BMJ Open Selective reporting bias in randomised controlled trials from two network meta-analyses: comparison of clinical trial registrations and their respective publications

Eric KC Wong,1,2 Chantelle C Lachance,†  Matthew J Page,3 Jennifer Watt,†  Areti Veroniki,1,4,5 Sharon E Straus,1,2 Andrea C Tricco1

ABSTRACT

Objective To determine (i) the difference in the frequency of serious adverse events (SAEs) reported in trial registrations and their respective primary publications and (ii) the effect of adding SAE data from registries to a network meta-analysis (NMA) in changing the surface under the cumulative ranking (SUCRA) curve values of interventions.

Design Secondary analysis of primary publications from two NMAs.

Eligibility criteria for selecting studies We included randomised trials published in English after 2005 that were included in two NMAs of pharmacological interventions for Alzheimer’s disease and chronic obstructive pulmonary disease.

Data extraction Two reviewers independently searched multiple international trial registries for registration status and abstracted data from the included study publications and ClinicalTrials.gov.

Results Of the 203 randomised trials included, 140 (69.0%) were registered with a trial registry and 72 (35.5%) posted results in the registry. The proportion of registered trials increased over time (38.5% in 2005 vs 78.6% in 2014). Of the publications with results posted in a trial registry, 14 (19.4%) had inconsistent reporting of overall SAEs; 7 (10.4%) studies did not report SAEs in the publication but did in the registry. In the 134 randomised trials with a prespecified primary outcome in the registry, 19 studies (9.4%) had a change in the primary outcome in the publication. Adding SAEs reported in registries to the NMAs did not affect the ranking of interventions.

Conclusion We identified inconsistent reporting of SAEs in randomised trials that were included in two NMAs. Findings highlight the importance of including trial registries in the grey literature search and verifying safety data before incorporating it into NMAs.

INTRODUCTION

Selective or incomplete reporting occurs when authors do not include results for any outcome that is expected to be reported for a study.1 Selective reporting of clinical trial results can lead to erroneous conclusions about drug safety and efficacy, which can have a major impact on patients.2–6 In response, the US government created a clinical trials registry in 2000 where investigators can disclose ongoing clinical trials with information about planned outcome measurement (https://clinicaltrials.gov).7 In 2005, the International Committee of Medical Journal Editors (ICMJE) mandated the registration of clinical trials for their results to be eligible for publication in its member journals.8 In 2007, the Food and Drug Administration (FDA) required registration and reporting of summary results for all new drugs seeking regulatory approval.7 The FDA further required mandatory posting of adverse events in 2009.7 Clinical trial registries in other countries were created in subsequent years,9 for example, the European Union Clinical Trials
The validity of a knowledge synthesis, including network meta-analysis (NMA), is dependent on the quality of primary studies, which includes appropriate outcome reporting. Registration of clinical trials provides transparency in interpreting published results because the intended primary outcome is known. Similarly, summary results for adverse events reported in trial registries should be identical to those reported in the primary publication. Adverse events (AEs) are often incompletely and inconsistently reported in publications compared with trial registries. ClinicalTrials.gov defines an AE as an unfavourable change in the health of a participant, including abnormal laboratory findings, which happens during a clinical study or within a certain amount of time after the study has ended; this change may or may not be caused by the intervention being studied. Serious adverse events (SAEs) are AEs that result in death, are life-threatening, require inpatient hospitalisation or extend a current hospital stay, result in an ongoing or significant incapacity or interfere substantially with normal life functions or cause a congenital anomaly or birth defect. According to Consolidated Standards of Reporting Trials (CONSORT) clinical trial reporting standards, all AEs, and particularly SAEs, should be completely reported in publications.

Any discrepancy between the information provided in the registry and publication that is not disclosed may indicate concealment of results because of the statistical significance, magnitude or direction of the effect, leading to selective reporting bias. For example, cognitive enhancers for managing Alzheimer’s disease (AD) are only modestly effective, as such, if selective outcome reporting occurs in published trials, it may significantly change the perceived risk-benefit ratio of this drug class. Selective reporting happens regardless of whether differences are explained by authors. Previous studies revealed changes in summary estimates with addition of trial registry data for pair-wise meta-analyses (MA); similar findings for NMAs have not been reported.

Tang et al investigated the consistency between SAEs in ClinicalTrials.gov and their corresponding publications in a random sample of 300 randomised trials. SAE reporting was consistent between the two sources in only 11% of the registered trials. We aimed to investigate the prevalence of discrepant reporting of SAEs in randomised trials included in two NMAs that compared the relative efficacy and safety of cognitive enhancers in AD NMA and long-acting inhaled agents for chronic obstructive pulmonary disease (COPD NMA). We evaluated SAEs and not all AEs because SAEs should be consistently reported in both ClinicalTrials.gov and the manuscript. We also examined the frequency of trial registration and the impact of incorporating unpublished data reported in trial registries on NMA results.

METHODS

Study design

We conducted a retrospective review of the published journal articles and corresponding registration records for randomised trials included in two systematic reviews, the AD NMA and the COPD NMA. Our protocol was registered with the Open Science Framework (Identifier: osf.io/mk6dr).

Objectives

Our primary objective was to determine if there was a difference in the frequency of overall SAEs reported in the clinical trial registrations and the respective primary publications. As secondary objectives, we investigated:

- The proportion of randomised trials that reported trial registration information (eg, ID number) in the publication.
- The proportion of randomised trials that were registered in any publicly accessible trial registry.
- The proportion of randomised trials that had consistent reporting of the frequency of overall SAE.
- The proportion of randomised trials that referred to the primary outcome specified in the trial registry.
- The relative risk of each type of primary outcome change (eg, new, exclusion, upgrade, downgrade, change in definition or measure) in relation to whether the study conclusion is positive, determined using a previously defined method.
- The difference in ranking of the treatment groups for SAEs in the two NMAs after adding SAE data from the trial registry.

Eligibility criteria

We included randomised trials from the NMAs, since other study designs were not likely to be registered. Eligible randomised trials were published in English in 2005 or later, aligned with the ICMJE mandate for clinical trial registration.

Study procedure

Eligible randomised trials were scanned by two independent reviewers (EKCW, CCL) for a trial registration number. If no number was identified, we searched for the study in the most frequently used trial registries including ClinicalTrials.gov, European Union Clinical Trials Register and International Standard Randomised Controlled Trial Number Register (via the WHO International Clinical Trials Registry Platform). If we could not find a trial in these registries, we searched the national registry in the country where the trial was conducted. For identification of SAEs, we only included trials registered on ClinicalTrials.gov because other registries currently do not allow for the posting of trial results. Two investigators...
EKCW, et al. BMJ Open 2019;9:e031138. doi:10.1136/bmjopen-2019-031138

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Figure 1 Flow diagram for included studies. AD, Alzheimer’s disease; COPD, chronic obstructive pulmonary disease; NMA, network meta-analysis; SAE, serious adverse event.

(EKCW, CCL) independently searched the registries for studies that did not declare registration status in its publication. In each database, the search strategy included drug name (generic and brand) and condition name (eg, AD), with manual review of the trial entries. Two investigators independently abstracted the data from the included publications and trial registrations. Abstraction of SAEs was adapted from a previously described method. A calibration exercise was conducted first to establish consistency in data extraction. A third reviewer (ACT) adjudicated any discrepancies that could not be resolved by the two research team members (EKCW, CCL). The following data were abstracted:

**Study details:** first author, year of publication, country (-ies) of trial conduct (number, name), clinical condition (AD, COPD), journal, journal impact factor (JIF), disclosure of industry funding, sample size (total and per treatment arm).

**Registration details:** registration status, registration number, presence of registration number in publication, presence of results on registration website.

**Outcome reporting:** presence of primary outcome (in registry, in publication), primary outcome study results (statistically negative or positive (unfavourable or favourable; p<0.05), non-statistically negative or positive (unfavourable or favourable; p≥0.05), neutral indeterminate/unclear, or non-comparative), study conclusions (positive (significant), positive (non-significant), no effect, negative (non-significant), negative (significant)).

Outcome data were abstracted in February 2018 for all studies, which would allow >12 months mandatory reporting period for all included clinical trials.

**SAE reporting in registry and publication:** definition of SAEs, total number of SAEs, number of SAEs per treatment arm, number of participants per treatment arm.

**Data analysis**

We used $\chi^2$ tests to determine if there were differences between the clinical trial registrations and the respective publications. If inconsistencies were found between trial registration and the publication for any outcome data, we reviewed the publication for an explanation (eg, determined if a non-pre-specified outcome with statistically significant results was substituted). Differences in the primary outcome between registry and publication were graded using a published method into the following categories: no change, change in definition or measure, added (completely new outcome measure), upgrade (secondary outcome changed to primary), omitted (excluded primary outcome), downgrade (primary outcome changed to secondary). The abstract was used for the primary outcome change grading. The OR (95% CI) of each type of primary outcome change was determined in relation to whether the study conclusion was positive or not. Differences between data in the registry and publication were described. Analyses were conducted using SAS V.9.4 (SAS Institute, Cary, North Carolina, USA).

**NMA re-analysis**

Newly identified SAE data from the registry were added to the initial dataset for re-analysis of the NMA. Transitivity and consistency were explored in the original NMAs. A frequentist random-effects NMA model was applied to derive the summary effect estimates, along with 95% CIs and 95% predictive intervals using Stata (V.15, StataCorp). For heterogeneity, we used a common within-network between-study variance estimated with the restricted maximum likelihood method. Surface under the cumulative ranking (SUCRA) curves were used to compare treatment rankings for total SAE and displayed in a rank-heat plot.

**Patient and public involvement**

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient-relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

**RESULTS**

**Included studies**

Of the 318 randomised trials in the original systematic reviews, 89 were excluded because they were published before 2005 and 26 were excluded because they were written in languages other than English (figure 1). Thus, this study included 203 studies (AD NMA n=67; COPD NMA n=136).
Table 1  Study characteristics by registration status

|                           | Registered, n (%) | Not registered, n (%) | Total | P value |
|---------------------------|-------------------|-----------------------|-------|---------|
| **Industry funding**      |                   |                       |       |         |
| Yes                       | 132 (80.0)        | 33 (20.0)             | 165   | <0.001  |
| No                        | 8 (72.7)          | 3 (27.2)              | 11    |         |
| Not reported              | 0                 | 27 (100.0)            | 27    |         |
| **Country**               |                   |                       |       |         |
| Multinational             | 82 (90.1)         | 9 (9.9)               | 91    | <0.001  |
| Europe                    | 26 (50.0)         | 26 (50.0)             | 78    |         |
| North America             | 18 (64.2)         | 10 (35.7)             | 28    |         |
| Asia                      | 6 (23.1)          | 20 (76.8)             | 26    |         |
| South America             | 2 (66.7)          | 1 (33.3)              | 3     |         |
| Australia (Oceania)       | 0                 | 1 (100.0)             | 1     |         |
| Africa                    | 1 (100.0)         | 0                     | 1     |         |
| Not reported              | 1 (100.0)         | 0                     | 1     |         |
| **Clinical condition**    |                   |                       |       |         |
| Alzheimer’s disease       | 40 (59.7)         | 27 (40.3)             | 67    | 0.045   |
| COPD                      | 100 (73.5)        | 36 (26.5)             | 136   |         |
| **Journal impact factor** |                   |                       |       |         |
| 0–1.999                   | 4 (23.5)          | 13 (76.5)             | 17    | <0.001  |
| 2.000–4.999               | 86 (69.9)         | 37 (30.1)             | 123   |         |
| 5.000–9.999               | 17 (60.7)         | 11 (39.3)             | 28    |         |
| 10.000–14.999             | 14 (87.5)         | 2 (12.5)              | 16    |         |
| ≥15.000                   | 19 (100.0)        | 0                     | 19    |         |
| **Registration stated in publication** |   |                       |       |         |
| Yes                       | 109 (100.0)       | 0                     | 109   | <0.001  |
| No                        | 31 (33.0)         | 63 (67.0)             | 94    |         |
| **Sample size**           |                   |                       |       |         |
| 0–49                      | 19 (46.3)         | 22 (53.7)             | 41    | <0.001  |
| 50–99                     | 6 (31.6)          | 13 (68.4)             | 19    |         |
| 100–199                   | 17 (65.4)         | 9 (34.6)              | 26    |         |
| 200–499                   | 41 (75.9)         | 13 (24.1)             | 54    |         |
| 500–999                   | 27 (81.8)         | 6 (18.2)              | 33    |         |
| ≥1000                     | 30 (100.0)        | 0                     | 30    |         |

COPD, chronic obstructive pulmonary disease.

**Registration status**

The registry search identified that 140 (69.0%) studies from the two NMAs had registered their trials (AD 59.7%, COPD 73.5%). However, only 49.3% (n=100) of studies reported trial registration in their publication. Significantly more registered trials reported an industry funding source (80.0% vs 20.0%, p<0.001; table 1) compared with non-registered trials. All trials that did not provide a funding source were not registered. Multinational trials were more likely to be registered (90.1% vs 9.9%, p<0.001). Studies published in journals with higher impact factors were more likely to be registered (100.0% in JIF ≥15.000 vs 23.0% in JIF <2000, p<0.001). Studies with a larger sample size were more likely to be registered (100.0% with n≥1000 vs 46.3% with n<50, p<0.001). Trial registration increased with more recent publications (78.6% in 2014 vs 38.5% in 2005, figure 2).

**Change in trial primary outcome**

Of the 140 registered trials, 134 (95.7%) reported a prespecified primary outcome in the registry (n=125 efficacy, n=7 safety and n=2 unclear). Most of the primary outcome results were statistically positive (n=74, 36.5%) or neutral (n=31, 15.5%), and a minority (n=15, 7.4%) were non-significant or negative (online supplementary appendix A,
Table 2  Outcome changes in relation to a positive conclusion

|                        | Positive conclusion | Non-positive conclusion | Total | OR (95% CI) |
|------------------------|---------------------|-------------------------|-------|-------------|
| No change              | 86 (74.8)           | 29 (25.2)               | 115   | Reference   |
| Change in definition or measure | 3 (50.0)           | 3 (50.0)               | 6     | 2.97 (0.57 to 15.51) |
| Added                  | 4 (80.0)            | 1 (20.0)                | 5     | 0.74 (0.08 to 6.90) |
| Upgrade                | 3 (75.0)            | 1 (25.0)                | 4     | 0.99 (0.10 to 9.88) |
| Omitted                | 3 (100.0)           | 0                       | 3     | --          |
| Downgrade              | 1 (100.0)           | 0                       | 1     | --          |

Re-analysis of NMAs for SAEs
We re-analysed the SAE outcomes of the AD NMA by adding new data as identified from ClinicalTrials.gov. The COPD NMA was not re-analysed because the total SAE was not an outcome of interest in the original NMA. We aimed to look at specific SAEs (eg, pneumonia, fractures), but the coding of the events was different between the registry and publications, making comparisons difficult. For example, a pneumonia may be classified as cough, dyspnoea, hypoxia, lung infiltration, acute respiratory failure, lung infection or lobar pneumonia.

Only two studies had undisclosed SAE from the AD NMA (nine new events), but the overall SUCRA ranking statistics were not changed when these data were added (online supplementary appendix A, online supplementary table 5). When the SUCRA ranking statistics were calculated by registration status, different treatments were favoured between registered, non-registered and combined subgroups (online supplementary appendix A, online supplementary table 6). The rankings are presented in a rank-heat plot (figure 3).

DISCUSSION
To our knowledge, this is the first study to explore selective reporting bias in trials included in NMAs by comparing the publication results to their respective trial registry data. We found that 19.4% of publications with results posted in a clinical trial registry had inconsistent reporting of overall treatment. The most common discrepancy was not reporting the SAE data in the primary publication (50.0%), which could be addressed by following the CONSORT guidelines to enhance reporting. This result is similar to counts in the publication (online supplementary appendix A, online supplementary table 4). Studies published more recently (p=0.160) and in journals with higher impact factor (p=0.258) had fewer discrepancies in total SAE count. Declaring registration information in the publication was associated with fewer SAE discrepancies (17.4% vs 66.7%, p=0.035). Other study characteristics (country of origin, clinical condition and total sample size) did not show a difference in total SAE counts. All studies with registry SAE data were industry-sponsored. The overall proportion of discrepant SAE events compared with total events was small (2.9%, n=452/15 807).
Table 3  Association between study characteristics and presence of discrepancy in total SAE count between publication and trial registry

|                          | Discrepancy in SAE, n (%) | No discrepancy in SAE, n (%) | Total | P value |
|--------------------------|---------------------------|------------------------------|-------|---------|
|                          | 14 (19.4)                 | 58 (80.5)                   | 72    |         |
| Year of publication      |                           |                              |       |         |
| 2008                     | 0                         | 1 (100.0)                   | 1     | 0.160   |
| 2009                     | 1 (100.0)                 | 0                            | 1     |         |
| 2010                     | 4 (44.4)                  | 5 (55.6)                    | 9     |         |
| 2011                     | 3 (20.0)                  | 12 (80.0)                   | 15    |         |
| 2012                     | 2 (11.1)                  | 16 (88.9)                   | 18    |         |
| 2013                     | 3 (14.3)                  | 18 (85.7)                   | 21    |         |
| 2014                     | 1 (14.3)                  | 6 (85.7)                    | 7     |         |
| Industry funding         |                           |                              |       | N/A     |
| Yes                      | 14 (19.4)                 | 58 (80.6)                   | 72    |         |
| No                       | 0                         | 0                            | 0     |         |
| Not reported             | 0                         | 0                            | 0     |         |
| Country                  |                           |                              |       |         |
| Multinational            | 11 (19.3)                 | 46 (80.7)                   | 57    |         |
| North America            | 2 (18.1)                  | 9 (81.8)                    | 11    |         |
| Europe                   | 1 (50.0)                  | 1 (50.0)                    | 2     |         |
| Asia                     | 0                         | 1 (100.0)                   | 1     |         |
| Not reported             | 0                         | 1 (100.0)                   | 1     |         |
| Clinical condition       |                           |                              |       |         |
| Alzheimer’s disease      | 2 (15.4)                  | 11 (84.6)                   | 13    | 0.683   |
| COPD                     | 1 (20.3)                  | 47 (79.7)                   | 59    |         |
| Journal impact factor    |                           |                              |       |         |
| 0–1.999                  | 1 (100.0)                 | 0                            | 1     | 0.258   |
| 2.000–4.999              | 9 (19.2)                  | 38 (80.6)                   | 47    |         |
| 5.000–9.999              | 1 (16.7)                  | 5 (83.3)                    | 6     |         |
| 10.000–14.999            | 2 (28.6)                  | 5 (71.4)                    | 7     |         |
| ≥15.000                  | 1 (9.1)                   | 10 (90.9)                   | 11    |         |
| Registration stated in publication |           |                              |       |         |
| Yes                      | 12 (17.4)                 | 57 (82.6)                   | 69    | 0.035   |
| No                       | 2 (66.7)                  | 1 (33.3)                    | 3     |         |
| Sample size              |                           |                              |       |         |
| 0–49                     | 1 (9.1)                   | 10 (90.9)                   | 11    | 0.870   |
| 50–99                    | 0                         | 2 100.0                     | 2     |         |
| 100–199                  | 1 (33.3)                  | 2 (66.7)                    | 3     |         |
| 200–499                  | 3 (18.8)                  | 13 (81.3)                   | 16    |         |
| 500–999                  | 4 (22.2)                  | 14 (77.8)                   | 18    |         |
| ≥1000                    | 5 (22.7)                  | 17 (77.3)                   | 22    |         |

COPD, chronic obstructive pulmonary; SAE, serious adverse effect.

Although we uncovered discrepancies in reporting, we did not find significant differences in the SAE rankings of interventions when we repeated the AD NMA with the corrected data; this is likely because the relative proportion of discrepant SAE events was small overall (~3%).
publication, we searched multiple international registries was suboptimal. Despite this, overall compliance with results transparency after trial completion, allowing for late data to be reviewed. 2 years. Our study searched the registry at least 3 years in clinical conditions published from 2008 to 2013 (38.3%). For example, 58.7% of oncology trials in solid tumours registered their trials. Only 51% of registered trials from our study included results and SAEs counts in the registry, which is more than a review of trials of diverse clinical conditions published from 2008 to 2013 (38.3%). Although the FDA Amendments Act requires clinical trials with any enrolment site in the USA to have trial results posted within 12 months of completion, compliance is low. Extensions may be allowed under certain circumstances, but full or partial results should be released within 2 years. Our study searched the registry at least 3 years after trial completion, allowing for late data to be reviewed. Despite this, overall compliance with results transparency was suboptimal.

To identify trial registrations not stated on the primary publication, we searched multiple international registries in duplicate. This strategy found a registry record for 38.8% (n=40/103) of publications not declaring trial registration, a proportion similar to the 35% in a similar study of trials in clinical geriatrics. In the clinical geriatrics study, the authors only searched the WHO International Clinical Trial Registry Platform, which searches multiple national registries simultaneously. There is no other amalgamated search tool to identify trial registrations internationally, highlighting an important gap for researchers and knowledge users.

Our study has certain limitations to consider. First, we included primary publications from NMAs investigating two clinical conditions (AD and COPD) and, therefore, results may not generalise to other fields. Second, we excluded primary publications if they were not written in English. As ClinicalTrials.gov is the most comprehensive clinical trial registry and requires results to be published in English, it is unlikely that our study conclusions would have changed. We sought to translate the non-English language articles. Third, we searched only a single trials registry (ClinicalTrials.gov) for SAE results because it is the only one that provides these data openly. Fourth, we were unable to repeat the COPD NMA because specific SAEs were classified differently in the publication and registry, and total SAE counts were not analysed in the original NMA. Fifth, we did not contact study authors to confirm SAE counts in the trial registry.

Conclusions
Our findings offer insights on how to improve transparency in trial data and comprehensiveness in knowledge synthesis. To improve consistency between trial registry data and publications, we recommend that all trial registry results are uploaded by the same responsible parties that prepare the published manuscript (ie, principal investigator, study sponsor). The authors of systematic reviews should be mindful about the possibility of reporting bias in primary publications and should routinely search trial registries to reduce the risk of reporting bias. Safety data should be verified within these registries before incorporating it into MAs and NMAs. Peer reviewers and journal editors should also consult the trial registry record of the manuscript under review to ensure that the results are consistent and accurately reported.

Author affiliations
1Knowledge Translation Program, Li Ka Shing Knowledge Institute, St. Michael’s Hospital, Toronto, Ontario, Canada
2Department of Geriatric Medicine, University of Toronto, Toronto, Ontario, Canada
3School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia
4Department of Primary Education, University of Ioannina, Ioannina, Greece
5Department of Surgery & Cancer, Institute of Reproductive and Developmental Biology, Faculty of Medicine, Imperial College, London, UK

Acknowledgements The authors would like to thank Ms. Sinit Michael for formatting the manuscript and appendices.

Contributors EKCW, CCL, SES and ACT conceived the study and wrote the manuscript. EKCW, CCL, MJP, JW, AV, SES and ACT revised the manuscript. EKCW,
CCL, JW and AV performed data analysis. JW re-analysed the NMA. All authors read and approved the final manuscript.

**Funding** ACT is funded by a Tier 2 Canada Research Chair in Knowledge Synthesis (No. 17-0126-AWA) and an Ontario Ministry of Research, Innovation, and Science Early Researcher Award (No. 15-0553-AWA); EW is funded through the University of Toronto Department of Medicine Clinician Scientist Training Program and a CIHR Vanier Canada Graduate Scholarship; JW is funded through the University of Toronto Department of Medicine Clinician Scientist Training Program and a CIHR Doctoral Research Award; AAV is funded from the European Union’s Horizon 2020 (No. 754936); MJP is supported by an Australian National Health and Medical Research Council (NHMRC) Early Career Fellowship (1088535) and SES is funded by a Tier 1 Canada Research Chair in Knowledge Translation (No. 17-0245-SUB).

**Competing interests** CCL is employed at the Canadian Agency for Drugs and Technologies in Health.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available on reasonable request.

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**REFERENCES**

1. Cochrane Handbook for systematic reviews of interventions 2011.
2. Solomon SD, Rizkala AR, Gong J, et al. Angiotensin Receptor Neprilysin Inhibition in Heart Failure With Preserved Ejection Fraction: Rationale and Design of the PARAGON-HF Trial. *JACC Heart Fail* 2017;5:471–82.
3. Terpenning M. Geriatric oral health and pneumonia risk. *Clinical Infectious Diseases* 2005;40:1807–10.
4. Scannapieco FA. Pneumonia in nonambulatory patients. The role of oral bacteria and oral hygiene. *J Am Dent Assoc* 2006;137 Suppl:21a–5.
5. Razak PA, Richard KMJ, Thankachan RP, et al. Geriatric oral health: a review article. *J Int Oral Health* 2014;6:110–8.
6. Chan A-W, Song F, Vickers A, et al. Increasing value and reducing waste: addressing inaccessible research. *The Lancet* 2014;383:257–66.
7. Dickerson K, Rennie D. The evolution of trial registries and their use to assess the clinical trial enterprise. *JAMA* 2012;307:1861–4.
8. De Angelis Cet al. Clinical trial registration: a statement from the International Committee of medical Journal editors. *Can Med Assoc J* 2004;171:606–7.
9. Panseri C, Pandolfini C, Bonati M. Clinical trial registries: more international, converging efforts are needed. *Trials* 2017;18:86.
10. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001; 2006; Brussels, Belgium.
11. World Health Organization. About the WHO International Clinical Trials Registry Platform (ICTRP) [World Health Organization]. Available: https://www.who.int/ictrp/about/en/ [Accessed 26 Jul 2019].
12. Rayhил Ml, Sharon R, Burch R, et al. Registration status and outcome reporting of trials published in core headache medicine journals. *Neurology* 2015;85:1789–94.
13. Pranić S, Marušić A. Changes to registration elements and results in a cohort of ClinicalTrials.gov trials were not reflected in published articles. *J Clin Epidemiol* 2016;70:26–37.
14. De Oliveira GS, Jung MJ, McCarty RJ. Discrepancies between randomized controlled trial registry entries and content of corresponding manuscripts reported in anesthesiology journals. *Anesthesia & Analgesia* 2015;121:1030–3.
15. Hartung DM, Zarin DA, Guise J-M, et al. Reporting discrepancies between the ClinicalTrials.gov results database and peer-reviewed publications. *Ann Intern Med* 2014;160:477–83.
16. Mathieu Set al. Comparison of registered and published primary outcomes in randomized controlled trials. *JAMA* 2009;302:977–84.
17. Riveros C, Dechartres A, Perrodeau E, et al. Timing and completeness of trial results posted at ClinicalTrials.gov and published in journals. *PLoS Med* 2013;10:e1001566.
18. ClinicalTrials.gov. Glossary of Common Site Terms - ClinicalTrials.gov. Government of the United States of America.
19. Ioannidis JPAet al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004;141:781–8.
20. Tricco AC, Ashoor HM, Soobiah C, et al. Comparative effectiveness and safety of cognitive enhancers for Alzheimer’s disease: systematic review and network Metaanalysis. *J Am Geriatr Soc* 2017.
21. Higgins SG J. Selective outcome reporting. *Cochrane Handbook for Systematic Reviews of Interventions: The Cochrane Collaboration*, 2011.
22. Hart B, Lundh A, Bero L. Effect of reporting bias on meta-analyses of drug trials: reanalysis of meta-analyses. *BMJ* 2011;344:d7202.
23. Baudard M, Yavchitz A, Ravaud P, et al. Impact of searching clinical trial registries in systematic reviews of pharmaceutical treatments: methodological systematic review and reanalysis of meta-analyses. *BMJ* 2017;356.
24. Tang E, Ravaud P, Riveros C, et al. Comparison of serious adverse events posted at ClinicalTrials.gov and published in corresponding journal articles. *BMJ* 2015;13:198.
25. Tricco AC, Strifler L, Veroniki A-A, et al. Comparative safety and effectiveness of long-acting inhaled agents for treating chronic obstructive pulmonary disease: a systematic review and network meta-analysis. *BMJ Open* 2015;5:e009183.
26. Page MJ, McKenzie JE, Findlay J, et al. Bias due to selective inclusion and reporting of outcomes and analyses in systematic reviews of randomised trials of healthcare interventions. *Cochrane Database Syst Rev* 2014;3:006.
27. Tricco AC, Tetzlaff J, Pham BA, et al. Non-Cochrane vs. Cochrane reviews were twice as likely to have positive conclusion statements: cross-sectional study. *J Clin Epidemiol* 2009;62:380–6.
28. Dal-Re R, Ioannidis JP, Bracken MB, et al. Making prospective registration of observational research a reality. *Sci Transl Med* 2014;6:224cm1.
29. Zarin DA, Ide NC, Tse T, et al. Issues in the registration of clinical trials. *JAMA* 2007;297:2112–20.
30. Viergever RF, Li K. Trends in global clinical trial registration: an analysis of numbers of registered clinical trials in different parts of the world from 2004 to 2013. *BMJ Open* 2015;5:e009892.
31. Anderson ML, Chiswell K, Peterson ED, et al. Compliance with results reporting at ClinicalTrials.gov. *N Engl J Med* 2015;372:1031–9.
32. Veroniki AA, Straus SE, Ashoor HM, et al. Comparative safety and effectiveness of cognitive enhancers for Alzheimer’s dementia: protocol for a systematic review and individual patient data network meta-analysis. *BMJ Open* 2016;6:e010251.
33. Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011;64:163–71.
34. Veroniki AA, Straus SE, Ashoor HM, et al. Impact of searching clinical trial registries on the identification of relevant trials for systematic reviews. *Science Transl Med* 2013;48:1474–83.
35. Killeen S, Sourlaouls P, Hunter IA, et al. Registration rates, adequacy of registration, and a comparison of registered and published primary outcomes in randomized controlled trials published in surgery journals. *Ann Surg* 2014;259:193–6.
36. Mann E, Nguyen N, Fleischer S, et al. Compliance with trial registration in five core journals of clinical genetics: a survey of original publications on randomised controlled trials from 2008 to 2012. *Age Ageing* 2014;43:872–6.
37. Jones OW, Platts-Mills TF. Quality of registration for clinical trials published in emergency medicine journals. *Ann Emerg Med* 2012;60:458–64.
38. You B, Gan HK, Pond G, et al. Consistency in the analysis and reporting of primary end points in oncology randomized controlled trials from registration to publication: a systematic review. *JCO* 2012;30:210–6.
39. Prayle AP, Hurley MN, Smyth AR. Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: cross sectional study. *BMJ* 2011;343:d3733.
40. Federal Drug Administration. FDAAA 801 and the Final Rule - ClinicalTrials.gov: ClinicalTrials.gov; [Federal Drug Administration]. Available: https://clinicaltrials.gov/ct2/manage-recs/fdada [Accessed 26 Jul 2019].
41. World Health Organization. Who international clinical trials registry platform (ICTRP) data providers: World Health organization. [World Health Organization, 2018.}