



University of Dundee

A systematic review of clinical trial registration in major respiratory journals 2010-2018

Suntila, Nelli S. M.; Smith, Alexandria; Al-Dabbagh, Yusuf; Chalmers, James D.

Published in:
European Respiratory Journal

DOI:
[10.1183/13993003.01491-2018](https://doi.org/10.1183/13993003.01491-2018)

Publication date:
2018

Document Version
Peer reviewed version

[Link to publication in Discovery Research Portal](#)

Citation for published version (APA):

Suntila, N. S. M., Smith, A., Al-Dabbagh, Y., & Chalmers, J. D. (2018). A systematic review of clinical trial registration in major respiratory journals 2010-2018. *European Respiratory Journal*, 52(6), [1801491]. <https://doi.org/10.1183/13993003.01491-2018>

General rights

Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from Discovery Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying the publication in the public portal.

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

A systematic review of clinical trial registration in major respiratory journals 2010-2018
Nelli SM Sunttila¹, Alexandria Smith², Yusuf Al-Dabbagh¹, James D Chalmers¹

1. Scottish Centre for Respiratory Research, University of Dundee, Dundee, UK
2. University of Cambridge, Cambridge, UK

Corresponding Author: Professor James D Chalmers, Division of Molecular and Clinical Medicine,
University of Dundee, Dundee, DD1 9SY. E-mail: jchalmers@dundee.ac.uk, phone: 01382 383642

Funding: JDC is supported by the GSK/BLF Chair of Respiratory Research.

Conflicts of interest: JDC is the deputy chief editor of the European Respiratory Journal

Running title: Retrospective trial registration remains common in respiratory clinical trials, and may be associated with reporting bias.

This is an author-submitted, peer-reviewed version of a manuscript that has been accepted for publication in the European Respiratory Journal, prior to copy-editing, formatting and typesetting. This version of the manuscript may not be duplicated or reproduced without prior permission from the copyright owner, the European Respiratory Society. The publisher is not responsible or liable for any errors or omissions in this version of the manuscript or in any version derived from it by any other parties. The final, copy-edited, published article, which is the version of record, is available without a subscription 18 months after the date of issue publication.

Randomized clinical trials are regarded as the highest level of evidence for informing clinical guidelines and clinical practice.^{1,2} The robustness of conduct and reporting of the results of randomized clinical trials is therefore of primary importance. To improve the transparency and quality of reporting of clinical trials, the International Committee of Medical Journal Editors (ICMJE) endorsed a policy on mandatory registration of clinical trials, which came into effect in July 2005³. The trial registration recommendations outlined by the ICMJE state that a trial must be registered in a publicly accessible registry, before the enrolment of the first study participants, in order to be considered for publication. This policy is designed to reduce publication bias, prevent selective reporting of desirable or non-reporting of undesirable results, and reduce research waste by making the research community aware of what questions are already being addressed by active trials.

Previous studies have suggested that although ICMJE guidance recommends that journals should not publish manuscripts from trials that were not registered or were retrospectively registered, such trials continue to be published in the medical literature, including in high-impact journals.⁴ While compliance with ICMJE registration has been investigated in individual specialities such as cardiology^{5,6}, no studies to date have reported on adherence to the ICMJE policy within respiratory medicine.

This review was conducted in order to evaluate the registration practices of clinical trials published in high-impact respiratory medical journals from 2010-2018. Our aim was to determine the frequency of publication of unregistered and retrospectively registered trials and to determine temporal trends in publication practices.

We conducted a systematic review based on the recommendations set in the PRISMA

statement{ADDIN CSL_CITATION {"citationItems":[{"id":"ITEM-

1","itemData":{"DOI":"10.1136/BMJ.B2535","ISSN":"1756-

1833","PMID":"19622551","abstract":"David Moher and colleagues introduce PRISMA, an update of

the QUOROM guidelines for reporting systematic reviews and meta-analyses\n\nSystematic reviews

and meta-analyses have become increasingly important in health care. Clinicians read them to keep up to date with their specialty,^{1 2} and they are often used as a starting point for developing clinical practice guidelines. Granting agencies may require a systematic review to ensure there is justification for further research,³ and some medical journals are moving in this direction.⁴ As with all research, the value of a systematic review depends on what was done, what was found, and the clarity of reporting. As with other publications, the reporting quality of systematic reviews varies, limiting readers' ability to assess the strengths and weaknesses of those reviews.

Several early studies evaluated the quality of review reports. In 1987 Mulrow examined 50 review articles published in four leading medical journals in 1985 and 1986 and found that none met all eight explicit scientific criteria, such as a quality assessment of included studies.⁵ In 1987 Sacks and colleagues evaluated the adequacy of reporting of 83 meta-analyses on 23 characteristics in six domains.⁶ Reporting was generally poor; between one and 14 characteristics were adequately reported (mean 7.7, standard deviation 2.7). A 1996 update of this study found little improvement.⁷

In 1996, to address the suboptimal reporting of meta-analyses, an international group developed a guidance called the QUOROM statement (QUality Of Reporting Of Meta-analyses), which focused on the reporting of meta-analyses of randomised controlled trials.⁸ In this article, we summarise a revision of these guidelines, renamed PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses), which have been updated to address several conceptual and practical advances in the science of systematic reviews (see box).

Conceptual issues in the evolution from QUOROM to PRISMA

Completing a systematic review is an iterative process

The conduct of a systematic ...

```
"author":{"dropping-particle":"","family":"Moher","given":"David","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"Liberati","given":"Alessandro","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"Tetzlaff","given":"Jennifer","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"Altman","given":"Douglas G","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"PRISMA Group","given":"","non-dropping-particle":"","parse-names":false,"suffix":""}],"container-title":"BMJ (Clinical research
```

ed.)", "id": "ITEM-1", "issued": {"date-parts": [{"2009", "7"}]}, "page": "b2535", "publisher": "British Medical Journal Publishing Group", "title": "Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.", "type": "article-journal", "volume": "339"}, "uris": [{"http://www.mendeley.com/documents/?uuid=cd8f695a-17fe-3164-b8b9-073773a7311b"}, {"http://www.mendeley.com/documents/?uuid=dbbfafdb-09fa-4aff-8689-cab5e163f887"}]}, "mendeley": {"formattedCitation": "⁷", "plainTextFormattedCitation": "7", "previouslyFormattedCitation": "⁷"}, "properties": {"noteIndex": 0}, "schema": "https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}. This review was prospectively registered at PROSPERO (CRD42018102819).

All searches were conducted using PubMed, as all publications included are PubMed-indexed. We used the sensitivity- and precision-maximizing version of The Cochrane search strategy⁸. Publication date was set between January 2010 and July 2018. 2010 was chosen since mandatory trial registration was introduced in 2005, and therefore we considered that by 2010 the majority of published trials would be eligible for registration. We studied published articles within 8 journals; The Lancet Respiratory Medicine, American Journal of Respiratory and Critical Care medicine, Thorax, European Respiratory Journal, Chest, Respiratory Research, Respirology and Annals of the American Thoracic Society. These journals were chosen on the basis of impact factor, publication of original research including clinical trials and publication across all sub-specialities within respiratory medicine.

No language restrictions were applied. All articles identified by search were reviewed by title and abstract, and the full text of the publication was reviewed if potentially relevant. We used the ICMJE definition of a clinical trial to determine study inclusion⁹. We excluded studies that reported on post-hoc analyses or secondary analyses based on trial datasets. This study was conducted by four reviewers, two of which were involved in both data extraction and analysis and two were involved in the data extraction step only. Discrepancies were resolved by discussion.

The following data were extracted for each study; publication title, whether or not the trial was a multi-centre study, region, registration number, date of enrolment of first patient, date of registration, funding source, whether the trial was academic or commercial based on the funding source, year of publication, and outcome of the trial.

Classification of trials followed a published approach used by the British Medical Journal.⁴ Briefly, a trial was considered to be registered if the publication included a registration number of an acceptable primary registry – one belonging to the WHO International Clinical Trials Registry Platform (ICTRP). If no registration number was reported in the publication, the trial was searched for using the ICTRP search platform. If no registration number was found or the trial was registered in a WHO non-compliant registry, the trial was considered ‘not registered’.

The study start date, which the ICMJE defines as the date of enrolment of first patient⁹, was recorded as that reported in the publication. The outcome of each trial was recorded as either ‘positive’ or ‘negative’ depending on whether or not the primary outcome measure of the trial reached statistical significance.

Trials included for further analysis were defined by their registration status as ‘prospective’ (registration before or on the day of enrolment of first patient), ‘retrospective’ (registration after the day of first patient enrolment) or ‘not registered’. Retrospectively registered trials were further divided into subclasses according to the time delay (in months) between the date of enrolment of first participant and date of registration.

We calculated simple proportions to describe the frequency of registered and non-registered trials. Logistic regression was used to identify factors associated with trial registration status. $P < 0.05$ was considered statistically significant.

The search strategy identified a total of 2109 records, of which 1108 were excluded by abstract as they did not fulfil the criteria for a clinical trial. Of the 1082 potentially eligible trials, a further 158 were excluded as they did not meet the full inclusion criteria – these were mainly publications which did not report the primary results of a trial. A total of 925 studies were included for further analysis. Some publications presented the primary results of two or more trials – most of these were combinations of two identical trials due to regulatory requirements – and accounting for these, the number of trials included was 955. These studies of multiple trials were included as single entries for our analyses.

Of the 925 studies included for our analyses, 57.1% were multi-centre trials. The majority (64.2%) of trials reported a positive outcome.

Overall, 47.7% of trials were prospectively registered, and 42.2% were regarded as retrospectively registered. A total of 10.2% of trials were not registered. Excluding trials that started before mandatory registration was introduced in 2005, 51.5% were prospectively registered, 39.0% were retrospectively registered and 9.5% were not registered. Examining publications by journal, the *Lancet Respiratory Medicine* had the highest percentage of prospectively registered trials (68.5%) and *Respirology* the lowest (32.4%) across the 8-year study period (Figure 1B). Commercially funded studies were more likely to be prospectively registered than academically funded studies ($p=0.003$, figure 1C). The proportion of retrospectively and non-registered studies decreased progressively from 2010 to 2018 from a mean of 72.4% in 2010 to 35.6% of trials in 2018 (figure 1D). Non-registered studies accounted for 24.6% of published studies in 2010 but were virtually eliminated by 2018 (0.4% of published studies, figure 1E). In Figure 1F, we show the publication factors associated with non-prospective trial publication. There was a significant effect of region ($p=0.004$), and date of publication ($p=0.008$) with failure to prospectively register trials being most common in Spain (OR 6.5 95% CI 2.65-15.8), followed by South America, Italy and China. Australia and New Zealand had the lowest odds of retrospective registration (OR 0.52 95% CI 0.27-1.01). Single-centre studies were more likely to be retrospectively or non-registered (OR 2.14 95% CI 1.48-3.10). Trials in cystic

fibrosis (71.1%), Pulmonary vascular disease (70.4%), interstitial lung disease (61.5%) and asthma (59.1%) were most likely to be prospectively registered. Studies in Sleep medicine (35.7% and cancer (47.6%) were least likely to be registered prospectively.

Retrospective trial registration was frequently just within 1 month of study start (29% of trials) but a total of 38.6% of all trials were registered >12 months after the first participant was enrolled (Figure 1G). These trials at higher risk of bias, which are registered more than 1 year after study start date, also decreased rapidly in numbers over time (figure 1H).

To evaluate the potential for registration status to bias the literature, we examined whether registration status impacted the likelihood of a positive result. Compared to prospectively registered studies, unregistered studies were 80% more likely to have a positive result (OR 1.80 95% CI 1.10-2.95, $p=0.02$). Retrospectively registered studies were 33% more likely to be positive (OR 1.33 95% CI 1.01-1.77, $p=0.04$).

Therefore In this review of clinical trials published between 2010 and present in eight high-impact respiratory medical journals, we found that a significant proportion of clinical trials remains retrospectively registered, years after the ICMJE introduced their policy on mandatory prospective trial registration. Additionally, we have shown that there is still a substantial number of trials which are not registered. Our results are in line with previous reports on trial registration practices in the post-implementation period of the ICMJE policy¹⁰. We observed a trend towards better registration compliance from 2010 to 2018, which was expected, and resonates with previous findings on the improvements seen over the years in clinical trial registration¹¹.

There is evidence that most retrospective registration may be inadvertent.¹² Some investigators may not be aware that their trial meets the criteria for a trial which should be registered. Some investigators may be completely unaware of registration policies, although thirteen years post-implementation of the ICMJE policy this is increasingly difficult to justify.¹² Nevertheless one of the main purposes of mandatory prospective registration is to prevent selective reporting of trial

outcomes. Our finding that retrospectively registered trials are more likely to be positive has two possible explanations, either researchers may register their trial retrospectively in order to engage in selective reporting of their results or editors are more likely to ignore requirement for prospective registration in the face of a positive trial.¹³ It is therefore important that investigators, journal editors and members of research or funding organisations are all involved in addressing this issue. There is a responsibility on journals to adequately check registration status at the time of submission.¹³ There is evidence for the majority of retrospectively registered studies being registered before submission to a journal¹⁰, and thus these inappropriately registered trials may go on to be published if there are no strict quality checks on the trial's registration status.

Commercially funded trials were more often registered prospectively, which may reflect more strict regulation imposed on studies with commercial interest. Studies from certain countries including Spain, South America, Italy and China, and single-centre studies in general, were more likely to be registered inappropriately. This may be explained by variation in regional registration policies and the availability of resources for project management¹¹.

The quality of registration reporting has been reported in detail elsewhere^{14,15}, but we also found inconsistencies and lack of clarity in trial reporting including failure to provide study dates in publications. We may therefore underestimate the scale of retrospective registration since we were conservative in our assessment of registration status.

In conclusion, adherence to clinical trial registration policies in respiratory medicine is improving rapidly. Publication of non-registered trials has been virtually eliminated and the challenge now is to encourage compliance with prospective registration among investigators and editors.

References

1. Polverino E, Goeminne PC, McDonnell MJ, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J*. 2017;50(3). doi:10.1183/13993003.00629-2017
2. Wedzicha JAEC-C, Miravittles M, Hurst JR, et al. Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J*. 2017;49(3). doi:10.1183/13993003.00791-2016
3. De Angelis C, Drazen JM, Frizelle FA, et al. Clinical Trial Registration: A Statement from the International Committee of Medical Journal Editors. *N Engl J Med*. 2004;351(12):1250-1251. doi:10.1056/NEJMe048225
4. Loder E, Loder S, Cook S. Characteristics and publication fate of unregistered and retrospectively registered clinical trials submitted to The BMJ over 4 years. *BMJ Open*. 2018;8(2):e020037. doi:10.1136/bmjopen-2017-020037
5. Scott A, Rucklidge JJ, Mulder RT. Is Mandatory Prospective Trial Registration Working to Prevent Publication of Unregistered Trials and Selective Outcome Reporting? An Observational Study of Five Psychiatry Journals That Mandate Prospective Clinical Trial Registration. *PLoS One*. 2015;10(8):e0133718. doi:10.1371/journal.pone.0133718
6. Emdin C, Oduyayo A, Hsiao A, et al. Association of Cardiovascular Trial Registration With Positive Study Findings. *JAMA Intern Med*. 2015;175(2):304. doi:10.1001/jamainternmed.2014.6924
7. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535. doi:10.1136/BMJ.B2535
8. The Cochrane Collaboration. Cochrane Work | Resources | Search strategies. The Cochrane highly sensitive search strategies for identifying randomized trials in PubMed.
9. International Committee of Medical Journal Editors. Recommendations | Clinical trials. 1. Registration.
10. Harriman SL, Patel J. When are clinical trials registered? An analysis of prospective versus

- retrospective registration. *Trials*. 2016;17(1):187. doi:10.1186/s13063-016-1310-8
11. 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(9):e008932. doi:10.1136/bmjopen-2015-008932
 12. 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. doi:10.1136/bmjopen-2017-019983
 13. Sotgiu G, Humbert M, Dinh-Xuan AT, Migliori GB. Clinical trials: registration and transparency. *Eur Respir J*. 2016;47(5):1342-1344. doi:10.1183/13993003.00479-2016
 14. Viergever RF, Karam G, Reis A, Ghersi D. The Quality of Registration of Clinical Trials: Still a Problem. Scherer RW, ed. *PLoS One*. 2014;9(1):e84727. doi:10.1371/journal.pone.0084727
 15. Huser V, Cimino JJ. Evaluating adherence to the International Committee of Medical Journal Editors' policy of mandatory, timely clinical trial registration. *J Am Med Informatics Assoc*. 2013;20(e1):e169-e174. doi:10.1136/amiajnl-2012-001501

Figure 1. Systematic review of clinical trial registration in respiratory medicine journals 2010-2018. A: Flow chart for identification of clinical trials, B: clinical trial registration status by journal 2010-2018, data presented as percentages of published trials, C: registration status stratified by funding status, D: retrospective and non-registered studies by journal over time, E: % of non-registered trials over time. F: Forest plot showing the results of the logistic regression analysis for risk of retrospective or non-registered trials. Data are shown as odds ratios with 95% CI. The upper 95% CI have been limited to 10 to allow easier visualisation of the overall data. G: Timing of retrospective trial registration. H: Proportion of trials registered greater than 1 year after study start date over time in all 8 journals.

Abbreviations: LRM = Lancet Respiratory Medicine, AJRCCM = American Journal of Respiratory and Critical Care Medicine, ERJ = European Respiratory Journal, Resp Res = Respiratory Research, Ann ATS = Annals of the American Thoracic Society.