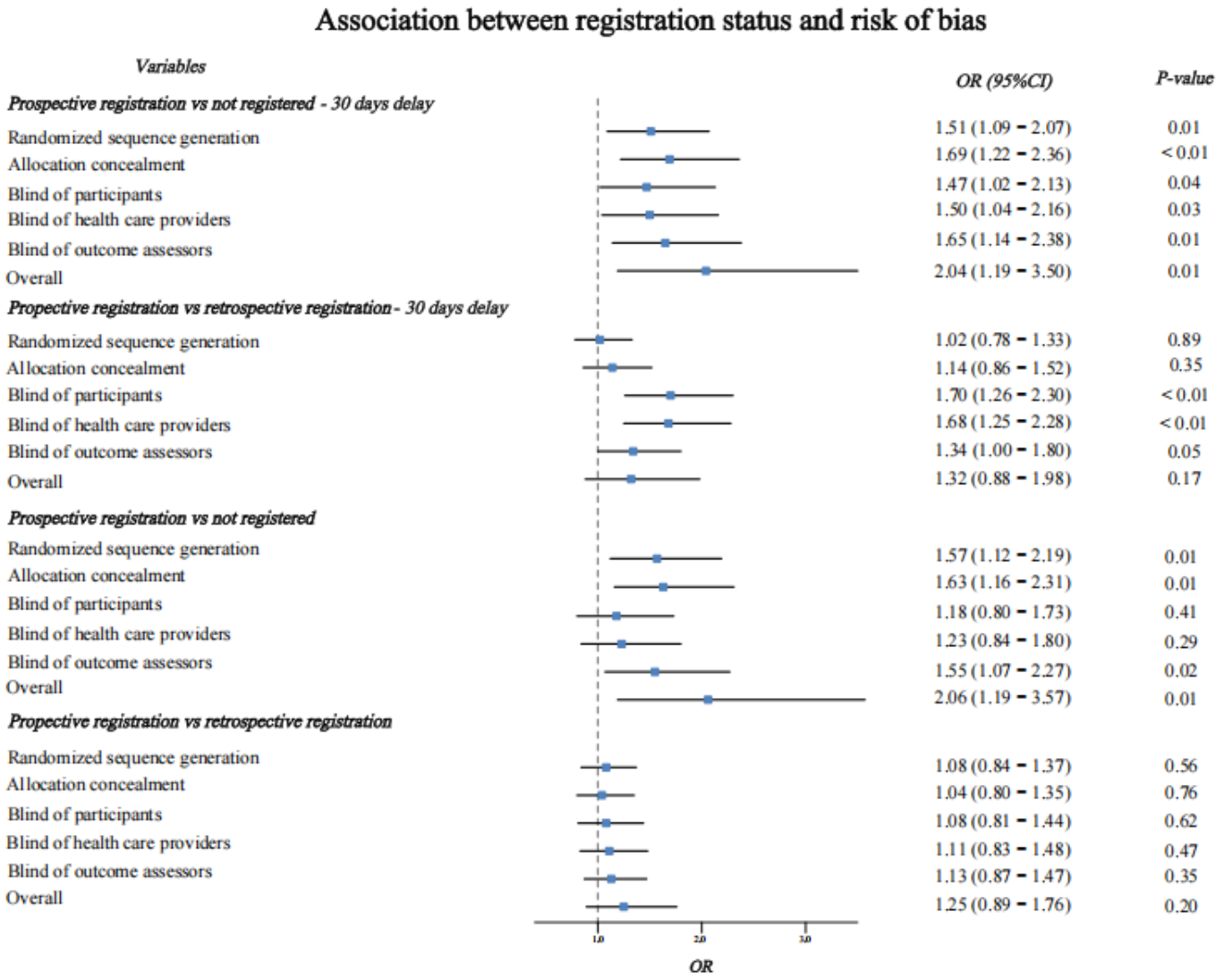


Figure 3. Forest plot depicting the odds of implementation of risk of bias or of low RoB by category of registration status.



Note: Prospective registration was defined as registration occurring before or within 30 days of the first participant's enrolment.