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Characteristics of registered clinical trials assessing strategies of medication errors prevention

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Abstract. *Background and aim:* ClinicalTrials.gov is the oldest and largest of these registries collecting clinical trials. Through this, the researchers can explore and monitor the clinical research landscape. In the last decades, the number of Medline-indexed publications on adverse events and medication errors has increased exponentially. The aims of this study are to define the prevalence of clinical trials that have as outcome the medication errors and to describe the characteristics of these trials, including their distribution across countries, and publication rate. *Methods:* A cross-sectional analysis of all clinical trials reporting as primary outcome medication errors identified through ClincialTrials.gov. *Results:* Among 5.881 trials, only 1,68% focused on intervention to improve medication safety process and prevent medication errors. 25,3% of clinical trials included had their primary outcome changed (p= ,005). Recording study results in ClinicalTrials.gov was associated with trials that had their primary outcome changed (OR: ,060; 95% C.I.: ,007 – ,541). Only few interventional trials were totally compliant with the ICMJE policy. For all trials completed in our sample, in mean 7,44 months (median: 12 months) elapsed between study completion and the first publication in Medline showing the trial's identification number. *Conclusions:* This study demonstrates several strengths of using ClinicalTrials.gov to track intervention to improve medication safety process. It is unknown how many trials are designed to focus on medication errors. However, 1,68% of trials focused on intervention to improve medication safety process.

Key words: Clinical trials; ICMJE policy; Medication errors; nursing; publication rate; Trend analysis.

Introduction

In the last decades, the number of Medline-indexed publications on causes, frequency and consequences of adverse events and medication errors has increased exponentially as well as the evaluation of the effects of interventions to prevent them [1]. The best source of evidence on the efficacy and safety of medication safety intervention is the clinical study.

An adverse drug event (ADE) is "an injury resulting from medical intervention related to a drug", that cause an unplanned hospital admissions and

deaths [2]. This expression covers the adverse drug reactions (ADRs) and preventable adverse drug events, associated with a medication error [3]. The Council of Europe [4] defines medication errors as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is under the control of the healthcare professional, patient or consumer.

Scientific literature divides the factors that contribute to the occurrence of harmful (or potential) events into:

1. human factors, based on personal and professional characteristics of the healthcare workers [5,6], and
2. organizational factors, based on drug management process [7,8].

The best source of evidence on the efficacy and safety of medication safety intervention is the clinical study, defined as "a research study involving human volunteers (also called participants) that is intended to add to medical knowledge. There are two types of clinical studies: interventional studies (also called clinical trials) and observational studies" [9].

To improve quality, visibility and discoverability of clinical study, the US Food and Drug Administration [10,11] imposed the registration of the study [12,13]. At the moment, seventeen are the clinical trial registry [14,15].

ClinicalTrials.gov is the oldest and largest of these registries. Through this, the researchers can explore, assess, and monitor the clinical research landscape and its related findings [12,16].

Previous studies aim to trends in quality, reporting rate, outcome change, publication rate, or potential publication bias about clinical research activity or clinical trials registered in the platform [17-26].

However, to our knowledge, no one has been previously undertaken the analysis of intervention to improve medication safety or prevent medication errors through the ClinicalTrials.gov.

The aim of the study is to define the prevalence of interventional trials that have as primary outcome the medication errors or medication safety and describe the characteristics of these trials, including their distribution across countries, sponsor, and publication rate.

Methods

Design

Cross-sectional analysis of Registered Clinical Trials.

Data collection

All clinical trials were download into an Excel file after searching the ClinicalTrials.gov the key words "medication errors", "drug error", "medication safety" or "drug safety", "adverse drug event", according the methodology proposed by Glanville et al. [27]. The screening of clinical trials was performed according to the PRISMA statement [28].

Sample

The authors defined the eligibility criteria used to rule in or out the collected clinical trials for this research study.

In this study, the term clinical trial or simply trials includes the interventional study, and observational study. The included trial had to be interventional or observational in nature, but interventional trials to study medication adherence or medication compliance by patients or adverse drug reactions were excluded. Interventional trials on efficacy of a specific treatment in a clinical condition or interventional trials that compare different drug were excluded. All data were downloaded from ClinicalTrials.gov on April 2020.

Validity and accuracy

For each trial registered, different factors were collected such as: the type of intervention under study according EPOC taxonomy [29], the setting (e.g. hospital, primary care setting, transitional care), study phase, start year, whether the study was randomized and, if so, the unit of randomization, the number of participants enrolled (or the estimated number if the study was ongoing), and the length of the study (calculated as the time from study start to completion date). Moreover, for each clinical trial the study site countries and funding sources were identified. Funding sources included industry, NIH, other US federal (excluding NIH), and other.

Each clinical trial is classified as university or non-university sponsored. The primary outcome measures were examined and, also, were identified discrepancies

with the primary outcome listed in the ClinicalTrials.gov before the study start date, primary completion date or study completion date. Two electronic databases (PubMed, and Google Scholar) are used to systematically searched for publication corresponding to the ClinicalTrials.gov trials.

Ethical considerations

Ethical approval was not required for this study as no human subjects were involved and all data used in the review are available in the public domain.

Data analysis

The Statistical Package for the Social Sciences (SPSS®), version25, was used to analyze the data. Descriptive statistics were used to analyze the distributions of clinical trials registered, while inferential statistics were used to determine the presence of statistically significant differences.

Logistic regression analysis was performed to calculate odds ratios (OR) with Wald 95% confidence intervals for factors associated with trials and Chi-square tests were used to evaluate the association between study types and trial characteristics. p<.05 was considered statistically significant.

Based on the requirements of the International Committee of Medical Journal Editors (ICMJE), each interventional trials included was assessed to evaluate the compliance with the minimum acceptable 24-item trial registration.

Results

On 10 April 2020, the search yielded 5.881 trials on medication errors prevention registered at the ClinicalTrials.gov site. After removal of the duplicates and trials that met study exclusion criteria, 99 trials remained, which were included in this study. Figure 1 presents a flow chart of the clinical trials selection process.

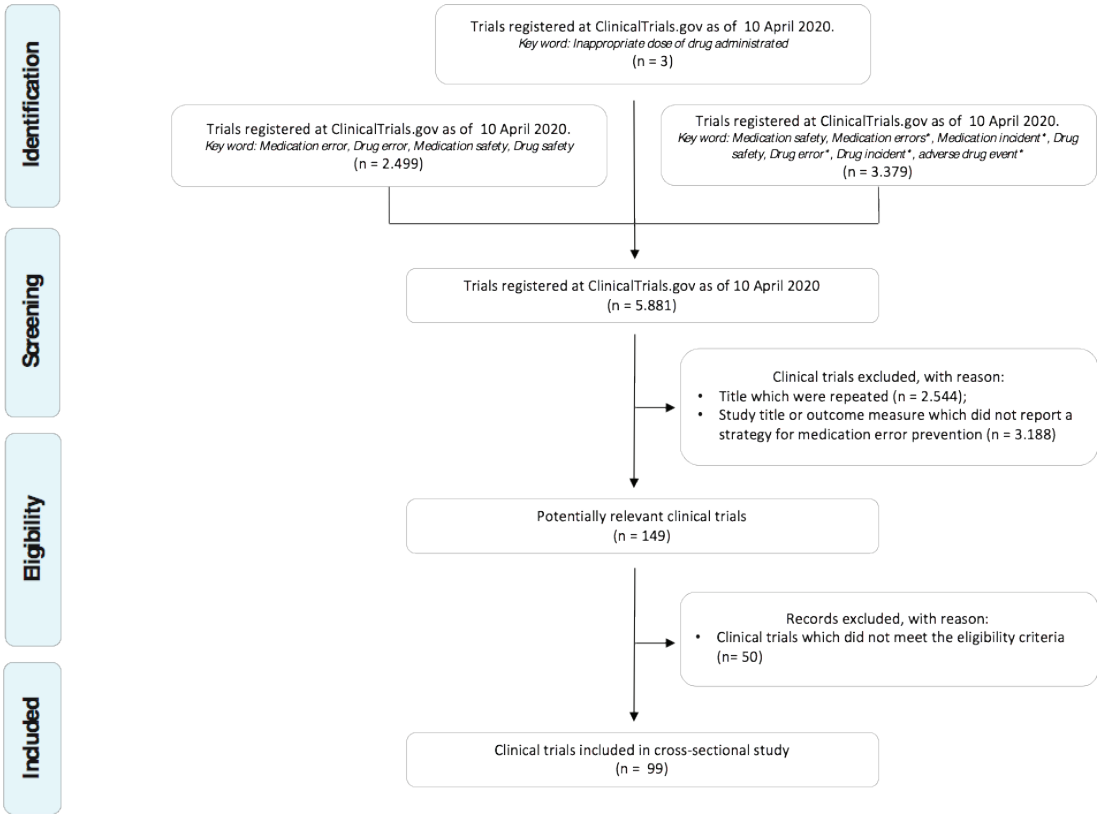

Figure 1. Flow diagram of the search and selection process of clinical trials

General characteristics of the clinical trials

Thirty-three (n=33, 33,3%) clinical trials registered on ClinicalTrials.gov were conducted in United States, thirteen (n=13, 12,1%) clinical trials were conducted in France; in Canada were conducted ten (n=10, 10,1%) clinical trials, five (n=5) clinical trials were conducted in Denmark; four clinical trials (n=4) were conducted in Switzerland and in Taiwan, respectively. Each country such as Ireland, Italy, Netherlands, Brazil, Argentina had registered only two (n=2) clinical studies. While, Belgium, Chile, Colombia, Germany, Israel, Jordan, Pakistan, Sweden, and United Kingdom had registered only one (n=1) clinical trials, respectively. The other twelve clinical trials (n=13, 13,13%) have not provided a location.

All clinical trials included involving human participants. There are two types of clinical studies: interventional studies (n=70, 70,7%) and observational studies (n=29, 29,3%). Table 1 shows the descriptive statistic about the status of study, characteristic of observational studies included (observational model, sampling methods and time perspective), and characteristic of interventional study included (interventional model, study phase, allocation). There were 73 (73,7%) trials classed as "other funded", that include individuals, universities, and community-based organizations [9], 18 (18,2%) trials classed as mixed (NIH|Other, Industry|Other, U.S. Fed|Other).

Table 1. General characteristic of clinical trials included

			n(%)
Study status		Active, not recruiting	5 (5,1)
Completed			60 (60,6)
Enrolling by invitation			2 (2)
Not yet recruiting			4 (4)
Recruiting			11 (11,1)
Unknown status			14 (14,1)
Withdrawn			3 (3)
Enrollment size Observational study [mean (range)]		Interventional study [mean (range)]	2.517,87 (6.000 – 15.000)
			4.190,28 (20 – 50.000)
Sponsored by Industry, government, others		University or research centers	62 (62,7)
			37 (37,4)
Collaborators		University or research centers	31 (31,3)
Industry, government, others			20 (20,2)
Not provided			48 (48,5)
Observational study [a]	Observational Model [a]	Defined Population - Natural History	1 (3,5)
		Ecologic or Community	1 (3,5)
		Case-control	2 (6,9)
		Case-only	3 (10,3)
		Cohort	14 (48,3)
		Other	5 (17,2)
		Not provided	3 (10,3)
	Sampling methods [a]	Non-Probability Sample	24 (82,7)
		Probability Sample	4 (13,8)
		Not Provided	1 (3,5)
	Time perspective [a]	Cross-sectional	1 (3,5)
		Longitudinal - Perspective	1 (3,5)
		Prospective	20 (68,8)
		Retrospective	5 (17,2)
		Other	1 (3,5)
		Not provided	1 (3,5)

Table 1. General characteristic of clinical trials included

			n(%)
Interventional study [b]	Interventional Model [b]	Crossover Assignment	8 (11,4)
		Factorial Assignment	3 (4,3)
		Parallel Assignment	45 (64,3)
		Sequential Assignment	5 (7,1)
		Single Group Assignment	9 (12,9)
	Study Phase [b]	Early Phase 1	1 (1,4)
		Phase 2	1 (1,4)
		Phase 2|Phase 3	1 (1,4)
		Phase 3	1 (1,4)
		Phase 4	4 (5,7)
		Not Applicable	62 (88,7)
	Allocation [b]	Non-Randomized	13 (18,6)
		Randomized	54 (77,1)
		Not provided	3 (4,3)

[a] % calculated on 29 observational studies included in this cross-sectional analysis
[b] % calculated on 70 interventional studies included in this cross-sectional analysis.

Primary outcome and primary changes in clinical trials registered

The primary outcome measure is the measure most important for evaluating the effect of an intervention. Only 6 (6,1%) clinical trials registered have not provided current primary outcome measure. 25 (25,3%) clinical trials had their primary outcome changed: of these 21 (30%) are interventional trials; 4 (13,8%) are observational trials (p=0.005). 20 (20,2%) clinical trials have changed the primary outcome after start of the study; 8 (8,1%) clinical trials have changed primary outcome after completion of the study. Also, 28 (28,3%) clinical trials have not provided a secondary outcome measure.

Recording study results in ClinicalTrials.gov was associated with trials that had their primary outcome changed (OR: 0,060; 95% C.I.: 0,007 – 0,541). Other variables such as study type or/and duration of the study in months or/and funding sources did not associated and did not materially change this associations. Table 2 shows records characteristic for clinical trials which have changed their primary outcome.

Table 2. Record characteristic for clinical trials which have changed their primary outcome (PO)

		Observational study[a]	Interventional study[b]	p value
		n(%)		
PO changed	No	20 (69,0)	48 (68,6)	,005
	Yes	4 (13,8)	21 (30,0)	
	Not provided	5 (17,2)	1 (1,4)	
PO changed after study start	No	20 (69,0)	53 (75,7)	,009
	Yes	4 (13,8)	16 (22,9)	
	Not provided	5 (17,2)	1 (1,4)	
PO changed after primary completion	No	21 (72,4)	61 (87,1)	,011
	Yes	3 (10,3)	8 (11,4)	
	Not provided	5 (17,2)	1 (1,4)	
PO changed after study completion	No	21 (72,4)	64 (91,4)	,008
	Yes	3 (10,3)	5 (7,1)	
	Not provided	5 (17,2)	1 (1,4)	

[a] % calculated on 29 observational studies included in this cross-sectional analysis
[b] % calculated on 70 interventional studies included in this cross-sectional analysis.

Trial Registration Practice and related effect of ICMJE Policy on Registration Practices

The first clinical trials submitted on ClinicalTrials.gov are dated to 2001. Nevertheless, some studies (n=4) started even before that date: one clinical trial is dated January, 1985 and three clinical studies (n=3) are dated to 2000. Perhaps, this is due to a new policy requiring trial registration by the International Committee of Medical Journal Editors [30] in September 2004. Figure 2 shows trend of number of studies started and submitted on ClinicalTrials.gov per years.

The median study length 21 months (mean: 33,25; SD: 43,01; range: 1-359 months). The time between first submission and study start date is 18,06 months on average (median: 3,00; SD: 45,66; range: 0-393 months) (Figure 3). Table 3 shows record characteristic for clinical trials included referred to study time.

Based on the requirements of the International Committee of Medical Journal Editors (ICMJE), each interventional trial included was assessed to evaluate the compliance with the minimum acceptable 24-item trial registration [31].

The majority of interventional trials included in the analysis (n=48; 68,57%) did not provide the IPD sharing statement, such as 29 (41,43%) interventional clinical trials did not provide the study start date. 30 (42,86%) interventional trials did not provide the secondary sponsor (collaborators). The primary outcome and the secondary outcome did not provide in 1 and 18 interventional trials, respectively (1,43%; 25,71%).

Lack of clinical trials data registration was related to the following items: investigators (10 interventional trials did not provided their investigators); listed location countries (8 interventional trials did not reported where the trials will be conduct); study arms (5 interventional trials); accepting healthy volunteers (1 interventional trials); original enrollment (2 interventional trials); and study competition date (1 interventional trials). Only 6 (8,57%) interventional trials were totally compliant with the ICMJE policy and reported the 24-item trial registration.

Time and characteristics of Trial Publication

Only 60 studies included in the analysis have been concluded. The analysis of time of findings publication is related to these clinical trials. The section Publications in ClinicalTrials.gov includes publications given by the data provider as well as publications identified by ClinicalTrials.gov Identifier (NCT Number) in Medline.

19 clinical trials completed (31,67%) did not pub-

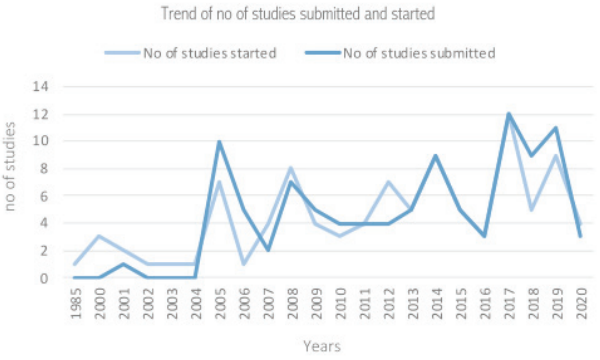

Figure 2. Trend of number of studies started and submitted on ClinicalTrials.gov

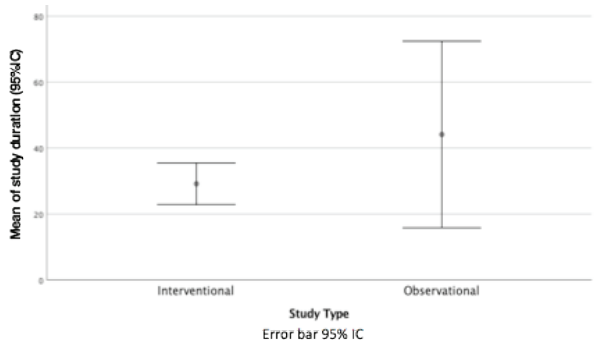

Figure 3. Mean proportion and 95% confidence intervals (error bars) of clinical trials duration.

Table 3. Record characteristic for clinical trials registered in ClinicalTrials.gov

		Observational study[a]	Interventional study[b]
		n(%)	
Time of trial registration	Before study start date	12 (41,38)	29 (41,43)
	Before study completation date	21 (72,41)	60 (85,71)
Lenght of study conduct	< 1 year	5 (17,24)	23 (32,86)
	- 2 year	10 (34,48)	16 (22,85)
	> 2 year	11 (37,93)	30 (42,86)
	Unknown	3 (10,35)	1 (1,43)

a % calculated on 29 observational studies included in this cross-sectional analysis; b % calculated on 70 interventional studies included in this cross-sectional analysis.

lish findings on ClinicalTrials.gov. However, two of these articles were found by NTC number in Medline [32,33].

The remaining 41 clinical trials (68,33%) had published a mean of 2,78 articles (n=168) on ClinicalTrials.gov. The search of publications identified by NCT Number in Medline yielded only 44 results (mean: 0.73). Only 13 clinical trials (31,71%) have displayed a consistent match between publicationson ClinicalTrials.gov and publications on Medline.

For all trials completed in our sample which have one or more article in ClinicalTrials.gov or Medline, on average 7,44 months elapsed between completion and the first publication in Medline shown the trial's identification number (NCT number).

Discussion

Based on the 99 medication safety trials registered at ClinicalTrials.gov and included in this survey, several observations can be made. Firstly, the distribution of trials included in the analysis come from the United Stated of America and all the medication safety trials included in the analysis focused on one of for EPOC taxonomy of intervention [29].

However, the portion of primary outcome which did not change their primary outcome during or after the study completion is very low (only 6,1% of all clinical trials included). This finding agrees with findings of the study conducted by Ramagopalan, et al. [34]. Even if in our study and in Ramagopalan, et al. [34] study a significant portion of trials have their primary outcome changed, Ramagopalan, et al. [34], in his study, showed the association between industry funding and primary outcome changes. In our study, this association is not statistically significant. On the other hand, we found a significant association between the type of study included (interventional or observational) and trials which have changed their primary outcome as well as the recording of study results (OR: 0,060; 95% C.I.: 0,007 – 0,541).

The median study length 21 months (mean: 33,25; SD: 43,01; range: 1-359 months). A minority of trials included in the analysis has been reported findings in publications on ClinicalTrails.gov or Medline database. For all trials completed in our sample which have one or more articles in ClinicalTrials.gov or Medline, on average 7,44 months (median: 12 months) elapsed between completion and the first publication in Medline shown the trial's identification number (NCT number). This finding disagrees with Ross, et al. [26] findings, that show the median time to publication equals to 23 months. Rates of trial publication within 24 months of study completion was associated to industry sponsored studies by Bourgeois, et al. [18]. In our study, there is not a significant association between the study length or time publication and funding sources.

Limitations

This study demonstrates several strengths of using ClinicalTrials.gov to track intervention improving medication safety process or medication errors preventions. Indeed, trial activity has grown and diversified over the years, especially since 2005 when a new policy was introduced in order to require trial registration.
Based on our knowledge, this is the first study that assesses the efficacy of intervention to improve medication safety through the ClinicalTrials.gov database and no filters have been used in the query search.
A limitation of our study is that the research of publication has been restricted just to two databases (PubMed and Google Scholar). It could be interesting to contact each principal investigator to understand the real status of study (especially to the trials in "unknown status") and related finding publication. On the other hand, we based our research of findings publication on the presence of a registry identifier (NCT number) in the abstract or full text of the journal article. If there was not an NCT number, the study was categorized as "without publications". This method could have led to misclassified publication status and, consequently, underestimated publication rates. This issue or concern is alleviated by medical journal policy or ICMJE and the CONSORT checklist that encourage reporting of registration numbers [35].
Also, it could be interesting to assess the real efficacy of each intervention studied to improve medication safety process in order to increase the scientific literature in this landscape. One more limitation is that we searched trials only in ClinicalTrials.gov database. It

could be interesting to search the same key words in other Clinical Trials Registry in order to study differences in trend analysis or trials distribution across countries.

Conclusions

Before this study, it is unknown how many trials are designed to focus exclusively on medication errors. This study demonstrates several strengths and limitation of using ClinicalTrials.gov to track intervention to improve medication safety process. Even if very few studies are registered in ClinicalTrials.gov on our topic, trial activity has grown and diversified over the years, especially since 2005 when a new policy was introduced.

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Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***			
	Item No	**Recommendation**	**Page No**
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	1
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	1
Objectives	3	State specific objectives, including any prespecified hypotheses	2
Methods			
Study design	4	Present key elements of study design early in the paper	2
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	2
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	2
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	/
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	*2*
Bias	9	Describe any efforts to address potential sources of bias	/
Study size	10	Explain how the study size was arrived at	3,4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4,5
		(*b*) Describe any methods used to examine subgroups and interactions	4,5
		(*c*) Explain how missing data were addressed	4,5
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	4,5
		(*e*) Describe any sensitivity analyses	4,5
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	/
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	3-7
		(b) Indicate number of participants with missing data for each variable of interest	3-7
Outcome data	15*	Report numbers of outcome events or summary measures	3-7
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	3-7
		(*b*) Report category boundaries when continuous variables were categorized	3-7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	3-7
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	/

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Discussion			
Key results	18	Summarise key results with reference to study objectives	7
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	7
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7
Generalisability	21	Discuss the generalisability (external validity) of the study results	7
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	/

*Give information separately for exposed and unexposed groups.

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.