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

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

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3 37 **Objectives:** to determine the accuracy of the recruitment status listed on ClinicalTrials.gov as compared
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5 38 to the actual trial status.
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8 39 **Design:** Cross-sectional analysis
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10 40 **Setting:** Random sample of interventional phase 2-4 clinical trials registered between 2012 and 2015 on
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12 41 ClinicalTrials.gov.
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14 42 **Primary outcome measure:** For each trial which was listed within ClinicalTrials.gov as ongoing, two
15
16 43 investigators performed a comprehensive literature search for evidence that the trial had actually been
17
18 44 completed. For each trial listed as completed or stopped early by ClinicalTrials.gov we compared the
19
20 45 date that the trial was actually concluded with the date the registry was updated to reflect the study's
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22 46 conclusion status.
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25 47 **Results:** Among the 405 included trials, 92 had a registry status indicating that study activity was either
26
27 48 ongoing or the recruitment status was unknown. Of these, published results were available for 34 (37%).
28
29 49 Among the 313 concluded trials, the median delay between study completion and a registry update
30
31 50 reflecting that the study had ended was 141 days (IQR 48-419), with delays of over one year present for
32
33 51 29%. In total, 125 trials (31%) either had a listed recruitment status which was incorrect or had a delay
34
35 52 of more than one year between the time the study was concluded and the time the registry recruitment
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37 53 status was updated.
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40 54 **Conclusions:** At present, registry recruitment status information in ClinicalTrials.gov is often outdated
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42 55 or wrong. This inaccuracy has implications for the ability of researchers to identify completed trials and
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44 56 accurately characterize all available medical knowledge on a given subject.
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3 58 **Article Summary**
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6 59 **Strengths and limitations of this study:**
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10 60 - Registry recruitment status is often used to identify completed clinical trials, yet the reliability of this
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12 61 information has not been previously assessed.
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15 62 - The study involved comprehensive, independent literature searches by multiple investigators, including
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17 63 a medical research librarian.
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21 64 - This study design is unable to identify studies which were completed but not published.
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66 INTRODUCTION

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

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

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

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3 88 The objective of this study is to quantify delays observed between the end of enrollment in registered
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5 89 clinical trials, and the time that the registry entries are updated to reflect that enrollment has ended.
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11 91 **METHODS**

15 92 **Study selection and data collection**

18 93 We searched ClinicalTrials.gov for phase 2-4 interventional studies registered between 01/01/2012 and
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20 94 12/31/2015. From these potentially eligible trials (n=30,524) we randomly selected 500 studies for
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23 95 analysis. Studies with a recruiting status of withdrawn were excluded, as this indicates that the study
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25 96 was halted prior to enrolling any participants. For each included trial, we obtained information on study
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27 97 phase, size, sponsor, participant demographics, and recruitment status as of January 1, 2017 directly
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30 98 from ClinicalTrials.gov.

33 99 Dates for the following events were also recorded from ClinicalTrials.gov for each included trial: initial
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35 100 registration, study start, and primary completion date (date on which primary outcome data for the last
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37 101 trial participant were collected). When the primary completion date field was missing, we used the
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40 102 study completion date (final date on which any trial data were collected). We considered trials with
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42 103 recruitment statuses of either completed (study concluded normally) or terminated (recruitment
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44 104 stopped prematurely and will not resume) to indicate that the study had ended and was unlikely to
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46 105 resume activity. These trials were classified as concluded. We recorded the dates on which the registry
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49 106 entries were updated to reflect that trials had concluded. Recruiting statuses which did not clearly
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51 107 reflect that the trial had concluded were recruiting, enrolling by invitation, not yet recruiting, active not
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53 108 recruiting, suspended, and unknown. Trials which were registered more than one month after the study
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56 109 start date were considered retrospectively registered.
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110 **Ongoing or Unknown Completion Status Trials**

111 For studies which were scheduled to have been completed prior to January 2016 and did not have an
112 updated recruitment status indicating that they had concluded, we performed a comprehensive
113 literature search to identify published evidence that the trial might in fact have been completed. An
114 investigator first searched Medline via PubMed using trial registration number, keywords, condition
115 studied, intervention, trial title, and investigators' names for matching manuscripts. When the first
116 search identified no corresponding publication, a research librarian repeated this search using PubMed,
117 Embase, and Google Scholar. The final publication search occurred between January and February of
118 2017.

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

128 **Concluded Trials**

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

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3 133 Secondary outcomes included the proportion of studies registered more than one month after study
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5 134 initiation, and the proportion of studies registered after study completion. We also compared results
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8 135 among subgroups based on trial phase, trial size, and funding source.
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11 136 We calculated descriptive data for the primary and secondary outcomes. We also compared the median
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13 137 time elapsed between the change in recruiting status and the time ClinicalTrials.gov was updated to
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15 138 reflect this change between subgroups using Mann Whitney and Kruskal Wallis tests. Chi-square tests
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17 139 were used to make comparisons between categorical variables. P values < 0.05 were considered
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19 140 statistically significant. Statistical analyses were performed using PASW version 18.0 (IBM, Armonk, NY).
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21 141 The dataset generated during the current study is available from the corresponding author on
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23 142 reasonable request.
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31 144 **RESULTS**
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34 145 Of the 500 potentially eligible trials which were randomly selected for evaluation, 405 were eligible for
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36 146 inclusion (Figure 1). Phase 2, 3, and 4 trials were all well represented within the study sample, and the
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38 147 majority of trials (53%) had received at least partial industry funding (Table 1). A large proportion of
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40 148 trials were registered retrospectively, more than one month after the study had started (39%).
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44 149 Out of the 405 included trials, 273 (67%) were listed in ClinicalTrials.gov with a study status of
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46 150 completed, and 40 (10%) had initiated enrollment but were terminated early. Ninety-two trials (23%)
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48 151 had a recruitment status which indicated that trial activities were ongoing or that the study status was
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50 152 unknown, including 22 (5%) listed as active or active but not recruiting, and 70 (17%) listed as having an
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52 153 unknown recruiting status. Of these 92 trials with statuses in ClinicalTrials.gov indicating potentially
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3 154 ongoing study activity, we identified a corresponding publication containing outcome data for 34 trials
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5 155 (37%).
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9 156 Among the trials with a completed or terminated status (n = 313), 2 were missing the study completion
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11 157 date. Of the remaining 311 trials, the median delay between when a trial was completed and when
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13 158 ClinicalTrials.gov was updated to reflect this change was 142 days (IQR 48-419), with a mean delay of
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15 159 340 days. In 91 trials (29%) this delay was greater than 1 year, and in 39 trials (13%) the delay was
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17 160 greater than two years (Figure 2). Eight trials had delays of more than five years. Retrospectively
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19 161 registered trials had a median delay of 266 days (IQR 62-650 days) between trial completion and when
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21 162 the registered recruitment status was updated, compared to a median of 116 days (IQR 38-260) for
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23 163 prospectively registered trials (p < 0.001). Observed delays did not differ between trials according to
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25 164 funding source or trial phase.
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30 165 When considering all 405 included trials, 125 (31%) either had a listed recruitment status which was
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32 166 incorrect (ie trial had been completed but was not listed as such) or had a delay of more than one year
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34 167 between the time the study was completed and the time the recruitment status was updated.
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36 168 Retrospectively registered trials were more likely than prospectively registered trials to have one of
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38 169 these major discrepancies in recruitment status, with discrepancies observed for 46% of retrospectively
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40 170 registered trials and 21% of prospectively registered trials (p < 0.001). These recruitment status
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42 171 discrepancies did not differ among trials based on funding source or trial phase.
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50 173 **DISCUSSION**

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53 174 Among this sample of over 400 phase 2-4 trials registered with ClinicalTrials.gov between 2012 and 2015
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55 175 we identified frequent discrepancies between trial recruitment statuses listed on ClinicalTrials.gov and
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3 176 the actual trial status. Specifically, 37% of trials which were indicated to be ongoing based on available
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5 177 information within the registry had been completed and published. Among completed trials, 29% had a
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8 178 delay of more than a year between trial completion and the ClinicalTrials.gov update reporting trial
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10 179 completion.

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13 180 Trial registries are an important tool by which both the authors of clinical guidelines and systematic
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15 181 reviewers can identify relevant clinical trials.[2 14] However, in both cases authors often assume that
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18 182 the listed enrollment status is accurate and either restrict their registry searches to completed trials,[7-
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20 183 9] or conclude that those trials with active enrollment statuses are actually still ongoing.[15-19] Our
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22 184 findings show that this assumption is incorrect for a substantial portion of trials. One potential solution
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25 185 is to not limit registry searches to completed trials. For trials which are listed as ongoing, efforts should
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27 186 be made to confirm the enrollment status or search for published results regardless of the registered
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29 187 enrollment status.

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32 188 Trial registries serve as a critical source of data about ongoing and completed trials which supplements
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34 189 the published medical literature. However, our findings are consistent with previous studies which have
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37 190 demonstrated that registry information is at times incomplete or out of date. [5 20] This work is
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39 191 performed by meta-researchers, who use registry information to measure compliance with trial
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42 192 registration requirements and to monitor the conduct and reporting of clinical trials.[1] In order to
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44 193 accurately perform this function, it is also important for meta-researches to recognize the limitations we
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46 194 describe with respect to registered trial recruiting statuses. This is particularly important for registry-
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49 195 based investigations into publication bias, as excluding registered trials with a registry status indicating
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51 196 that recruitment is ongoing may miss trials which have actually finished enrollment without updating
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53 197 the associated registry entry.[5 10-13]

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3 198 Several important limitations should be considered when interpreting these results. First, our findings
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5 199 are based on a sample of phase 2-4 trials registered from 2012 to 2015; these general results may not be
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8 200 applicable to specific classes of clinical trials, and the patterns we observed may change over time.
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10 201 Additionally, we performed a literature search to identify trials which were listed in the registry as being
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12 202 ongoing, but which had actually been completed. It is likely that some additional trials were completed
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14 203 but not yet published; our search would not have identified these trials. Similarly, our literature search
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16 204 may have missed some trials. For these reasons, we may have underestimated the percentage of trials
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19 205 which were completed without updating the registry's recruitment status.
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22 206 **CONCLUSIONS**

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26 207 In summary, we observed that a significant percentage of clinical trials registered in ClinicalTrials.gov
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28 208 with a recruitment status indicating that the trial is ongoing have actually been completed. Additionally,
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30 209 among completed trials, we observed significant delays in updating the ClinicalTrials.gov recruitment
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32 210 status. Individuals utilizing registry data to supplement a systematic literature search and meta-
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34 211 researchers using registry data to study the conduct and reporting of clinical trials should be aware of
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37 212 these findings to avoid unwarranted assumptions about the recruitment status of registered trials.
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14
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16

17 219 CJ, MS, and AA performed data collection. CJ performed data analysis and interpretation and drafted the
18
19 220 article. All authors provided critical revisions to the article, and all authors read and approved the final
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21 221 manuscript.
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27

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29

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31

32 226 declare no additional competing interests.
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38 228 **Ethics approval:** N/a
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42 229 **Data sharing:** The full dataset is available from the corresponding author on reasonable request.
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300 **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 ² /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)

301 ¹ Trials could have more than one funding source302 ² National Institutes of Health303 ³ Registration timing relative to enrollment could not be determined for one study

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306 **Figure 1.** Flowchart of included trials.

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

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

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

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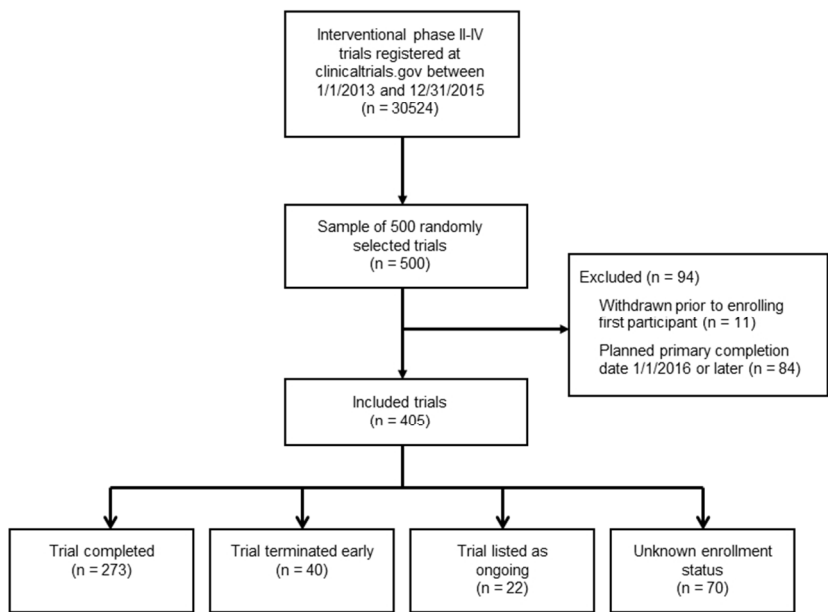


Figure 1. Flowchart of included trials

Figure 1

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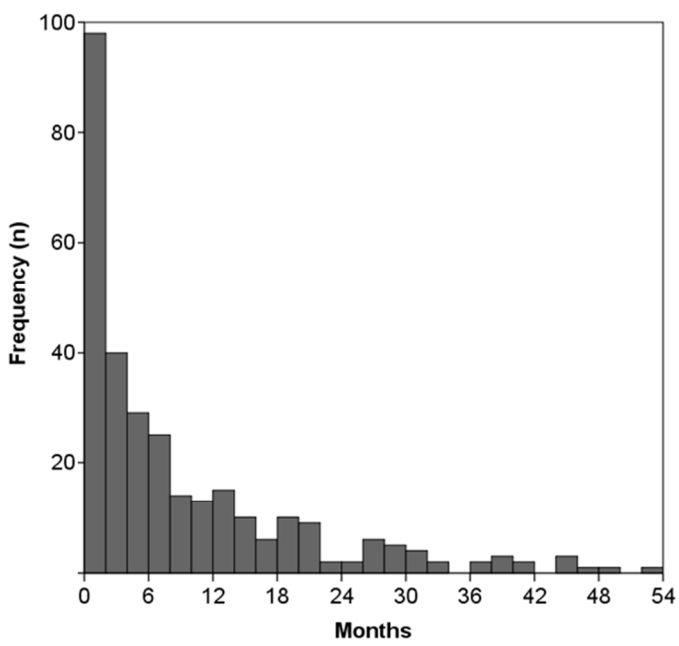


Figure 2
215x279mm (96 x 96 DPI)

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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest	Table 1 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 (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7-8 Table 1
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.

BMJ Open

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

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

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3 37 **Objectives:** To determine the accuracy of the recruitment status listed on ClinicalTrials.gov as compared
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5 38 to the actual trial status.
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8 39 **Design:** Cross-sectional analysis
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10 40 **Setting:** Random sample of interventional phase 2-4 clinical trials registered between 2012 and 2015 on
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12 41 ClinicalTrials.gov.
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14 42 **Primary outcome measure:** For each trial which was listed within ClinicalTrials.gov as ongoing, two
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16 43 investigators performed a comprehensive literature search for evidence that the trial had actually been
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18 44 completed. For each trial listed as completed or terminated early by ClinicalTrials.gov we compared the
19
20 45 date that the trial was actually concluded with the date the registry was updated to reflect the study's
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22 46 conclusion status.
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25 47 **Results:** Among the 405 included trials, 92 had a registry status indicating that study activity was either
26
27 48 ongoing or the recruitment status was unknown. Of these, published results were available for 34 (37%).
28
29 49 Among the 313 concluded trials, the median delay between study completion and a registry update
30
31 50 reflecting that the study had ended was 141 days (IQR 48-419), with delays of over one year present for
32
33 51 29%. In total, 125 trials (31%) either had a listed recruitment status which was incorrect or had a delay
34
35 52 of more than one year between the time the study was concluded and the time the registry recruitment
36
37 53 status was updated.
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40 54 **Conclusions:** At present, registry recruitment status information in ClinicalTrials.gov is often outdated
41
42 55 or wrong. This inaccuracy has implications for the ability of researchers to identify completed trials and
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44 56 accurately characterize all available medical knowledge on a given subject.
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3 58 **Article Summary**
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6 59 **Strengths and limitations of this study:**
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10 60 - Registry recruitment status is often used to identify completed clinical trials, yet the reliability of this
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12 61 information has not been previously assessed.
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15 62 - The study involved comprehensive, independent literature searches by multiple investigators, including
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17 63 a medical research librarian.
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21 64 - This study design is unable to identify studies which were completed but not published.
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66 INTRODUCTION

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

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

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

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3 88 never updated to reflect study completion, then limiting registry searches to only entries with a
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5 89 completed registry status might miss otherwise relevant trials.
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9 90 The objective of this study is to quantify delays observed between the end of subject recruitment in
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11 91 registered clinical trials, and the time that the registry entries are updated to reflect that recruitment
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13 92 has ended.
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18 19 20 94 **METHODS**

21 22 23 95 **Study selection and data collection**

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26 96 We searched ClinicalTrials.gov for phase 2-4 interventional studies registered between 01/01/2010 and
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28 97 12/31/2012. From these potentially eligible trials (n=30,524) we randomly selected 500 studies for
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30 98 analysis. Studies with a recruiting status of withdrawn were excluded, as this indicates that the study
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32 99 was halted prior to enrolling any participants. Trials with a recruiting status indicating that recruitment
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34 100 was ongoing and a planned Primary Completion Date (date that primary outcome data for the final
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36 101 subject is collected) listed within ClinicalTrials.gov as being after 1/1/2016 were also excluded, as we
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38 102 hypothesized that the yield from a publication search for trials completed after this date would be low.
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40 103 For each included trial, we obtained information on study phase, size, sponsor, participant
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42 104 demographics, and recruitment status as of January 1, 2017 directly from ClinicalTrials.gov.
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48 105 Dates for the following events were also recorded from ClinicalTrials.gov for each included trial: initial
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50 106 registration, study start, and primary completion date (date on which primary outcome data for the last
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52 107 trial participant were collected). When the primary completion date field was missing, we used the
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54 108 study completion date (final date on which any trial data were collected). We considered trials with
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56 109 recruitment statuses of either completed (study concluded normally) or terminated (recruitment
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3 110 stopped prematurely and will not resume) to indicate that the study had ended and was unlikely to
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5 111 resume activity. These trials were classified as concluded. We recorded the dates on which the registry
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7 112 entries were updated to reflect that trials had concluded from the History of Changes section within
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9 113 each registry entry. Recruiting statuses which did not clearly reflect that the trial had concluded were
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11 114 recruiting, enrolling by invitation, not yet recruiting, active not recruiting, suspended, and unknown.
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13 115 Trials which were registered more than one month after the study start date were considered
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15 116 retrospectively registered.
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20 117 **Ongoing or Unknown Completion Status Trials**

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23 118 For studies which did not have an updated recruitment status indicating that they had concluded, we
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25 119 performed a comprehensive literature search to identify published evidence that the trial might in fact
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27 120 have been completed. An investigator first reviewed the relevant ClinicalTrials.gov entry for relevant
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29 121 publications and searched Medline via PubMed using trial registration number, keywords, condition
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31 122 studied, intervention, trial title, and investigators' names for matching manuscripts. When the first
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33 123 search identified no corresponding publication, a research librarian repeated this search using PubMed,
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35 124 Embase, and Google Scholar. The final publication search occurred between January and February of
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37 125 2017.
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42 126 We assessed matches between registry entries and publications identified by this search strategy using
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44 127 the following trial characteristics: study title, trial design, interventions, primary and secondary
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46 128 outcomes, number of participants, recruitment dates, location, and funding sources. We did not
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48 129 consider trials to be published if the publication did not include outcome data from the primary trial. For
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50 130 example, trial protocols for ongoing trials were not considered evidence of trial completion. We did
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52 131 consider published abstracts and presentations at scientific meetings to be evidence of trial completion,
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54 132 and counted these as publications for this analysis. For the group of included trials with an ongoing or
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3 133 unknown recruitment status listed in the registry, the primary outcome was the proportion of studies
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6 134 with outcomes published in the medical literature.
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8 9 135 **Concluded Trials**

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12 136 For studies which were indicated to be concluded based on the recruitment status listed in
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14 137 ClinicalTrials.gov, the primary outcome was the amount of time elapsed between the primary
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16 138 completion date listed in ClinicalTrials.gov and the date on which the ClinicalTrials.gov registry entry was
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19 139 actually updated to indicate that the study had ended and was unlikely to resume activity.
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22 140 Secondary outcomes included the proportion of studies registered more than one month after study
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24 141 initiation, and the proportion of studies registered after study completion. We also compared results
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26 142 among subgroups based on trial phase, trial size, and funding source.
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30 143 We calculated descriptive data for the primary and secondary outcomes. We also compared the median
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32 144 time elapsed between the change in recruiting status and the time ClinicalTrials.gov was updated to
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34 145 reflect this change between subgroups using Mann Whitney and Kruskal Wallis tests. Chi-square tests
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36 146 were used to make comparisons between categorical variables. P values < 0.05 were considered
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39 147 statistically significant. Statistical analyses were performed using PASW version 18.0 (IBM, Armonk, NY).

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41 148 The dataset generated during the current study is available from the corresponding author on
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44 149 reasonable request.
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48 49 151 **RESULTS**

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53 152 Of the 500 potentially eligible trials which were randomly selected for evaluation, 405 were eligible for
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55 153 inclusion (Figure 1). Phase 2, 3, and 4 trials were all well represented within the study sample, and the
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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

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3 158 ² National Institutes of Health
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5 159 ³ Registration timing relative to recruitment could not be determined for one study
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8 160 ⁴ Listed recruitment status within ClinicalTrials.gov was incorrect or there was a delay of more than one
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10 161 year between when the study concluded and when the registry recruitment status was updated to
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12 162 reflect that recruitment ended.
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18 164 Out of the 405 included trials, 273 (67%) were listed in ClinicalTrials.gov with a study status of
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20 165 completed, and 40 (10%) had initiated subject recruitment but were terminated early. Ninety-two trials
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22 166 (23%) had a recruitment status which indicated that trial activities were ongoing or that the study status
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24 167 was unknown, including 22 (5%) listed as active or active but not recruiting, and 70 (17%) listed as
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26 168 having an unknown recruiting status. Of these 92 trials with statuses in ClinicalTrials.gov indicating
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28 169 potentially ongoing study activity, we identified a corresponding publication containing outcome data
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30 170 for 34 trials (37%).
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35 171 Among the trials with a completed or terminated status (n = 313), 2 were missing the study completion
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37 172 date. Of the remaining 311 trials, the median delay between when a trial was completed and when
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39 173 ClinicalTrials.gov was updated to reflect this change was 142 days (IQR 48-419), with a mean delay of
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41 174 340 days. For 127 trials (41%), the recruitment status was changed promptly, with a delay of less than or
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43 175 equal to 90 days. In 91 trials (29%) this delay was greater than 1 year, and in 39 trials (13%) the delay
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45 176 was greater than two years (Figure 2). Eight trials had delays of more than five years. Retrospectively
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47 177 registered trials had a median delay of 266 days (IQR 62-650 days) between trial completion and when
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49 178 the registered recruitment status was updated, compared to a median of 116 days (IQR 38-260) for
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51 179 prospectively registered trials (p < 0.001). Observed delays did not differ between trials according to
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53 180 funding source or trial phase.
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3 181 When considering all 405 included trials, 125 (31%) either had a listed recruitment status which was
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5 182 incorrect (ie trial had been completed but was not listed as such) or had a delay of more than one year
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7 183 between the time the study was completed and the time the recruitment status was updated.
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10 184 Retrospectively registered trials were more likely than prospectively registered trials to have one of
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12 185 these major discrepancies in recruitment status, with discrepancies observed for 46% of retrospectively
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14 186 registered trials and 21% of prospectively registered trials ($p < 0.001$). Major recruitment status
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16 187 discrepancies were particularly common among those trials registered more than one year after the
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18 188 onset of recruitment (37/56, 66%). Major recruitment status discrepancies were also very common
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20 189 among trials which started recruitment before 2006 (14/15, 93%), though this estimate is based on a
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22 190 very small number of trials. Major discrepancies were less common, but not unusual among trials which
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24 191 started recruitment from 2006-2009 (21/37, 57%), from 2010-2011 (59/235, 25%), and from 2012-2014
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26 192 (31/116, 27%). Recruitment status discrepancies did not differ among trials based on funding source or
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28 193 trial phase.
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37 195 **DISCUSSION**

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40 196 Among this sample of over 400 phase 2-4 trials registered with ClinicalTrials.gov between 2010 and 2012
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42 197 we identified frequent discrepancies between trial recruitment statuses listed on ClinicalTrials.gov and
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44 198 the actual trial status. Specifically, 37% of trials which were indicated to be ongoing based on available
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46 199 information within the registry had been completed and published. Among completed trials, 29% had a
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48 200 delay of more than a year between trial completion and the ClinicalTrials.gov update reporting trial
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50 201 completion.
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55 202 Trial registries are an important tool by which both the authors of clinical guidelines and systematic
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57 203 reviewers can identify relevant clinical trials.[2 14] However, in both cases authors often assume that
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3 204 the listed recruitment status is accurate and either restrict their registry searches to completed trials,[7-
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5 205 9] or conclude that those trials with active recruitment statuses are actually still ongoing.[15-19] Our
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8 206 findings show that this assumption is incorrect for a substantial portion of trials. Recruitment status
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10 207 discrepancies were particularly common among trials registered before 2006 and among retrospectively
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12 208 registered trials, which may reflect poor investigator familiarity with registry use in general, failure to
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14 209 prioritize correct registry use, or changing registration patterns over time.

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18 210 One potential solution to the problem of outdated recruitment status information is to not limit registry
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20 211 searches to completed trials. For trials which are listed as ongoing, efforts should be made to confirm
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22 212 the recruitment status or search for published results regardless of the registered recruitment status. In
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24 213 addition to a comprehensive search for published results, in some cases these efforts should include
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26 214 contacting investigators or study sponsors to confirm recruitment status. Given the high rate of
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28 215 recruitment status discrepancies observed among retrospectively registered trials and trials registered
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30 216 prior to 2006, the listed ClinicalTrials.gov recruitment status should be considered particularly unreliable
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32 217 for these trials.

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37 218 Trial registries serve as a critical source of data about ongoing and completed trials which supplements
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39 219 the published medical literature. However, our findings are consistent with previous studies which have
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41 220 demonstrated that registry information is at times incomplete or out of date. [5 20] This work is
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43 221 performed by meta-researchers, who use registry information to measure compliance with trial
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45 222 registration requirements and to monitor the conduct and reporting of clinical trials.[1] In order to
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47 223 accurately perform this function, it is also important for meta-researches to recognize the limitations we
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49 224 describe with respect to registered trial recruiting statuses. This is particularly important for registry-
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51 225 based investigations into publication bias, as excluding registered trials with a registry status indicating
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3 226 that recruitment is ongoing may miss trials which have actually finished enrollment without updating
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6 227 the associated registry entry.[5 10-13]
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9 228 Several important limitations should be considered when interpreting these results. First, our findings
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11 229 are based on a sample of phase 2-4 trials registered from 2012 to 2015; these general results may not be
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13 230 applicable to specific classes of clinical trials, and the patterns we observed may change over time.
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15 231 Additionally, we performed a literature search to identify trials which were listed in the registry as being
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17 232 ongoing, but which had actually been completed. It is likely that some additional trials were completed
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20 233 but not yet published; our search would not have identified these trials. Similarly, our literature search
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22 234 may have missed some trials. For these reasons, we may have underestimated the percentage of trials
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25 235 which were completed without updating the registry's recruitment status.
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27 28 236 **CONCLUSIONS** 29

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31 237 In summary, we observed that a significant percentage of clinical trials registered in ClinicalTrials.gov
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33 238 with a recruitment status indicating that the trial is ongoing have actually been completed. Additionally,
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35 239 among completed trials, we observed significant delays in updating the ClinicalTrials.gov recruitment
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37 240 status. Individuals utilizing registry data to supplement a systematic literature search and meta-
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40 241 researchers using registry data to study the conduct and reporting of clinical trials should be aware of
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42 242 these findings to avoid unwarranted assumptions about the recruitment status of registered trials.
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9

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14
15 248 **Authors' contributions:** CJ conceived the study. CJ, MS, AA, and TP all contributed to the study design.
16

17 249 CJ, MS, and AA performed data collection. CJ performed data analysis and interpretation and drafted the
18
19 250 article. All authors provided critical revisions to the article, and all authors read and approved the final
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21 251 manuscript.
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26 253 **Competing interests:** We have read and understood BMJ policy on declaration of interests and declare
27

28 254 the following interests: CJ is an investigator on unrelated studies sponsored by AstraZeneca, Roche
29

30 255 Diagnostics, Inc, and Janssen, for which his department received research grants. The remaining authors
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33 256 declare no additional competing interests.
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38 258 **Ethics approval:** N/a
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42 259 **Data sharing:** The full dataset is available from the corresponding author on reasonable request.
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3 330 **Figure 1.** Flowchart of included trials.
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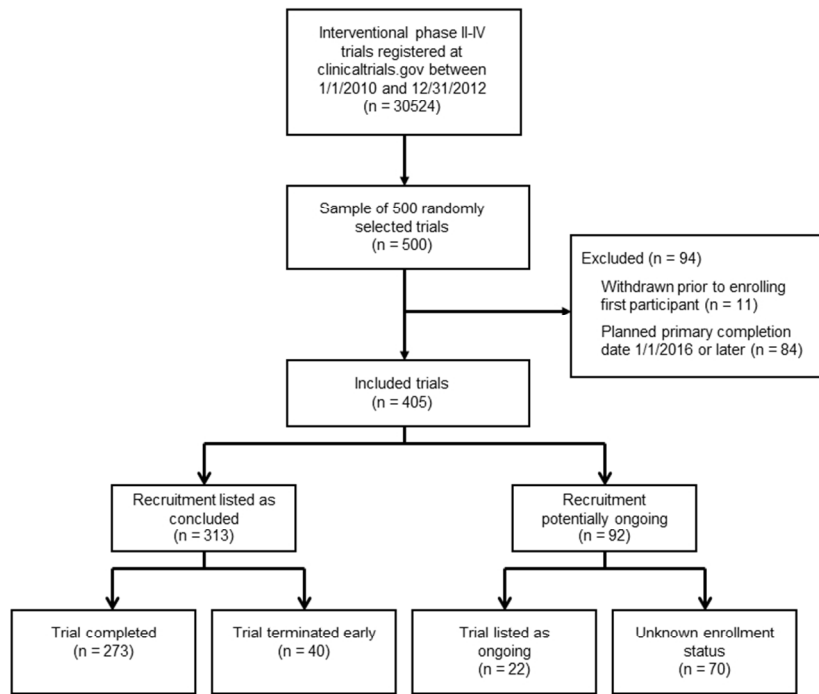
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10 333 **Figure 2.** Delays in updating ClinicalTrials.gov following trial conclusion.

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12 334 Legend: Histogram of completed or terminated trials (n=311), depicting delays between the actual date
13 335 of trial conclusion and the date on which ClinicalTrials.gov was updated to indicate trial conclusion.¹

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18 337 ¹ Does not show eight outliers with delays of greater than 54 months. Trial completion dates were also
19 338 not listed for two trials.



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Figure 1. Flowchart of included trials

Flowchart of included trials.

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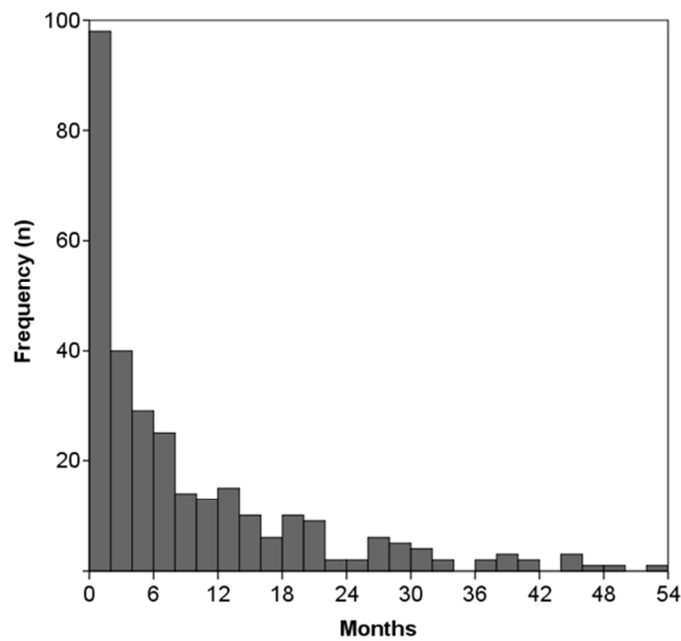


Figure 2

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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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest	Table 1 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 (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7-8 Table 1
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.