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Discrepancies between ClinicalTrials.gov Recruitment Status and Actual Trial Status: a Cross-Sectional Analysis

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Objectives: to determine the accuracy of the recruitment status listed on ClinicalTrials.gov as compared to the actual trial status.

Design: Cross-sectional analysis

Setting: Random sample of interventional phase 2-4 clinical trials registered between 2012 and 2015 on ClinicalTrials.gov.

Primary outcome measure: For each trial which was listed within ClinicalTrials.gov as ongoing, two investigators performed a comprehensive literature search for evidence that the trial had actually been completed. For each trial listed as completed or stopped early by ClinicalTrials.gov we compared the date that the trial was actually concluded with the date the registry was updated to reflect the study's conclusion status.

Results: Among the 405 included trials, 92 had a registry status indicating that study activity was either ongoing or the recruitment status was unknown. Of these, published results were available for 34 (37%). Among the 313 concluded trials, the median delay between study completion and a registry update reflecting that the study had ended was 141 days (IQR 48-419), with delays of over one year present for 29%. In total, 125 trials (31%) either had a listed recruitment status which was incorrect or had a delay of more than one year between the time the study was concluded and the time the registry recruitment status was updated.

Conclusions: At present, registry recruitment status information in ClinicalTrials.gov is often outdated or wrong. This inaccuracy has implications for the ability of researchers to identify completed trials and accurately characterize all available medical knowledge on a given subject.

Article Summary

Strengths and limitations of this study:

- Registry recruitment status is often used to identify completed clinical trials, yet the reliability of this information has not been previously assessed.

- The study involved comprehensive, independent literature searches by multiple investigators, including a medical research librarian.

- This study design is unable to identify studies which were completed but not published.

INTRODUCTION

Clinical trial registries play an essential role in helping to ensure the integrity of the published medical literature.[1] When utilized appropriately by investigators and sponsors, registration helps to ensure that a publically accessible trial record exists even when results are not published in a peer-reviewed journal, and that published outcome measures are consistent with prospectively specified trial outcomes. For these reasons, trial registries are a particularly important tool for systematic reviewers as they attempt to identify both published and unpublished trial data in order to assess for the possibility of publication bias.[2]

Despite the critical importance of trial registration, compliance with requirements from both the International Committee of Medical Journal Editors (ICMJE) and governmental regulators which mandate the prospective registration of clinical trials has been imperfect.[3 4] Meta-researchers have begun using data from ClinicalTrials.gov and other registries to identify these patterns of limited compliance in order to publicize and monitor deficiencies.[1 5 6]

Systematic reviewers and meta-researchers often limit registry searches to trials for which enrollment is documented to have been completed in the registry.[5 7-13] Restricting reviews to completed studies makes sense because these are the studies for which all the data is completed and for which the results either are known or could be known. However, little is known about delays between the time of study completion and the time that ClinicalTrials.gov is updated to reflect this completion, or the percentage of completed trials which remain listed with an ongoing status in ClinicalTrials.gov indefinitely. If these delays are significant or a large proportion of registry entries are never updated to reflect study completion, then limiting registry searches to only entries with a completed registry status might miss otherwise relevant trials.

The objective of this study is to quantify delays observed between the end of enrollment in registered clinical trials, and the time that the registry entries are updated to reflect that enrollment has ended.

METHODS

Study selection and data collection

We searched ClinicalTrials.gov for phase 2-4 interventional studies registered between 01/01/2012 and 12/31/2015. From these potentially eligible trials (n=30,524) we randomly selected 500 studies for analysis. Studies with a recruiting status of withdrawn were excluded, as this indicates that the study was halted prior to enrolling any participants. For each included trial, we obtained information on study phase, size, sponsor, participant demographics, and recruitment status as of January 1, 2017 directly from ClinicalTrials.gov.

Dates for the following events were also recorded from ClinicalTrials.gov for each included trial: initial registration, study start, and primary completion date (date on which primary outcome data for the last trial participant were collected). When the primary completion date field was missing, we used the study completion date (final date on which any trial data were collected). We considered trials with recruitment statuses of either completed (study concluded normally) or terminated (recruitment stopped prematurely and will not resume) to indicate that the study had ended and was unlikely to resume activity. These trials were classified as concluded. We recorded the dates on which the registry entries were updated to reflect that trials had concluded. Recruiting statuses which did not clearly reflect that the trial had concluded were recruiting, enrolling by invitation, not yet recruiting, active not recruiting, suspended, and unknown. Trials which were registered more than one month after the study start date were considered retrospectively registered.

Ongoing or Unknown Completion Status Trials

For studies which were scheduled to have been completed prior to January 2016 and did not have an updated recruitment status indicating that they had concluded, we performed a comprehensive literature search to identify published evidence that the trial might in fact have been completed. An investigator first searched Medline via PubMed using trial registration number, keywords, condition studied, intervention, trial title, and investigators' names for matching manuscripts. When the first search identified no corresponding publication, a research librarian repeated this search using PubMed, Embase, and Google Scholar. The final publication search occurred between January and February of 2017.

We assessed matches between registry entries and publications identified by this search strategy using the following trial characteristics: study title, trial design, interventions, primary and secondary outcomes, number of participants, recruitment dates, location, and funding sources. We did not consider trials to be published if the publication did not include outcome data from the primary trial. For example, trial protocols for ongoing trials were not considered evidence of trial completion. We did consider published abstracts and presentations at scientific meetings to be evidence of trial completion, and counted these as publications for this analysis. For the group of included trials with an ongoing or unknown recruitment status listed in the registry, the primary outcome was the proportion of studies with outcomes published in the medical literature.

Concluded Trials

For studies which were indicated to be concluded based on the recruitment status listed in ClinicalTrials.gov, the primary outcome was the amount of time elapsed between the primary completion date listed in ClinicalTrials.gov and the date on which the Clinicaltrials.gov registry entry was actually updated to indicate that the study had ended and was unlikely to resume activity.

Secondary outcomes included the proportion of studies registered more than one month after study initiation, and the proportion of studies registered after study completion. We also compared results among subgroups based on trial phase, trial size, and funding source.

We calculated descriptive data for the primary and secondary outcomes. We also compared the median time elapsed between the change in recruiting status and the time ClinicalTrials.gov was updated to reflect this change between subgroups using Mann Whitney and Kruskal Wallis tests. Chi-square tests were used to make comparisons between categorical variables. P values < 0.05 were considered statistically significant. Statistical analyses were performed using PASW version 18.0 (IBM, Armonk, NY). The dataset generated during the current study is available from the corresponding author on reasonable request.

RESULTS

Of the 500 potentially eligible trials which were randomly selected for evaluation, 405 were eligible for inclusion (Figure 1). Phase 2, 3, and 4 trials were all well represented within the study sample, and the majority of trials (53%) had received at least partial industry funding (Table 1). A large proportion of trials were registered retrospectively, more than one month after the study had started (39%).

Out of the 405 included trials, 273 (67%) were listed in ClinicalTrials.gov with a study status of completed, and 40 (10%) had initiated enrollment but were terminated early. Ninety-two trials (23%) had a recruitment status which indicated that trial activities were ongoing or that the study status was unknown, including 22 (5%) listed as active or active but not recruiting, and 70 (17%) listed as having an unknown recruiting status. Of these 92 trials with statuses in ClinicalTrials.gov indicating potentially

ongoing study activity, we identified a corresponding publication containing outcome data for 34 trials (37%).

Among the trials with a completed or terminated status (n = 313), 2 were missing the study completion date. Of the remaining 311 trials, the median delay between when a trial was completed and when ClinicalTrials.gov was updated to reflect this change was 142 days (IQR 48-419), with a mean delay of 340 days. In 91 trials (29%) this delay was greater than 1 year, and in 39 trials (13%) the delay was greater than two years (Figure 2). Eight trials had delays of more than five years. Retrospectively registered trials had a median delay of 266 days (IQR 62-650 days) between trial completion and when the registered recruitment status was updated, compared to a median of 116 days (IQR 38-260) for prospectively registered trials ($p < 0.001$). Observed delays did not differ between trials according to funding source or trial phase.

When considering all 405 included trials, 125 (31%) either had a listed recruitment status which was incorrect (ie trial had been completed but was not listed as such) or had a delay of more than one year between the time the study was completed and the time the recruitment status was updated. Retrospectively registered trials were more likely than prospectively registered trials to have one of these major discrepancies in recruitment status, with discrepancies observed for 46% of retrospectively registered trials and 21% of prospectively registered trials ($p < 0.001$). These recruitment status discrepancies did not differ among trials based on funding source or trial phase.

DISCUSSION

Among this sample of over 400 phase 2-4 trials registered with ClinicalTrials.gov between 2012 and 2015 we identified frequent discrepancies between trial recruitment statuses listed on ClinicalTrials.gov and

the actual trial status. Specifically, 37% of trials which were indicated to be ongoing based on available information within the registry had been completed and published. Among completed trials, 29% had a delay of more than a year between trial completion and the ClinicalTrials.gov update reporting trial completion.

Trial registries are an important tool by which both the authors of clinical guidelines and systematic reviewers can identify relevant clinical trials.[2 14] However, in both cases authors often assume that the listed enrollment status is accurate and either restrict their registry searches to completed trials,[7-9] or conclude that those trials with active enrollment statuses are actually still ongoing.[15-19] Our findings show that this assumption is incorrect for a substantial portion of trials. One potential solution is to not limit registry searches to completed trials. For trials which are listed as ongoing, efforts should be made to confirm the enrollment status or search for published results regardless of the registered enrollment status.

Trial registries serve as a critical source of data about ongoing and completed trials which supplements the published medical literature. However, our findings are consistent with previous studies which have demonstrated that registry information is at times incomplete or out of date. [5 20] This work is performed by meta-researchers, who use registry information to measure compliance with trial registration requirements and to monitor the conduct and reporting of clinical trials.[1] In order to accurately perform this function, it is also important for meta-researches to recognize the limitations we describe with respect to registered trial recruiting statuses. This is particularly important for registry-based investigations into publication bias, as excluding registered trials with a registry status indicating that recruitment is ongoing may miss trials which have actually finished enrollment without updating the associated registry entry.[5 10-13]

Several important limitations should be considered when interpreting these results. First, our findings are based on a sample of phase 2-4 trials registered from 2012 to 2015; these general results may not be applicable to specific classes of clinical trials, and the patterns we observed may change over time. Additionally, we performed a literature search to identify trials which were listed in the registry as being ongoing, but which had actually been completed. It is likely that some additional trials were completed but not yet published; our search would not have identified these trials. Similarly, our literature search may have missed some trials. For these reasons, we may have underestimated the percentage of trials which were completed without updating the registry's recruitment status.

CONCLUSIONS

In summary, we observed that a significant percentage of clinical trials registered in ClinicalTrials.gov with a recruitment status indicating that the trial is ongoing have actually been completed. Additionally, among completed trials, we observed significant delays in updating the ClinicalTrials.gov recruitment status. Individuals utilizing registry data to supplement a systematic literature search and meta-researchers using registry data to study the conduct and reporting of clinical trials should be aware of these findings to avoid unwarranted assumptions about the recruitment status of registered trials.

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Authors' contributions: CJ conceived the study. CJ, MS, AA, and TP all contributed to the study design. CJ, MS, and AA performed data collection. CJ performed data analysis and interpretation and drafted the article. All authors provided critical revisions to the article, and all authors read and approved the final manuscript.

Competing interests: We have read and understood BMJ policy on declaration of interests and declare the following interests: CJ is an investigator on unrelated studies sponsored by AstraZeneca, Roche Diagnostics, Inc, and Janssen, for which his department received research grants. The remaining authors declare no additional competing interests.

Ethics approval: N/a

Data sharing: The full dataset is available from the corresponding author on reasonable request.

REFERENCES

1. Zarin DA, Tse T, Williams RJ, et al. Update on Trial Registration 11 Years after the ICMJE Policy Was Established. The New England journal of medicine 2017;**376**(4):383-91 doi: 10.1056/NEJMsr1601330[published Online First: Epub Date]|.
2. Jones CW, Keil LG, Weaver MA, et al. Clinical trials registries are under-utilized in the conduct of systematic reviews: a cross-sectional analysis. Systematic reviews 2014;**3**:126 doi: 10.1186/2046-4053-3-126[published Online First: Epub Date]|.
3. Ross JS, Mulvey GK, Hines EM, et al. Trial publication after registration in ClinicalTrials.Gov: a cross-sectional analysis. PLoS medicine 2009;**6**(9):e1000144 doi: 10.1371/journal.pmed.1000144[published Online First: Epub Date]|.
4. Mathieu S, Boutron I, Moher D, et al. Comparison of registered and published primary outcomes in randomized controlled trials. Jama 2009;**302**(9):977-84 doi: 10.1001/jama.2009.1242[published Online First: Epub Date]|.
5. Anderson ML, Chiswell K, Peterson ED, et al. Compliance with results reporting at ClinicalTrials.gov. The New England journal of medicine 2015;**372**(11):1031-9 doi: 10.1056/NEJMsa1409364[published Online First: Epub Date]|.
6. Jones CW, Keil LG, Holland WC, et al. Comparison of registered and published outcomes in randomized controlled trials: a systematic review. BMC medicine 2015;**13**:282 doi: 10.1186/s12916-015-0520-3[published Online First: Epub Date]|.
7. Jun M, Foote C, Lv J, et al. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. Lancet 2010;**375**(9729):1875-84 doi: 10.1016/S0140-6736(10)60656-3[published Online First: Epub Date]|.
8. Karagiannis T, Paschos P, Paletas K, et al. Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. Bmj 2012;**344**:e1369 doi: 10.1136/bmj.e1369[published Online First: Epub Date]|.
9. Li L, Shen J, Bala MM, et al. Incretin treatment and risk of pancreatitis in patients with type 2 diabetes mellitus: systematic review and meta-analysis of randomised and non-randomised studies. Bmj 2014;**348**:g2366 doi: 10.1136/bmj.g2366[published Online First: Epub Date]|.
10. Dechartres A, Riveros C, Harroch M, et al. Characteristics and Public Availability of Results of Clinical Trials on Rare Diseases Registered at Clinicaltrials.gov. JAMA internal medicine 2016;**176**(4):556-8 doi: 10.1001/jamainternmed.2016.0137[published Online First: Epub Date]|.
11. Jones CW, Handler L, Crowell KE, et al. Non-publication of large randomized clinical trials: cross sectional analysis. Bmj 2013;**347**:f6104 doi: 10.1136/bmj.f6104[published Online First: Epub Date]|.
12. Powell-Smith A, Goldacre B. The TrialsTracker: Automated ongoing monitoring of failure to share clinical trial results by all major companies and research institutions. F1000Research 2016;**5**:2629 doi: 10.12688/f1000research.10010.1[published Online First: Epub Date]|.
13. Ross JS, Tse T, Zarin DA, et al. Publication of NIH funded trials registered in ClinicalTrials.gov: cross sectional analysis. Bmj 2012;**344**:d7292 doi: 10.1136/bmj.d7292[published Online First: Epub Date]|.
14. Methodology Manual and Policies From the ACCF/AHA Task Force on Practice Guidelines. https://professional.heart.org/idc/groups/ahamah-public/@wcm/@sop/documents/downloadable/ucm_319826.pdf Accessed 2/9/2017, 2010.
15. Robinson PD, Kalkanis SN, Linskey ME, et al. Methodology used to develop the AANS/CNS management of brain metastases evidence-based clinical practice parameter guidelines. Journal of neuro-oncology 2010;**96**(1):11-6 doi: 10.1007/s11060-009-0059-2[published Online First: Epub Date]|.

16. Zarychanski R, Abou-Setta AM, Turgeon AF, et al. Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis. Jama 2013;**309**(7):678-88 doi: 10.1001/jama.2013.430[published Online First: Epub Date]|.
17. Ker K, Edwards P, Perel P, et al. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. Bmj 2012;**344**:e3054 doi: 10.1136/bmj.e3054[published Online First: Epub Date]|.
18. Bergman P, Lindh AU, Bjorkhem-Bergman L, et al. Vitamin D and Respiratory Tract Infections: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. PloS one 2013;**8**(6):e65835 doi: 10.1371/journal.pone.0065835[published Online First: Epub Date]|.
19. Masters GA, Temin S, Azzoli CG, et al. Systemic Therapy for Stage IV Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2015;**33**(30):3488-515 doi: 10.1200/JCO.2015.62.1342[published Online First: Epub Date]|.
20. Riveros C, Dechartres A, Perrodeau E, et al. Timing and completeness of trial results posted at ClinicalTrials.gov and published in journals. PLoS medicine 2013;**10**(12):e1001566 doi: 10.1371/journal.pmed.1001566[published Online First: Epub Date]|.

Table 1. Characteristics of included trials.

Trial Characteristics	All Trials (n = 405)
Number of participants, median (IQR)	80 (32-225)
Trial phase, n (%)	
Phase 2	186 (46)
Phase 3 or 2/3	132 (33)
Phase 4	87 (21)
Funding source, n (%)[1]	
Industry	214 (53)
NIH‡/US Government	23 (6)
Other	233 (58)
Trial start date, n (%)	
Unlisted	2 (0)
Prior to 2006	15 (4)
2006-2009	37 (9)
2010-2011	235 (58)
2012-2014	116 (29)
Registered retrospectively, n (%)[3]	159 (39)
Registered prospectively, n (%)	245 (61)

[1] Trials could have more than one funding source

[2] National Institutes of Health

[3] Registration timing relative to enrollment could not be determined for one study

Figure 1. Flowchart of included trials.

Figure 2. Delays in updating ClinicalTrials.gov following trial conclusion.

Legend: Histogram of completed or terminated trials (n=311), depicting delays between the actual date of trial conclusion and the date on which ClinicalTrials.gov was updated to indicate trial conclusion.[1]

[1] Does not show eight outliers with delays of greater than 54 months. Trial completion dates were also not listed for two trials.

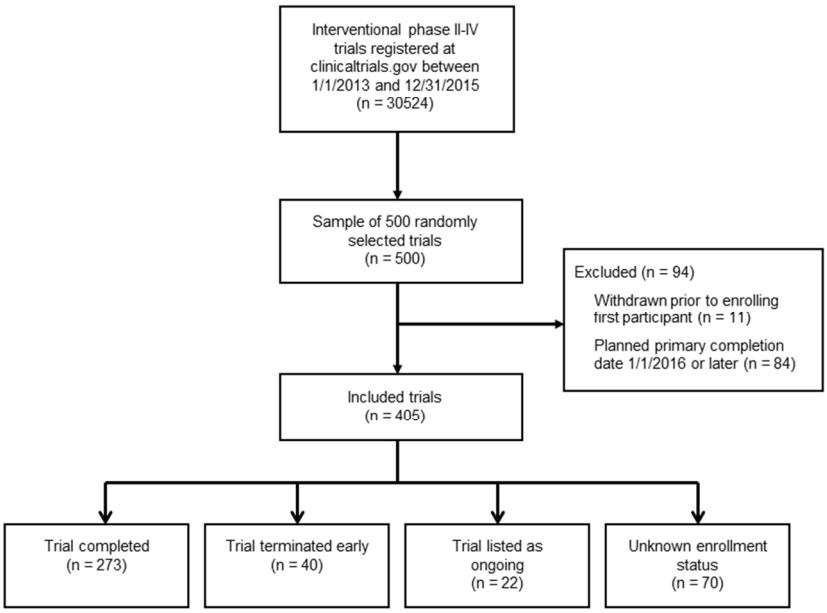

Figure 1. Flowchart of included trials

Figure 1

254x190mm (96 x 96 DPI)

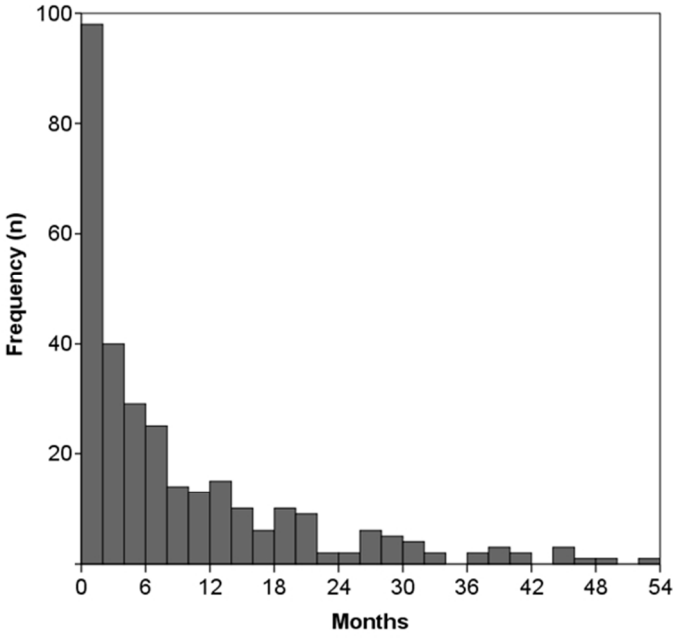

Figure 2

215x279mm (96 x 96 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	Table 1
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	n/a
		(*e*) Describe any sensitivity analyses	n/a
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 1
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-8
		(*b*) Report category boundaries when continuous variables were categorized	Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Design: Cross-sectional analysis

Setting: Random sample of interventional phase 2-4 clinical trials registered between 2012 and 2015 on ClinicalTrials.gov.

Primary outcome measure: For each trial which was listed within ClinicalTrials.gov as ongoing, two investigators performed a comprehensive literature search for evidence that the trial had actually been completed. For each trial listed as completed or terminated early by ClinicalTrials.gov we compared the date that the trial was actually concluded with the date the registry was updated to reflect the study's conclusion status.

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- The study involved comprehensive, independent literature searches by multiple investigators, including a medical research librarian.

- This study design is unable to identify studies which were completed but not published.

INTRODUCTION

Clinical trial registries play an essential role in helping to ensure the integrity of the published medical literature.[1] When utilized appropriately by investigators and sponsors, registration helps to ensure that a publically accessible trial record exists even when results are not published in a peer-reviewed journal, and that published outcome measures are consistent with prospectively specified trial outcomes. For these reasons, trial registries are a particularly important tool for systematic reviewers as they attempt to identify both published and unpublished trial data in order to assess for the possibility of publication bias.[2]

Despite the critical importance of trial registration, compliance with requirements from both the International Committee of Medical Journal Editors (ICMJE) and governmental regulators which mandate the prospective registration of clinical trials has been imperfect.[3 4] Meta-researchers have begun using data from ClinicalTrials.gov and other registries to identify these patterns of limited compliance in order to publicize and monitor deficiencies.[1 5 6]

Within ClinicalTrials.gov, users have the option of utilizing the "advanced search" function to restrict search results to only those trials with a particular recruitment status (ie. not yet recruiting, recruiting, completed, etc.). Systematic reviewers and meta-researchers often limit registry searches to trials for which subject recruitment is documented in the registry as having been completed.[5 7-13] Restricting reviews to completed studies makes sense because these are the studies for which all the data is completed and for which the results either are known or could be known. However, little is known about delays between the time of study completion and the time that ClinicalTrials.gov is updated to reflect this completion, or the percentage of completed trials which remain listed with an ongoing status in ClinicalTrials.gov indefinitely. If these delays are significant or a large proportion of registry entries are

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The objective of this study is to quantify delays observed between the end of subject recruitment in registered clinical trials, and the time that the registry entries are updated to reflect that recruitment has ended.

METHODS

Study selection and data collection

We searched ClinicalTrials.gov for phase 2-4 interventional studies registered between 01/01/2010 and 12/31/2012. From these potentially eligible trials (n=30,524) we randomly selected 500 studies for analysis. Studies with a recruiting status of withdrawn were excluded, as this indicates that the study was halted prior to enrolling any participants. Trials with a recruiting status indicating that recruitment was ongoing and a planned Primary Completion Date (date that primary outcome data for the final subject is collected) listed within ClinicalTrials.gov as being after 1/1/2016 were also excluded, as we hypothesized that the yield from a publication search for trials completed after this date would be low. For each included trial, we obtained information on study phase, size, sponsor, participant demographics, and recruitment status as of January 1, 2017 directly from ClinicalTrials.gov.

Dates for the following events were also recorded from ClinicalTrials.gov for each included trial: initial registration, study start, and primary completion date (date on which primary outcome data for the last trial participant were collected). When the primary completion date field was missing, we used the study completion date (final date on which any trial data were collected). We considered trials with recruitment statuses of either completed (study concluded normally) or terminated (recruitment

stopped prematurely and will not resume) to indicate that the study had ended and was unlikely to resume activity. These trials were classified as concluded. We recorded the dates on which the registry entries were updated to reflect that trials had concluded from the History of Changes section within each registry entry. Recruiting statuses which did not clearly reflect that the trial had concluded were recruiting, enrolling by invitation, not yet recruiting, active not recruiting, suspended, and unknown. Trials which were registered more than one month after the study start date were considered retrospectively registered.

Ongoing or Unknown Completion Status Trials

For studies which did not have an updated recruitment status indicating that they had concluded, we performed a comprehensive literature search to identify published evidence that the trial might in fact have been completed. An investigator first reviewed the relevant ClinicalTrials.gov entry for relevant publications and searched Medline via PubMed using trial registration number, keywords, condition studied, intervention, trial title, and investigators' names for matching manuscripts. When the first search identified no corresponding publication, a research librarian repeated this search using PubMed, Embase, and Google Scholar. The final publication search occurred between January and February of 2017.

We assessed matches between registry entries and publications identified by this search strategy using the following trial characteristics: study title, trial design, interventions, primary and secondary outcomes, number of participants, recruitment dates, location, and funding sources. We did not consider trials to be published if the publication did not include outcome data from the primary trial. For example, trial protocols for ongoing trials were not considered evidence of trial completion. We did consider published abstracts and presentations at scientific meetings to be evidence of trial completion, and counted these as publications for this analysis. For the group of included trials with an ongoing or

unknown recruitment status listed in the registry, the primary outcome was the proportion of studies with outcomes published in the medical literature.

Concluded Trials

For studies which were indicated to be concluded based on the recruitment status listed in ClinicalTrials.gov, the primary outcome was the amount of time elapsed between the primary completion date listed in ClinicalTrials.gov and the date on which the Clinicaltrials.gov registry entry was actually updated to indicate that the study had ended and was unlikely to resume activity.

Secondary outcomes included the proportion of studies registered more than one month after study initiation, and the proportion of studies registered after study completion. We also compared results among subgroups based on trial phase, trial size, and funding source.

We calculated descriptive data for the primary and secondary outcomes. We also compared the median time elapsed between the change in recruiting status and the time ClinicalTrials.gov was updated to reflect this change between subgroups using Mann Whitney and Kruskal Wallis tests. Chi-square tests were used to make comparisons between categorical variables. P values < 0.05 were considered statistically significant. Statistical analyses were performed using PASW version 18.0 (IBM, Armonk, NY). The dataset generated during the current study is available from the corresponding author on reasonable request.

RESULTS

Of the 500 potentially eligible trials which were randomly selected for evaluation, 405 were eligible for inclusion (Figure 1). Phase 2, 3, and 4 trials were all well represented within the study sample, and the

majority of trials (53%) had received at least partial industry funding (Table 1). A large proportion of trials were registered retrospectively, more than one month after the study had started (39%).

Table 1. Characteristics of included trials.

Trial Characteristics	All Trials (n = 405)	Concluded (n = 313)	Potentially Ongoing (n = 92)
Number of participants, median (IQR)	80 (32-225)	80 (30-230)	80 (40-173)
Trial phase, n (%)			
Phase 2	186	147 (79)	39 (21)
Phase 3 or 2/3	132	101 (77)	31 (23)
Phase 4	87	65 (75)	22 (25)
Funding source, n (%)[1]			
Industry	214	187 (87)	27 (13)
NIH‡/US Government	23	17 (74)	6 (26)
Other	233	155 (67)	78 (33)
Trial start date, n (%)			
Unlisted	2	1 (50)	1 (50)
Prior to 2006	15	14 (93)	1 (7)
2006-2009	37	29 (78)	8 (22)
2010-2011	235	176 (75)	59 (25)
2012-2014	116	93 (80)	23 (20)
Registered retrospectively, n (%)[3]	159	124 (78)	35 (22)
Registered prospectively, n (%)	245	189 (77)	56 (23)
Major discrepancy in recruitment status[4]	125	91 (73)	34 (27)

[1] Trials could have more than one funding source

[2] National Institutes of Health

[3] Registration timing relative to recruitment could not be determined for one study

[4] Listed recruitment status within ClinicalTrials.gov was incorrect or there was a delay of more than one year between when the study concluded and when the registry recruitment status was updated to reflect that recruitment ended.

Out of the 405 included trials, 273 (67%) were listed in ClinicalTrials.gov with a study status of completed, and 40 (10%) had initiated subject recruitment but were terminated early. Ninety-two trials (23%) had a recruitment status which indicated that trial activities were ongoing or that the study status was unknown, including 22 (5%) listed as active or active but not recruiting, and 70 (17%) listed as having an unknown recruiting status. Of these 92 trials with statuses in ClinicalTrials.gov indicating potentially ongoing study activity, we identified a corresponding publication containing outcome data for 34 trials (37%).

Among the trials with a completed or terminated status (n = 313), 2 were missing the study completion date. Of the remaining 311 trials, the median delay between when a trial was completed and when ClinicalTrials.gov was updated to reflect this change was 142 days (IQR 48-419), with a mean delay of 340 days. For 127 trials (41%), the recruitment status was changed promptly, with a delay of less than or equal to 90 days. In 91 trials (29%) this delay was greater than 1 year, and in 39 trials (13%) the delay was greater than two years (Figure 2). Eight trials had delays of more than five years. Retrospectively registered trials had a median delay of 266 days (IQR 62-650 days) between trial completion and when the registered recruitment status was updated, compared to a median of 116 days (IQR 38-260) for prospectively registered trials ($p < 0.001$). Observed delays did not differ between trials according to funding source or trial phase.

When considering all 405 included trials, 125 (31%) either had a listed recruitment status which was incorrect (ie trial had been completed but was not listed as such) or had a delay of more than one year between the time the study was completed and the time the recruitment status was updated. Retrospectively registered trials were more likely than prospectively registered trials to have one of these major discrepancies in recruitment status, with discrepancies observed for 46% of retrospectively registered trials and 21% of prospectively registered trials ($p < 0.001$). Major recruitment status discrepancies were particularly common among those trials registered more than one year after the onset of recruitment (37/56, 66%). Major recruitment status discrepancies were also very common among trials which started recruitment before 2006 (14/15, 93%), though this estimate is based on a very small number of trials. Major discrepancies were less common, but not unusual among trials which started recruitment from 2006-2009 (21/37, 57%), from 2010-2011 (59/235, 25%), and from 2012-2014 (31/116, 27%). Recruitment status discrepancies did not differ among trials based on funding source or trial phase.

DISCUSSION

Among this sample of over 400 phase 2-4 trials registered with ClinicalTrials.gov between 2010 and 2012 we identified frequent discrepancies between trial recruitment statuses listed on ClinicalTrials.gov and the actual trial status. Specifically, 37% of trials which were indicated to be ongoing based on available information within the registry had been completed and published. Among completed trials, 29% had a delay of more than a year between trial completion and the ClinicalTrials.gov update reporting trial completion.

Trial registries are an important tool by which both the authors of clinical guidelines and systematic reviewers can identify relevant clinical trials.[2 14] However, in both cases authors often assume that

the listed recruitment status is accurate and either restrict their registry searches to completed trials,[7-9] or conclude that those trials with active recruitment statuses are actually still ongoing.[15-19] Our findings show that this assumption is incorrect for a substantial portion of trials. Recruitment status discrepancies were particularly common among trials registered before 2006 and among retrospectively registered trials, which may reflect poor investigator familiarity with registry use in general, failure to prioritize correct registry use, or changing registration patterns over time.

One potential solution to the problem of outdated recruitment status information is to not limit registry searches to completed trials. For trials which are listed as ongoing, efforts should be made to confirm the recruitment status or search for published results regardless of the registered recruitment status. In addition to a comprehensive search for published results, in some cases these efforts should include contacting investigators or study sponsors to confirm recruitment status. Given the high rate of recruitment status discrepancies observed among retrospectively registered trials and trials registered prior to 2006, the listed ClinicalTrials.gov recruitment status should be considered particularly unreliable for these trials.

Trial registries serve as a critical source of data about ongoing and completed trials which supplements the published medical literature. However, our findings are consistent with previous studies which have demonstrated that registry information is at times incomplete or out of date. [5 20] This work is performed by meta-researchers, who use registry information to measure compliance with trial registration requirements and to monitor the conduct and reporting of clinical trials.[1] In order to accurately perform this function, it is also important for meta-researches to recognize the limitations we describe with respect to registered trial recruiting statuses. This is particularly important for registry-based investigations into publication bias, as excluding registered trials with a registry status indicating

that recruitment is ongoing may miss trials which have actually finished enrollment without updating the associated registry entry.[5 10-13]

Several important limitations should be considered when interpreting these results. First, our findings are based on a sample of phase 2-4 trials registered from 2012 to 2015; these general results may not be applicable to specific classes of clinical trials, and the patterns we observed may change over time. Additionally, we performed a literature search to identify trials which were listed in the registry as being ongoing, but which had actually been completed. It is likely that some additional trials were completed but not yet published; our search would not have identified these trials. Similarly, our literature search may have missed some trials. For these reasons, we may have underestimated the percentage of trials which were completed without updating the registry's recruitment status.

CONCLUSIONS

In summary, we observed that a significant percentage of clinical trials registered in ClinicalTrials.gov with a recruitment status indicating that the trial is ongoing have actually been completed. Additionally, among completed trials, we observed significant delays in updating the ClinicalTrials.gov recruitment status. Individuals utilizing registry data to supplement a systematic literature search and meta-researchers using registry data to study the conduct and reporting of clinical trials should be aware of these findings to avoid unwarranted assumptions about the recruitment status of registered trials.

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Competing interests: We have read and understood BMJ policy on declaration of interests and declare the following interests: CJ is an investigator on unrelated studies sponsored by AstraZeneca, Roche Diagnostics, Inc, and Janssen, for which his department received research grants. The remaining authors declare no additional competing interests.

Ethics approval: N/a

Data sharing: The full dataset is available from the corresponding author on reasonable request.

REFERENCES

1. Zarin DA, Tse T, Williams RJ, et al. Update on Trial Registration 11 Years after the ICMJE Policy Was Established. The New England journal of medicine 2017;**376**(4):383-91 doi: 10.1056/NEJMsr1601330[published Online First: Epub Date]|.
2. Jones CW, Keil LG, Weaver MA, et al. Clinical trials registries are under-utilized in the conduct of systematic reviews: a cross-sectional analysis. Systematic reviews 2014;**3**:126 doi: 10.1186/2046-4053-3-126[published Online First: Epub Date]|.
3. Ross JS, Mulvey GK, Hines EM, et al. Trial publication after registration in ClinicalTrials.Gov: a cross-sectional analysis. PLoS medicine 2009;**6**(9):e1000144 doi: 10.1371/journal.pmed.1000144[published Online First: Epub Date]|.
4. Mathieu S, Boutron I, Moher D, et al. Comparison of registered and published primary outcomes in randomized controlled trials. Jama 2009;**302**(9):977-84 doi: 10.1001/jama.2009.1242[published Online First: Epub Date]|.
5. Anderson ML, Chiswell K, Peterson ED, et al. Compliance with results reporting at ClinicalTrials.gov. The New England journal of medicine 2015;**372**(11):1031-9 doi: 10.1056/NEJMsa1409364[published Online First: Epub Date]|.
6. Jones CW, Keil LG, Holland WC, et al. Comparison of registered and published outcomes in randomized controlled trials: a systematic review. BMC medicine 2015;**13**:282 doi: 10.1186/s12916-015-0520-3[published Online First: Epub Date]|.
7. Jun M, Foote C, Lv J, et al. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. Lancet 2010;**375**(9729):1875-84 doi: 10.1016/S0140-6736(10)60656-3[published Online First: Epub Date]|.
8. Karagiannis T, Paschos P, Paletas K, et al. Dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta-analysis. Bmj 2012;**344**:e1369 doi: 10.1136/bmj.e1369[published Online First: Epub Date]|.
9. Li L, Shen J, Bala MM, et al. Incretin treatment and risk of pancreatitis in patients with type 2 diabetes mellitus: systematic review and meta-analysis of randomised and non-randomised studies. Bmj 2014;**348**:g2366 doi: 10.1136/bmj.g2366[published Online First: Epub Date]|.
10. Dechartres A, Riveros C, Harroch M, et al. Characteristics and Public Availability of Results of Clinical Trials on Rare Diseases Registered at Clinicaltrials.gov. JAMA internal medicine 2016;**176**(4):556-8 doi: 10.1001/jamainternmed.2016.0137[published Online First: Epub Date]|.
11. Jones CW, Handler L, Crowell KE, et al. Non-publication of large randomized clinical trials: cross sectional analysis. Bmj 2013;**347**:f6104 doi: 10.1136/bmj.f6104[published Online First: Epub Date]|.
12. Powell-Smith A, Goldacre B. The TrialsTracker: Automated ongoing monitoring of failure to share clinical trial results by all major companies and research institutions. F1000Research 2016;**5**:2629 doi: 10.12688/f1000research.10010.1[published Online First: Epub Date]|.
13. Ross JS, Tse T, Zarin DA, et al. Publication of NIH funded trials registered in ClinicalTrials.gov: cross sectional analysis. Bmj 2012;**344**:d7292 doi: 10.1136/bmj.d7292[published Online First: Epub Date]|.
14. Methodology Manual and Policies From the ACCF/AHA Task Force on Practice Guidelines. https://professional.heart.org/idc/groups/ahamah-public/@wcm/@sop/documents/downloadable/ucm_319826.pdf Accessed 2/9/2017, 2010.
15. Robinson PD, Kalkanis SN, Linskey ME, et al. Methodology used to develop the AANS/CNS management of brain metastases evidence-based clinical practice parameter guidelines. Journal of neuro-oncology 2010;**96**(1):11-6 doi: 10.1007/s11060-009-0059-2[published Online First: Epub Date]|.

16. Zarychanski R, Abou-Setta AM, Turgeon AF, et al. Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis. Jama 2013;**309**(7):678-88 doi: 10.1001/jama.2013.430[published Online First: Epub Date]|.
17. Ker K, Edwards P, Perel P, et al. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. Bmj 2012;**344**:e3054 doi: 10.1136/bmj.e3054[published Online First: Epub Date]|.
18. Bergman P, Lindh AU, Bjorkhem-Bergman L, et al. Vitamin D and Respiratory Tract Infections: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. PloS one 2013;**8**(6):e65835 doi: 10.1371/journal.pone.0065835[published Online First: Epub Date]|.
19. Masters GA, Temin S, Azzoli CG, et al. Systemic Therapy for Stage IV Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2015;**33**(30):3488-515 doi: 10.1200/JCO.2015.62.1342[published Online First: Epub Date]|.
20. Riveros C, Dechartres A, Perrodeau E, et al. Timing and completeness of trial results posted at ClinicalTrials.gov and published in journals. PLoS medicine 2013;**10**(12):e1001566 doi: 10.1371/journal.pmed.1001566[published Online First: Epub Date]|.

Figure 1. Flowchart of included trials.

Figure 2. Delays in updating ClinicalTrials.gov following trial conclusion.

Legend: Histogram of completed or terminated trials (n=311), depicting delays between the actual date of trial conclusion and the date on which ClinicalTrials.gov was updated to indicate trial conclusion.[1]

[1] Does not show eight outliers with delays of greater than 54 months. Trial completion dates were also not listed for two trials.

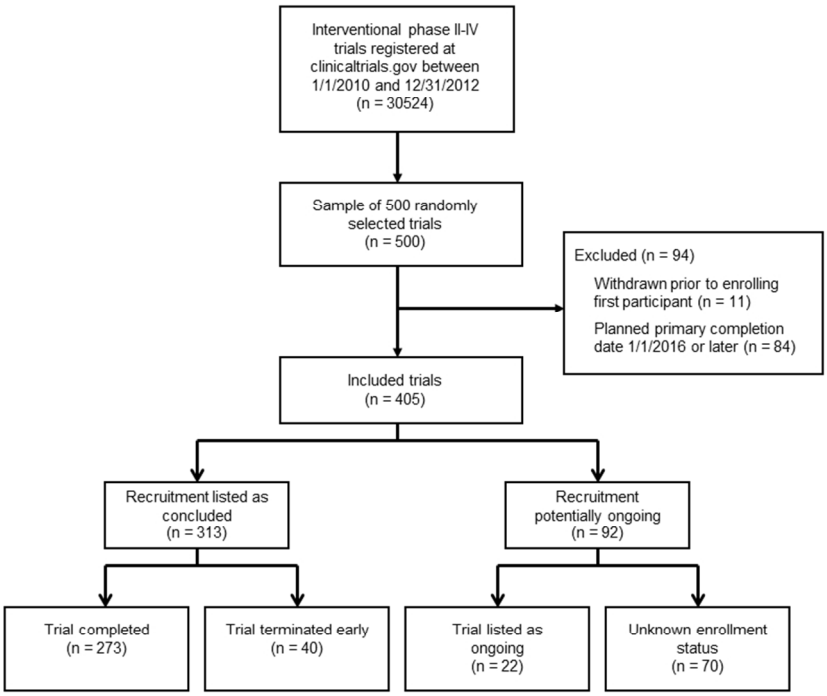

Figure 1. Flowchart of included trials

Flowchart of included trials.

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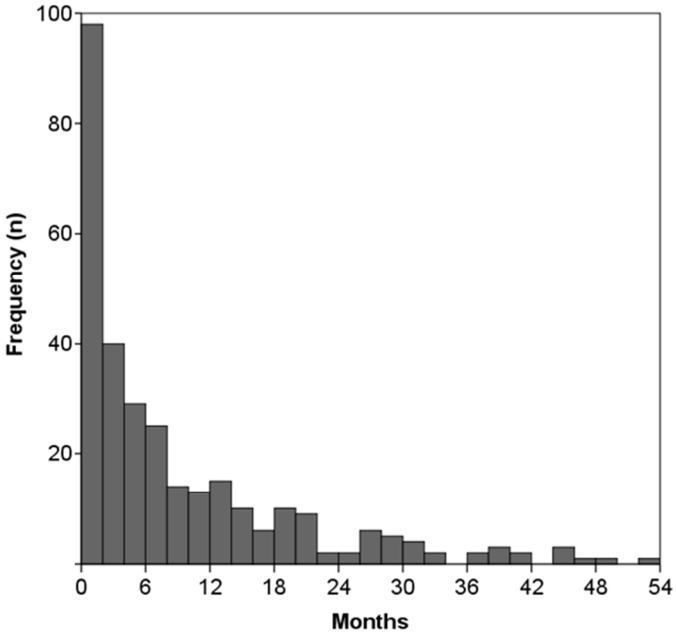

Figure 2

215x279mm (96 x 96 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	Table 1
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	n/a
		(*e*) Describe any sensitivity analyses	n/a
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 1
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures	7-8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-8
		(*b*) Report category boundaries when continuous variables were categorized	Table 1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.