Characteristics of randomised trials on diseases in the digestive system registered in ClinicalTrials.gov - a retrospective analysis

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Characteristics of randomised trials on diseases in the digestive system registered in ClinicalTrials.gov

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Abstract

Objectives: To evaluate the adequacy of reporting of protocols for randomised trials on diseases of the digestive system registered in ClinicalTrials.gov and the consistency between primary outcomes, secondary outcomes and sample size specified in ClinicalTrials.gov and published trials.

Design: Randomised phase III trials on adult patients with gastrointestinal diseases registered before January 2009 in ClinicalTrials.gov were eligible for inclusion. From ClinicalTrials.gov all data elements in the database required by the International Committee of Medical Journal Editors (ICMJE) member journals were extracted. The subsequent publications for registered trials were identified. For published trials, data concerning publication date, primary and secondary endpoint, sample size, and whether the journal adhered to ICMJE principles were extracted. Differences between primary and secondary outcomes, sample size and sample size calculations data in ClinicalTrials.gov and in the published paper were registered.

Results: 105 trials were evaluated. Fifty-nine trials (56%) were published. Thirty-two percent of trials were registered incorrectly after their completion date. Several data of the required ICMJE data list were not filled in, with lacking data in 25% and 12% concerning the primary outcome measure and sample size. In 17% of the published papers data of sample size calculations were missing and discrepancies between sample size reporting in ClinicalTrials.gov and published trials existed.

Conclusion: The quality of registration of randomised controlled trials still needs improvement.

Article summary section:

Article focus:

Outcome reporting bias is a considerable problem.

A number of journals only publish trials that are registered before their completion in relevant trial registration databases such as ClinicalTrials.gov.

Previous studies of published trials suggest that many are registered inadequately

Key messages:

A number of trials are registered inadequately in ClinicalTrials.gov without information about basic methodological issues.

Several trials published in journals that require registration in online databases are registered after their date of completion.

Discrepancies between the registered information in trial registrations and the trial publications still exist (such as the planned sample size calculations).

Strenght and limitations of this study:

The study is small, only evaluating 105 trials. The real extent of inadequate trial registration may be under- or overestimated.

Only trials concerning gastrointestinal diseases were evaluated, which makes it difficult to generalise to other medical specialities.

Introduction

Since 2005, the International Committee of Medical Journal Editors (ICMJE) have initiated a policy requiring investigators to register clinical trials on health care interventions in a public trial registry as a condition for consideration for publication [1]. ClinicalTrials.gov and similar clinical trial registries available through the WHO International Clinical Trials Portal are classed as acceptable. Trials must register at or before the onset of patient enrolment. The registration should include information about the trial design. The registration policy is applicable to any trial starting enrolment after July 1, 2005. For trials that begun enrolment prior to this date, the ICMJE member journals required registration by Sep 13, 2005 [1]. Trials are only eligible for publication in ICMJE journals if registered correctly.

The purpose of trial registries is to reduce the risk of dissemination and reporting bias and to ensure that clinicians, researchers, and patients can find key information about every clinical trial whose principal aim is to shape medical decision-making. Overviews of published trials suggest that the registration of several trials is inadequate [2-10]. Likewise, the quality and completeness of trial registration in specific trial registries have been found inadequate [4,10]. Inadequate registration will not reduce the risk of bias, but give the reader and journals a false impression of adequate bias control.

The objective of this study was to evaluate the adequacy of reporting of randomised trials on diseases of the digestive system registered in ClinicalTrials.gov and to evaluate the consistency between primary outcomes, secondary outcomes and sample size specified in trial protocols and published trials.

Methods

The present work is based on a written protocol, which can be obtained from the authors.

Identification of eligible trials

To obtain a homogenous sample, and as all authors have special interest in gastroenterology and hepatology, we focused on phase III trials on adult patients with diseases in the digestive system. To achieve a larger proportion of trials with subsequent publication , trials registered after January 2009 were not included. Accordingly any randomised trial on adult patients with gastrointestinal diseases registered before January 2009 in ClinicalTrials.gov were eligible for inclusion.

Eligible trials were identified through electronic searches in ClinicalTrials.gov using the search strategy: Closed Studies | Interventional Studies | digestive system disease | Adult Senior | Phase III | updated on or before 01/01/2009. Subsequent publications of clinical trials were identified through electronic searches in PubMed, Medline, Embase, Science Citation Index, and Cochrane Library using investigator names and keywords.

Data extraction

The adequacy of reporting of protocols was assessed through data extracted from the ClinicalTrials.gov database and their subsequent publications. Initially, all trials identified through the electronic search in ClinicalTrials.gov were listed and two authors evaluated whether the trials fulfilled the inclusion criteria. Excluded trials were listed with the reason for exclusion. Authors' independently extracted data from included trials based on pilot tested data extraction forms. Disagreements between authors were resolved through discussion before analyses.

Data extracted from ClinicalTrials.gov. included all data elements in the database required by the ICMJE member journals (Table 2). For each trial, the start date, completion date and registration date in ClinicalTrials.gov were recorded. Data extracted from the published articles included publication date, journal name and whether the journal adhered to ICMJE principles. Primary and secondary outcomes measures were extracted and any differences between primary and secondary outcomes specified in ClinicalTrials.gov and those defined in the published articles were recorded , and whether changes were reported. Finally data regarding sample size and sample size calculation were extracted, and potential differences between the planned sample size and number of randomised patients were recorded, and whether discrepancies between sample size data in ClinicalTrials.gov and in the published paper were present.

Statistical analysis

Statistical analysis were performed using STATA version 10,0 for windows (STATA Corp, Texas, USA). Characteristics of included trials were summarized as medians with ranges. The relation between key trial characteristics and whether trials were published were assessed based on multiple logistic regression analysis with results presented as odds ratios with 95% confidence intervals and P values. All tests were two tailed and p-values < 0.05 were considered significant.

Post hoc analysis

The proportion of published studies that identified positive vs. negative results were examined. We defined authors conclusions as the reported interpretation of the extent to which the overall trial result favoured the experimental over the control intervention. We graded authors conclusions according to the phrasing in the abstract and the

summarised conclusion on a previously validated 6- point scale.[11,12] (box 1). Higher scores indicate a more positive conclusion towards the experimental intervention: scores of 1-3 favoured the control and scores of 4-6 favoured the experimental intervention

Results

Initially, we retrieved 150 references through our electronic search. After excluding trials that turned out to be observational, trials that were not initiated (because of lack of funding or for logistic reasons) and trials that turned out to be safety studies in healthy participants, we identified 105 trials that fulfilled our inclusion criteria. The description of the included trials is presented in Table 1. The majority of trials assessed interventions for malignant diseases, inflammatory bowel disease or liver diseases. Most trials investigated drugs.

The included trials were registered in ClinicalTrials.gov during 1998 to 2008 (median 2005). 96 of the 105 trials provided information regarding the date the trial was initiated, (Table 2). Based on the registered data, the trials were initiated during 1978 to 2006 (median 2002). 81 of the 96 trials were initiated before 2005. Only 67 trials reported the date the trial was completed. The date of completion ranged from 1996 to 2008 (median 2006). Twenty-nine (27,6%) trials were registered correctly according to IMCJE criteria (i.e., before or at the time of initiation for trials conducted after July 1, 2005, and before September 13, 2005 for trials starting before July 1, 2005). 34 (32,4%) trials were registered after the trial was completed.

Of the 105 included trials, 25 (24%) did not describe the primary or secondary outcome measures (Table 2). In one trial, one of the initially registered outcome measures was changed to a secondary outcome measure (NCT00204750). Secondary outcomes were changed in two trials on Crohn's disease (some outcomes

were omitted and new outcomes introduced). However, for several trials changes were difficult to classify due to the wording and non specific definitions. For example a trial on Crohn's disease (NCT00338650) reported that primary outcome measures included adverse events, lab data, physical examinations and vital signs.

All 105 trials, reported the study type, provided a brief title, design, condition, intervention, recruitment, eligibility criteria, and contacts. Twelve trials (12%) did not report the planned number of patients enrolled in the trial (Table 2). For the remaining trials, the median planned sample size was 300 (range 40 to 1500 participants).

We identified published reports for 59 trials (56%), in 27 different journals. The trials were published during 1980 to 2010 (median 2007). Nine out of the 34 trials registered after the completion date in ClinicalTrials.gov were published after 2005 in journals proclaiming to adhere to ICMJE principles (data not shown). No changes were identified in the definitions of the primary outcome measure between registrations in ClinicalTrials.gov and the published reports, (Table 3). Changes in the secondary outcomes were identified for six trials and primarily included introduction of additional outcomes (e.g., compliance) or omission of outcomes (e.g., quality of life). Of the 59 trials that were published, 52 (88%) reported the planned number of patients enrolled in the trial in ClinicalTrials.gov and 48 (81%) described sample size calculations in the published report. Based on the published trial reports, seven trials did not reach the planned sample size due to unexpectedly low recruitment rates, or because the trial was terminated early after promising or disappointing interim analyses. The number of participants in the included trials ranged from 34 to 1135 (median 374). For ten trials, discrepancies between the planned sample size registered in ClinicalTrials.gov and the number of patients randomized based on the published reports were identified without

any apparent explanation in the published trial report. The difference ranged from -131 participants fewer than planned to 135 participants more than planned.

The planned sample size provided in ClinicalTrials.gov ranged from 44 to 1500 participants (median 374) in trials that were published and from 40 to 1200 (median 135) for trials that were not published. There was clear, but weak association between the reported planned sample size reported in ClinicalTrials.gov and the chance that the trial was published (odds ratio 1.002; 95% CI 1.001 to 1.033; P = 0.022). There was no apparent association between publication and registrations in ClinicalTrials.gov of the primary outcome measure, (odds ratio 0.575; 95% CI 0.222 to 1.485; P = 0.253) or the secondary outcome measure (odds ratio 0.513; 95% CI 0.219 to 1.207; P = 0.224).

In most published trials authors conclusions favoured the experimental intervention (fig 1).

Discussion

In this study we demonstrated that the reporting of data in the public trial registry ClinicalTrials.gov is inadequate. First, one third of trials were registered after the completion date. Second, several data of the required ICMJE data list were not filled in, with lacking data in 25% and 12% concerning the important issues outcome measures and sample size. Third, we demonstrated that only half of the studies registered were published and an association was found between the probability of having your study published and sample size number; the bigger the sample size the higher probability of publication.. Several articles (17%) lacked sample size calculations and there were discrepancies between sample size reporting in ClinicalTrials.gov and published trials.

One of the purposes of reporting protocols in a clinical trial registry is to improve the quality of reporting of biomedical research, The policy of registration of

protocols at the start or before termination of the study is to minimize the likelihood of authors introducing bias into their papers by making major changes that otherwise might remain undisclosed and undetectable [13]. We were surprised to se that a third of trials examined in our study were registered after the completion date, this kind of registration seems inappropriate or irrelevant and are a challenge for the credibility of the registers. Registration after the study is complete gives the reader a false sense of security since the published information in the journal only consists of the trial registration number. In one study (NCT00766805) that was registered post hoc both number of patients and number of events differed from a previous published abstract. These changes in the numbers and outcomes altered the conclusions of a meta-analyse on the subject [14]. Such changes clearly hampers the validity of trials, however, it is not possible to trace and document if the trials are not registered correctly. Since the requirements regarding trial registration have been established for several years, investigators have had time to get acquainted with the procedures. In most submission procedures for randomised clinical trials, journals ask authors to provide their registration number but not the date. Providing the date of registration and the start and completion date for the trial would provide a better overview than just the registration number.

Bias in trial registry has previously been demonstrated. Zarin et al. and Ross et al. found that the primary outcome measure field in ClinicalTrials.gov was completed in 66-89% of cases [4,10] . These data correspond to our findings, which show that 75 % of trials provided information regarding their primary outcome measure. However, this also means that several trials still lack crucial information regarding basic components. Likewise it has previously been found that changes in sample size exist between protocols and articles, and that statistically significant outcomes were favoured in being fully reported [2,15]. In this study we did not examined whether outcome-reporting

bias favoured significant primary outcomes, but we did find that studies in favour of the experimental intervention were published more frequently than studies in favour of the control intervention. On the positive side, we did not find any discrepancies between the data in the trial registration and in published papers concerning primary outcome measures. We did, however, find changes concerning secondary outcome measures. These discrepancies suggest that post hoc changes are being made to the trial protocols after the trial is initiated. None of the publications provided any explanations regarding the underlying reasons for the discrepancies.

In the present study, we found disagreements between the sample size calculations reported in the trial registry and the subsequent trial publications in ten cases. Since discrepancies were identified for registrations that were made for trials that were already running, the data suggests that alterations were made post hoc. As changes in sample size might lead to changes in study power, deviation from the planned sample size should be explained in the article. Without this information, we were unable to determine whether the trials were terminated prematurely or continued beyond the originally intended size after interim analyses or for some other reason such as lack of funding or lower than expected recruitment rates or low event rates. Since we did not have information from the authors, we were unable to analyse this finding further.

Our study has it limitations. First it is a small study only evaluating 105 trials. ClinicalTrials.gov have several thousands trials registered, and consequently the real extent of inadequate trial registration may be under- or overestimated. Second, we only evaluated trials concerning phase III trials evaluating gastrointestinal diseases, which makes it difficult to generalise to other medical specialities. Third, we only found published articles from 59 of published trials. A greater proportion of trials may be or may become published, as we did not contact the primary investigator to double-check

publication status and as some studies were completed within the year of this study, publication may be possible in the near future.

In conclusion, adequate registration is supposed to protect against publication bias and to ensure that clinicians, researchers and patients can find key information about clinical trials. Our findings emphasises that inadequate reporting can make the transparency and interpretation of randomised clinical trial results difficult and that timing and quality of registration of randomised controlled trials still needs improvement. Editors should be encouraged to enforce correct registration of trials to be published.

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Table 1. Characteristics of the selected trials (N = 105)

Characteristic	Trials, no. (%)
Disease examined	
Malignant disease	45 (43%)
Inflammatory bowel disease	16 (15%)
Liver failure	16 (15%)
Gastro-oesophageal reflux disease	6 (6%)
Alcoholic hepatitis	3 (3%)
Primary biliary cirrhosis	2 (2%)
Other diseases	18 (16%)
Experimental intervention	
Drugs	86 (82%)
Surgery	12 (11%)
Other interventions	7 (7%)
Control group intervention	
Drugs	50 (48%)
Placebo	36 (34%)
Surgery	10 (10%)
Other intervention	5 (5%)
No intervention	4 (4%)
Funding source	
Profit	61(58%)
Non-profit	40 (38%)
Profit and non-profit	2 (2%)
Not reported	2 (2%)

Table 2. Data extracted from 105 trials in ClinicalTrial.gov

	No. reported, (%)	No. not reported, (%)
Tracking information:		
Registration date in ClinicalTrial.gov	105 (100%)	0
Study start date	96 (91%)	9 (9%)
Completion date	67 (64%)	38 (36%)
Primary outcome measures	80 (76%)	25 (24%)
Secondary outcome measures	80 (76%)	25 (24%)
Changes in primary outcome measures	1	
Changes in secondary outcome measures	2	
Descriptive information:		
Brief title	105 (100%)	0
Official title	102 (97%)	3 (3%)
Study type	105 (100%)	0
Study design	105 (100%)	0
Condition	105 (100%)	0
Intervention	105 (100%)	0
Recruitment information:		
Recruitment status	105 (100%)	0
Enrolment number	93 (88%)	12 (12%)
Eligibility criteria	105 (100%)	0
Location countries *	84 (80%)	21 (20%)
Administrative information:		
NCT ID	105 (100%)	0
Study sponsor	103 (98%)	2 (2%)
Collaborators	42 (40%)	63 (60%)

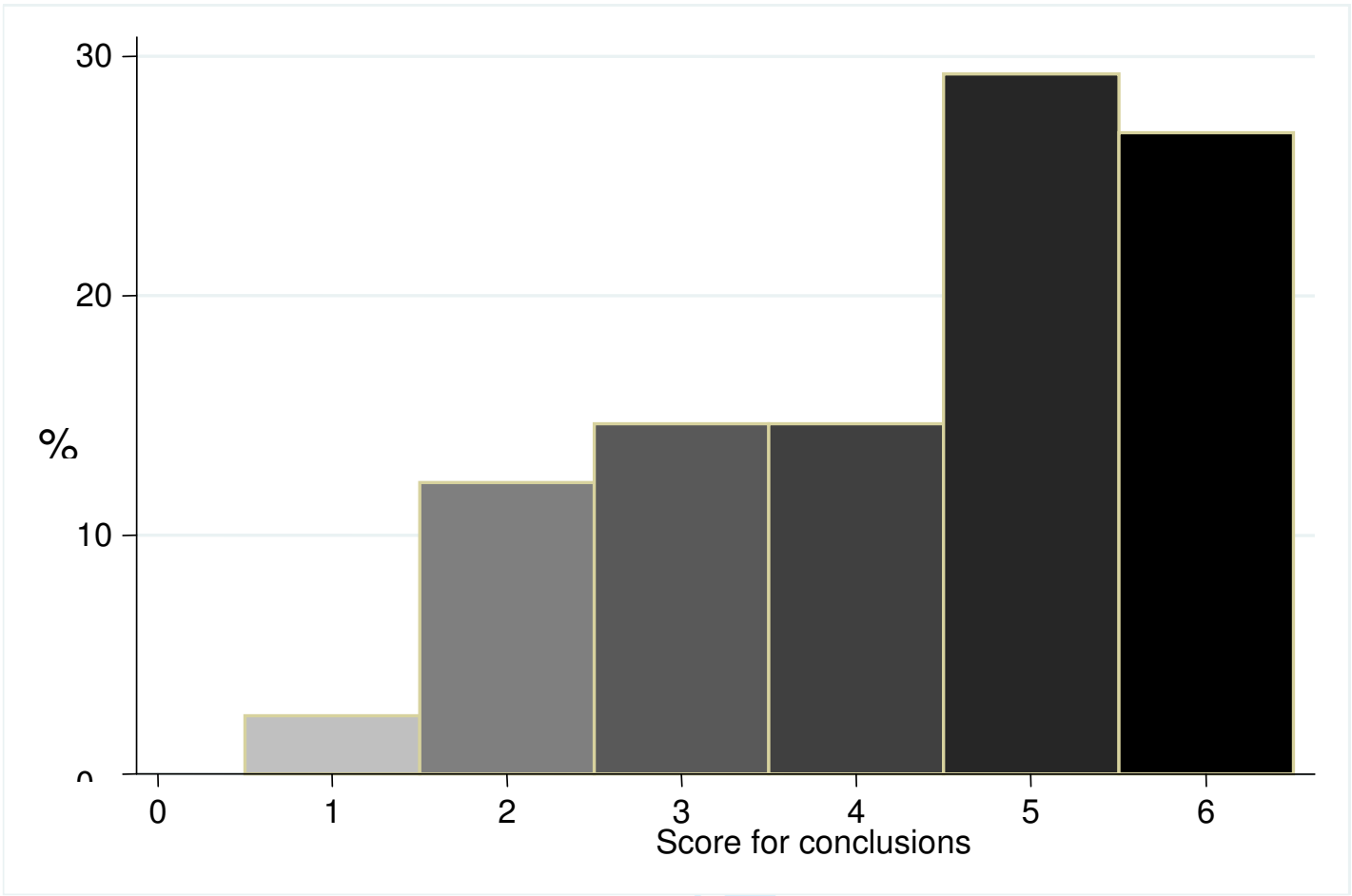
Investigators	91 (87%)	14 (13%)

* some sponsors remove location information once a trial closes to recruitment [3].

Table 3: Differences between data in trial registration and in published paper concerning outcome measures and sample size in 59 studies.

Changes in primary outcome measures	0
Changes in secondary outcomes measures	6 (10%)
Sample size calculation not reported in article	11 (19%)
Planned sample size not randomized, but described	7 (12%)
Difference between planned enrollment registered in ClinicalTrials.gov and sample size calculation in published paper	10 (17%)

Figure 1: Equipoise, authors conclusions in 59 published trials.



Box 1: Equipoise Scale

Experimental intervention highly preferred and should now be considered the standard intervention in all patients or similar statement (6 points)

Experimental intervention preferred to standard but further trials still indicated; may be more costly or similar disclaimer (5 points)

Experimental and control intervention about equal but experimental intervention successful because of minor advantage (4 points)

Experimental and control intervention about equal, but experimental intervention disappointing as control intervention had some minor advantage (3 points)

Control intervention preferred to experimental intervention but experimental intervention might be promising under some circumstances or similar (2 points)

Control intervention highly preferred and is best alternative; should be considered the standard intervention in all patients or similar (1 point)

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Contributorship: All authors contributed to the design, data extraction and interpretation of results. All authors contributed to the writing and final approvel of the paper.

Data sharing: Dataset available from the corresponding author at: LILOGL01@geh.regionh.dk

Ethical approval: Not required.

SQUIRE Guidelines
(Standards for QUality Improvement Reporting Excellence)
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- These guidelines provide a framework for reporting formal, planned studies designed to assess the nature and effectiveness of interventions to improve the quality and safety of care.
- It may not be possible to include information about every numbered guideline item in reports of original formal studies, but authors should at least consider every item in writing their reports.
- Although each major section (i.e., Introduction, Methods, Results, and Discussion) of a published original study generally contains some information about the numbered items within that section, information about items from one section (for example, the Introduction) is often also needed in other sections (for example, the Discussion).

Text section; Item number and name	***Section or Item description***
Title and abstract	*Did you provide clear and accurate information for finding, indexing, and scanning your paper?*
1. Title	a. Indicates the article concerns the improvement of quality (broadly defined to include the safety, effectiveness, patient-centeredness, timeliness, efficiency, and equity of care) b. States the specific aim of the intervention c. Specifies the study method used (for example, "A qualitative study," or "A randomized cluster trial")
2. Abstract	Summarizes precisely all key information from various sections of the text using the abstract format of the intended publication
Introduction	*Why did you start?*
3. Background Knowledge	Provides a brief, non-selective summary of current knowledge of the care problem being addressed, and characteristics of organizations in which it occurs
4. Local problem	Describes the nature and severity of the specific local problem or system dysfunction that was addressed
5. Intended improvement	a. Describes the specific aim (changes/improvements in care processes and patient outcomes) of the proposed intervention b. Specifies who (champions, supporters) and what (events, observations) triggered the decision to make changes, and why now (timing)
6. Study question	States precisely the primary improvement-related question and any secondary questions that the study of the intervention was designed to answer
Methods	*What did you do?*
7. Ethical issues	Describes ethical aspects of implementing and studying the improvement, such as privacy concerns, protection of participants' physical well-being, and potential author conflicts of interest, and how ethical concerns were addressed
8. Setting	Specifies how elements of the local care environment considered most likely to influence change/improvement in the involved site or sites were identified and characterized
9. Planning the intervention	a. Describes the intervention and its component parts in sufficient detail that others could reproduce it b. Indicates main factors that contributed to choice of the specific intervention (for example, analysis of causes of dysfunction; matching relevant improvement experience of others with the local situation)

Text section; Item number and name	*Section or Item description*
Planning the intervention (continued)	c. Outlines initial plans for how the intervention was to be implemented: e.g., *what* was to be done (initial steps; functions to be accomplished by those steps; how tests of change would be used to modify intervention), and *by whom* (intended roles, qualifications, and training of staff)
10. Planning the study of the intervention	a. Outlines plans for assessing how well the intervention was implemented (dose or intensity of exposure) b. Describes mechanisms by which intervention components were expected to cause changes, and plans for testing whether those mechanisms were effective c. Identifies the study design (for example, observational, quasi-experimental, experimental) chosen for measuring impact of the intervention on primary and secondary outcomes, if applicable d. Explains plans for implementing essential aspects of the chosen study design, as described in publication guidelines for specific designs, if applicable (see, for example, www.equator-network.org) e. Describes aspects of the study design that specifically concerned internal validity (integrity of the data) and external validity (generalizability)
11. Methods of evaluation	a. Describes instruments and procedures (qualitative, quantitative, or mixed) used to assess a) the effectiveness of implementation, b) the contributions of intervention components and context factors to effectiveness of the intervention, and c) primary and secondary outcomes b. Reports efforts to validate and test reliability of assessment instruments c. Explains methods used to assure data quality and adequacy (for example, blinding; repeating measurements and data extraction; training in data collection; collection of sufficient baseline measurements)
12. Analysis	a. Provides details of qualitative and quantitative (statistical) methods used to draw inferences from the data b. Aligns unit of analysis with level at which the intervention was implemented, if applicable c. Specifies degree of variability expected in implementation, change expected in primary outcome (effect size), and ability of study design (including size) to detect such effects d. Describes analytic methods used to demonstrate effects of time as a variable (for example, statistical process control)
Results	*What did you find?*
13. Outcomes	a) Nature of setting and improvement intervention i. Characterizes relevant elements of setting or settings (for example, geography, physical resources, organizational culture, history of change efforts), and structures and patterns of care (for example, staffing, leadership) that provided context for the intervention ii. Explains the actual course of the intervention (for example, sequence of steps, events or phases; type and number of participants at key points), preferably using a time-line diagram or flow chart iii. Documents degree of success in implementing intervention components iv. Describes how and why the initial plan evolved, and the most important lessons learned from that evolution, particularly the effects of internal feedback from tests of change (reflexiveness) b) Changes in processes of care and patient outcomes associated with the intervention i. Presents data on changes observed in the care delivery process ii. Presents data on changes observed in measures of patient outcome (for example, morbidity, mortality, function, patient/staff satisfaction, service utilization, cost, care disparities)

Text section; Item number and name	*Section or Item description*
Outcomes (continued)	iii. Considers benefits, harms, unexpected results, problems, failures iv. Presents evidence regarding the strength of association between observed changes/improvements and intervention components/context factors v. Includes summary of missing data for intervention and outcomes
Discussion	*What do the findings mean?*
14. Summary	a. Summarizes the most important successes and difficulties in implementing intervention components, and main changes observed in care delivery and clinical outcomes b. Highlights the study's particular strengths
15. Relation to other evidence	Compares and contrasts study results with relevant findings of others, drawing on broad review of the literature; use of a summary table may be helpful in building on existing evidence
16. Limitations	a. Considers possible sources of confounding, bias, or imprecision in design, measurement, and analysis that might have affected study outcomes (internal validity) b. Explores factors that could affect generalizability (external validity), for example: representativeness of participants; effectiveness of implementation; dose-response effects; features of local care setting c. Addresses likelihood that observed gains may weaken over time, and describes plans, if any, for monitoring and maintaining improvement; explicitly states if such planning was not done d. Reviews efforts made to minimize and adjust for study limitations e. Assesses the effect of study limitations on interpretation and application of results
17. Interpretation	a. Explores possible reasons for differences between observed and expected outcomes b. Draws inferences consistent with the strength of the data about causal mechanisms and size of observed changes, paying particular attention to components of the intervention and context factors that helped determine the intervention's effectiveness (or lack thereof), and types of settings in which this intervention is most likely to be effective c. Suggests steps that might be modified to improve future performance d. Reviews issues of opportunity cost and actual financial cost of the intervention
18. Conclusions	a. Considers overall practical usefulness of the intervention b. Suggests implications of this report for further studies of improvement interventions
Other information	*Were other factors relevant to conduct and interpretation of the study?*
19. Funding	Describes funding sources, if any, and role of funding organization in design, implementation, interpretation, and publication of study

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Characteristics of randomised trials on diseases in the digestive system registered in ClinicalTrials.gov – a retrospective analysis

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Abstract

Objectives: To evaluate the adequacy of reporting of protocols for randomised trials on diseases of the digestive system registered in ClinicalTrials.gov and the consistency between primary outcomes, secondary outcomes and sample size specified in ClinicalTrials.gov and published trials.

Design: Randomised phase III trials on adult patients with gastrointestinal diseases registered before January 2009 in ClinicalTrials.gov were eligible for inclusion. From ClinicalTrials.gov all data elements in the database required by the International Committee of Medical Journal Editors (ICMJE) member journals were extracted. The subsequent publications for registered trials were identified. For published trials, data concerning publication date, primary and secondary endpoint, sample size, and whether the journal adhered to ICMJE principles were extracted. Differences between primary and secondary outcomes, sample size and sample size calculations data in ClinicalTrials.gov and in the published paper were registered.

Results: 105 trials were evaluated. Sixty-six trials (63%) were published. Thirty percent of trials were registered incorrectly after their completion date. Several data elements of the required ICMJE data list were not filled in, with lacking data in 22% and 11% of cases concerning the primary outcome measure and sample size. In 26% of the published papers data of sample size calculations were missing and discrepancies between sample size reporting in ClinicalTrials.gov and published trials existed.

Conclusion: The quality of registration of randomised controlled trials still needs improvement.

Article summary section: Article focus:

Outcome reporting bias is a considerable problem.

A number of journals (ICMJE journals) only publish clinical trials that are registered in relevant trial databases such as ClinicalTrials.gov before recruitment of participants. Older trials commenced after 1 July 2005 will be considered for publication only if they are adequately registered before journal submission

Previous studies of published trials suggest that many are registered inadequately

Key messages:

A number of trials are registered inadequately in ClinicalTrials.gov without information about basic methodological issues.

Several trials published in journals that require registration in online databases are registered after their date of completion.

Discrepancies between the registered information in trial registrations and the trial publications still exist (such as the planned sample size calculations).

Strength and limitations of this study:

The study is small, only evaluating 105 trials. The real extent of inadequate trial registration may be under- or overestimated.

Only trials concerning gastrointestinal diseases were evaluated, which makes it difficult to generalise to other medical specialities.

Introduction

Since 2005, the International Committee of Medical Journal Editors (ICMJE) has initiated a policy requiring investigators to register clinical trials on health care interventions in a public trial registry as a condition for consideration for publication [1]. ClinicalTrials.gov and similar clinical trial registries available through the WHO International Clinical Trials Portal are classed as acceptable. Trials must register at or before the onset of patient enrolment. The registration should include information about the trial design. The registration policy is applicable to any trial starting enrolment after July 1, 2005. For trials that begun enrolment prior to this date, the ICMJE member journals originally required registration by Sep 13, 2005 [1]. However, beginning on September 13, 2005, ICMJE journals will consider such trials only if they are adequately registered before journal submission [2]. Trials are only eligible for publication in ICMJE journals if registered correctly.

The purpose of trial registries is to reduce the risk of dissemination and reporting bias and to ensure that clinicians, researchers, and patients can find key information about every clinical trial whose principal aim is to shape medical decision-making. Overviews of published trials suggest that the registration of several trials is inadequate [3-11]. Likewise, the quality and completeness of trial registration in specific trial registries have been found inadequate [5,11]. Inadequate registration will not reduce the risk of bias, but give the reader and journals a false impression of adequate bias control.

The objective of this study was to evaluate the adequacy of reporting of randomised trials on diseases of the digestive system registered in ClinicalTrials.gov and to evaluate the consistency between primary outcomes, secondary outcomes, and sample size specified in trial protocols and published trials.

Methods

The present work is based on a written protocol, which is included as a supplementary file to the paper at BMJ Open.

Identification of eligible trials

To obtain a homogenous sample, and as all authors have special interest in gastroenterology and hepatology, we focused on phase III trials on adult patients with diseases in the digestive system. To achieve a larger proportion of trials with subsequent publication, trials registered after January 2009 were not included. Accordingly any randomised trial on adult patients with gastrointestinal diseases registered before January 2009 in ClinicalTrials.gov was eligible for inclusion.

Eligible trials were identified through electronic searches in ClinicalTrials.gov using the search strategy: Closed Studies | Interventional Studies | digestive system disease | Adult Senior | Phase III | updated on or before 01/01/2009. Subsequent publications of clinical trials were identified through electronic searches in PubMed, Medline, Embase, Science Citation Index, and Cochrane Library using investigator names and keywords.

Data extraction

The adequacy of reporting of protocols was assessed through data extracted from the ClinicalTrials.gov database and their subsequent publications. Initially, all trials identified through the electronic search in ClinicalTrials.gov were listed and two authors evaluated whether the trials fulfilled the inclusion criteria. Excluded trials were listed with the reason for exclusion. Authors' independently extracted data from included trials based on pilot tested data extraction forms. Disagreements between authors were resolved through discussion before analyses.

Data extracted from ClinicalTrials.gov included all data elements in the database required by the ICMJE member journals (Table 2). For each trial, the start date, completion date and registration date in ClinicalTrials.gov were recorded. Data extracted from the published articles included publication date, journal name and whether the journal adhered to ICMJE principles. Primary and secondary outcomes measures were extracted and any differences between primary and secondary outcomes specified in ClinicalTrials.gov and those defined in the published articles were recorded, and whether changes were reported. Finally data regarding sample size and sample size calculation were extracted, and potential differences between the planned sample size and number of randomised patients were recorded, and whether discrepancies between sample size data in ClinicalTrials.gov and in the published paper were present.

Statistical analysis

Statistical analysis was performed using STATA version 10.0 for windows (STATA Corp, Texas, USA). Characteristics of included trials were summarized as frequencies or medians with ranges. The relation between key trial characteristics and whether trials were published were assessed based on multiple logistic regression analysis with results presented as odds ratios with 95% confidence intervals and P values. All tests were two tailed and p-values < 0.05 were considered significant.

Post hoc analysis

The proportion of published studies that identified positive vs. negative results was examined. We defined authors conclusions as the reported interpretation of the extent to which the overall trial result favoured the experimental over the control intervention. We graded authors conclusions according to the phrasing in the abstract and the

summarised conclusion on a previously validated 6- point scale [12,13] (box 1). Higher scores indicate a more positive conclusion towards the experimental intervention: scores of 1-3 favoured the control and scores of 4-6 favoured the experimental intervention

Results

Initially, we retrieved 150 references through our electronic search. After excluding trials that turned out to be observational, trials that were not initiated (because of lack of funding or for logistic reasons), and trials that turned out to be safety studies in healthy participants, we identified 105 trials that fulfilled our inclusion criteria. The description of the included trials is presented in Table 1. The majority of trials assessed interventions for malignant diseases, inflammatory bowel disease or liver diseases. Most trials investigated drugs.

The included trials were registered in ClinicalTrials.gov during 1998 to 2008 (median 2005). 99 of the 105 trials provided information regarding the date the trial was initiated, (Table 2). Based on the registered data, the trials were initiated during 1978 to 2006 (median 2002). 76 of the 99 trials were initiated before 2005. Only 73 trials reported the date the trial was completed. The date of completion ranged from 1996 to 2009 (median 2006). Fifty-eigth (55%) trials were registered correctly according to IMCJE criteria (i.e., before or at the time of initiation for trials conducted after July 1, 2005, and before September 13, 2005 for trials starting before July 1, 2005). 31 (30%) trials were registered after the trial was completed.

Of the 105 included trials, 23 (22%) did not describe the primary outcome measures and 24 (32%) did not describe the secondary outcome measures (Table 2). In two trials one of the initially registered outcome measures was changed to a secondary outcome measure (NCT00204750) and (NCT00606619) . Secondary

outcomes were changed in three trials (some outcomes were omitted and new outcomes introduced). However, for several trials changes were difficult to classify due to the wording and non specific definitions.

All 105 trials, reported the study type, provided a brief title, design, condition, intervention, recruitment, eligibility criteria, and contacts. Twelve trials (11%) did not report the planned number of patients enrolled in the trial (Table 2).

We identified published reports for 66 trials (63%), in 28 different journals. The trials were published during 1980 to 2011 (median 2008). Twelve out of the 31 trials registered after the completion date in ClinicalTrials.gov were published after 2005 in journals proclaiming to adhere to ICMJE principles (data not shown). No changes were identified in the definitions of the primary outcome measure between registrations in ClinicalTrials.gov and the published reports, (Table 3). Changes in the secondary outcomes were identified for six trials and primarily included introduction of additional outcomes (e.g., compliance) or omission of outcomes (e.g., quality of life). Of the 66 trials that were published, 49 (74%) described sample size calculations in the published report. Based on the published trial reports, nine trials did not reach the planned sample size due to unexpectedly low recruitment rates, or because the trial was terminated early after promising or disappointing interim analyses. For 7 trials, discrepancies between the planned sample size registered in ClinicalTrials.gov and the number of patients randomised based on the published reports were identified without any apparent explanation. In 4 cases the number of patients in the preset sample size and/or the number of patients randomised were less in the published report than the sample size specified in the trial registry. In 3 cases the preset sample size and/or randomisation number were higher in the published reports than specified in the trial registry. The number of participants in the included trials ranged from 16 to 1135

(median 305). The difference ranged from -545 participants fewer than planned to 138 participants more than planned.

The planned sample size provided in ClinicalTrials.gov ranged from 36 to 1500 participants (median 220) in trials that were published and from 30 to 660 (median 60) for trials that were not published. There was no clear association between the reported planned sample size reported in ClinicalTrials.gov and the chance that the trial was published (odds ratio 1.01; 95% CI 1.00 to 1.01). There was no apparent association between publication and registrations in ClinicalTrials.gov of the primary outcome measure, (odds ratio 0.80; 95% CI 0.29 to 2.17) or the secondary outcome measure (odds ratio 0.58; 95% CI 0.224 to 1.44).

In most published trials authors conclusions favoured the experimental intervention (fig 1).

Discussion

The results of this study suggest that the reporting of data in the public trial registry ClinicalTrials.gov is inadequate. First, 30 % of the trials analysed were registered after the completion date. Second, several data of the required ICMJE data list were not filled in, with lacking data in 22% and 11% of cases concerning the important issues primary outcome measures and sample size. Third, only 63% of the analysed trials registered were published. Several articles (26%) lacked sample size calculations and there were discrepancies between sample size reporting in ClinicalTrials.gov and published trials.

One of the purposes of reporting protocols in a clinical trial registry is to improve the quality of reporting of biomedical research, The policy of registration of protocols at the start or before termination of the study is to minimize the likelihood of authors introducing bias into their papers by making major changes that otherwise might remain undisclosed and undetectable [14]. We were surprised to see that about a

third of trials examined in our study were registered after the completion date, this kind of registration seems inappropriate or irrelevant and are a challenge to the credibility of the registers. Registration after the study is complete gives the reader a false sense of security since the published information in the journal only consists of the trial registration number. In one study (NCT00766805) that was registered post hoc both number of patients and number of events differed from a previous published abstract. These changes in the numbers and outcomes altered the conclusions of a meta-analysis on the subject [15]. Such changes clearly hamper the validity of trials, however, it is not possible to trace and document if the trials are not registered correctly. Since the requirements regarding trial registration have been established for several years, investigators have had time to get acquainted with the procedures. In most submission procedures for randomised clinical trials, journals ask authors to provide their registration number but not the date. Providing the date of registration and the start and completion date for the trial would provide a better overview than just the registration number.

Bias in trial registry has previously been demonstrated. Zarin et al. and Ross et al. found that the primary outcome measure field in ClinicalTrials.gov was completed in 66-89% of cases [5, 11].These data correspond to our findings, which show that 78 % of trials provided information regarding their primary outcome measure. However, this also means that several trials still lack crucial information regarding basic components. Likewise it has previously been found that changes in sample size exist between protocols and articles, and that statistically significant outcomes were favoured in being fully reported [3,16]. In this study we did not examined whether outcome-reporting bias favoured significant primary outcomes, but we did find that studies in favour of the experimental intervention were published more frequently than studies in favour of the control intervention. On the positive side, we did not find any discrepancies between the

data in the trial registration and in published papers concerning primary outcome measures. We did, however, find changes concerning secondary outcome measures. These discrepancies suggest that post hoc changes are being made to the trial protocols after the trial is initiated. None of the publications provided any explanations regarding the underlying reasons for the discrepancies.

In the present study, we found disagreements between the sample size calculations reported in the trial registry and the subsequent trial publications in seven cases. Since discrepancies were identified for registrations that were made for trials that were already running, the data suggests that alterations were made post hoc. As changes in sample size might lead to changes in study power, deviation from the planned sample size should be explained in the article. Without this information, we were unable to determine whether the trials were continued beyond the originally intended size after interim analyses or stopped for some other reason such as lack of funding or lower than expected recruitment rates or low event rates. Since we did not have information from the authors, we were unable to analyse this finding further.

Our study has its limitations. First it is a small study only evaluating 105 trials. ClinicalTrials.gov has several thousands of trials registered, and consequently the real extent of inadequate trial registration may be under- or overestimated. Second, we only evaluated trials concerning phase III trials evaluating gastrointestinal diseases, which make it difficult to generalise to other medical specialities. Third, we only found published articles from 66 out of 105 trials. A greater proportion of trials may be or may become published, as we did not contact the primary investigator to double-check publication status and as some studies were completed within the year of this study, publication may be possible in the near future.

In conclusion, adequate registration is supposed to protect against publication bias and to ensure that clinicians, researchers and patients can find key

information about clinical trials. Our findings emphasise that inadequate reporting can make the transparency and interpretation of randomised clinical trial results difficult and that timing and quality of registration of randomised controlled trials still needs improvement. Editors should be encouraged to enforce correct registration of trials to be published.

Table 1. Characteristics of 105 trials registered in ClinicalTrials.gov

Characteristic	Trials, no. (%)
Disease examined	
Malignant disease	45 (43%)
Inflammatory bowel disease	16 (15%)
Viral hepatitis	11 (10%)
Gastro-oesophageal reflux disease	6 (6%)
Liver (autoimmune and cirrhosis)	8 (8%)
Other diseases	19 (18%)
Experimental intervention	
Drugs	86 (82%)
Surgery	12 (11%)
Other interventions	7 (7%)
Control group intervention	
Drugs	50 (47%)
Placebo or no intervention	40 (38%)
Surgery	10 (10%)
Other intervention	5 (5%)
Funding source	
Profit	62 (59%)
Non-profit	38 (36%)
Profit and non-profit	3 (3%)
Not reported	2 (2%)

Table 2. Data extracted from 105 trials in ClinicalTrials.gov

	No. reported, (%)	No. not reported, (%)
Tracking information:		
Registration date in ClinicalTrial.gov	105 (100%)	0
Study start date	99 (94%)	6 (6%)
Completion date	73 (70%)	32 (30%)
Primary outcome measures*	82 (78%)	23 (22%)
Secondary outcome measures□	71 (68%)	34 (32%)
Descriptive information:		
Brief title	105 (100%)	0
Official title	102 (97%)	3 (3%)
Study type	105 (100%)	0
Study design	105 (100%)	0
Condition	105 (100%)	0
Intervention	105 (100%)	0
Recruitment information:		
Recruitment status	105 (100%)	0
Enrolment number	93 (89%)	12 (11%)
Eligibility criteria	105 (100%)	0
Location countries ¤	85 (81%)	20 (19%)
Administrative information:		
NCT ID	105 (100%)	0
Study sponsor	103 (98%)	2 (2%)
Collaborators	45 (43%)	60 (57%)
Investigators	90 (86%)	15 (14%)

*Changes in primary outcome measures were recorded in two trials

- Changes in secondary outcome measures were recorded in three trials
- some sponsors remove location information once a trial closes to recruitment [3].

Table 3: Characteristics of 66 published trials from a sample of 105 trials registered in ClinicalTrials.gov - concerning changes in outcome measures and sample size.

Changes in primary outcome measures	0
Changes in secondary outcomes measures	6 (9%)
Sample size calculation reported in article	49 (74%)
Planned sample size not randomized, but described	9 (13%)
Difference between planned enrolment registered in ClinicalTrials.gov and sample size calculation in published paper	7 (11%)

Box 1: Equipoise Scale

Experimental intervention highly preferred and should now be considered the standard intervention in all patients or similar statement (6 points)

Experimental intervention preferred to standard but further trials still indicated; may be more costly or similar disclaimer (5 points)

Experimental and control intervention about equal but experimental intervention successful because of minor advantage (4 points)

Experimental and control intervention about equal, but experimental intervention disappointing as control intervention had some minor advantage (3 points)

Control intervention preferred to experimental intervention but experimental intervention might be promising under some circumstances or similar (2 points)

Control intervention highly preferred and is best alternative; should be considered the standard intervention in all patients or similar (1 point)

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Competing interest: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that no authors have financial relationships with any organisations that might have interest in the submitted work in the previous three years no other relationsship or activities that could appear to have influenced the submitted work.

Contributorship: All authors contributed to the design, data extraction and interpretation of results. All authors contributed to the writing and final approvel of the paper.

Data sharing: Dataset available at the Dryad repository. Doi:10.5061/dryad.s38s0g00

Ethical approval: Not required.

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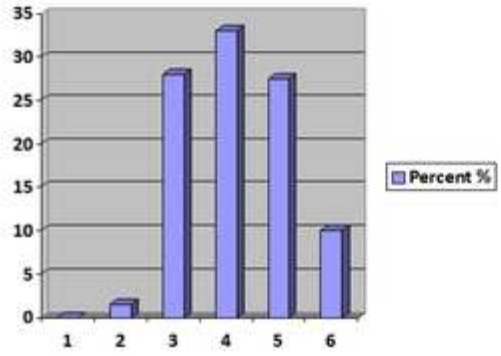
Figure 1: Equipoise scale, authors score for conclusions in 66 published trials.



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SQUIRE Guidelines
(Standards for QUality Improvement Reporting Excellence)
Final revision – 4-29-08

- These guidelines provide a framework for reporting formal, planned studies designed to assess the nature and effectiveness of interventions to improve the quality and safety of care.
- It may not be possible to include information about every numbered guideline item in reports of original formal studies, but authors should at least consider every item in writing their reports.
- Although each major section (i.e., Introduction, Methods, Results, and Discussion) of a published original study generally contains some information about the numbered items within that section, information about items from one section (for example, the Introduction) is often also needed in other sections (for example, the Discussion).

Text section; Item number and name	*Section or Item description*	
Title and abstract	*Did you provide clear and accurate information for finding, indexing, and scanning your paper?*	*Page no*
1. Title	a. Indicates the article concerns the improvement of quality (broadly defined to include the safety, effectiveness, patient-centeredness, timeliness, efficiency, and equity of care) b. States the specific aim of the intervention c. Specifies the study method used (for example, "A qualitative study," or "A randomized cluster trial")	1
2. Abstract	Summarizes precisely all key information from various sections of the text using the abstract format of the intended publication	2
Introduction	*Why did you start?*	
3. Background Knowledge	Provides a brief, non-selective summary of current knowledge of the care problem being addressed, and characteristics of organizations in which it occurs	4
4. Local problem	Describes the nature and severity of the specific local problem or system dysfunction that was addressed	
5. Intended improvement	a. Describes the specific aim (changes/improvements in care processes and patient outcomes) of the proposed intervention b. Specifies who (champions, supporters) and what (events, observations) triggered the decision to make changes, and why now (timing)	
6. Study question	States precisely the primary improvement-related question and any secondary questions that the study of the intervention was designed to answer	4
Methods	*What did you do?*	
7. Ethical issues	Describes ethical aspects of implementing and studying the improvement, such as privacy concerns, protection of participants' physical well-being, and potential author conflicts of interest, and how ethical concerns were addressed	18
8. Setting	Specifies how elements of the local care environment considered most likely to influence change/improvement in the involved site or sites were identified and characterized	
9. Planning the intervention	a. Describes the intervention and its component parts in sufficient detail that others could reproduce it b. Indicates main factors that contributed to choice of the specific intervention (for example, analysis of causes of dysfunction; matching relevant improvement experience of others with the local situation)	5-7

Text section; Item number and name	*Section or Item description*	
Planning the intervention (continued)	c. Outlines initial plans for how the intervention was to be implemented: e.g., *what* was to be done (initial steps; functions to be accomplished by those steps; how tests of change would be used to modify intervention), and *by whom* (intended roles, qualifications, and training of staff)	5-7
10. Planning the study of the intervention	a. Outlines plans for assessing how well the intervention was implemented (dose or intensity of exposure) b. Describes mechanisms by which intervention components were expected to cause changes, and plans for testing whether those mechanisms were effective c. Identifies the study design (for example, observational, quasi-experimental, experimental) chosen for measuring impact of the intervention on primary and secondary outcomes, if applicable d. Explains plans for implementing essential aspects of the chosen study design, as described in publication guidelines for specific designs, if applicable (see, for example, www.equator-network.org) e. Describes aspects of the study design that specifically concerned internal validity (integrity of the data) and external validity (generalizability)	
11. Methods of evaluation	a. Describes instruments and procedures (qualitative, quantitative, or mixed) used to assess a) the effectiveness of implementation, b) the contributions of intervention components and context factors to effectiveness of the intervention, and c) primary and secondary outcomes b. Reports efforts to validate and test reliability of assessment instruments c. Explains methods used to assure data quality and adequacy (for example, blinding; repeating measurements and data extraction; training in data collection; collection of sufficient baseline measurements)	6-7
12. Analysis	a. Provides details of qualitative and quantitative (statistical) methods used to draw inferences from the data b. Aligns unit of analysis with level at which the intervention was implemented, if applicable c. Specifies degree of variability expected in implementation, change expected in primary outcome (effect size), and ability of study design (including size) to detect such effects d. Describes analytic methods used to demonstrate effects of time as a variable (for example, statistical process control)	6-7
Results	*What did you find?*	
13. Outcomes	a) Nature of setting and improvement intervention i. Characterizes relevant elements of setting or settings (for example, geography, physical resources, organizational culture, history of change efforts), and structures and patterns of care (for example, staffing, leadership) that provided context for the intervention ii. Explains the actual course of the intervention (for example, sequence of steps, events or phases; type and number of participants at key points), preferably using a time-line diagram or flow chart iii. Documents degree of success in implementing intervention components iv. Describes how and why the initial plan evolved, and the most important lessons learned from that evolution, particularly the effects of internal feedback from tests of change (reflexiveness) b) Changes in processes of care and patient outcomes associated with the intervention i. Presents data on changes observed in the care delivery process ii. Presents data on changes observed in measures of patient outcome (for example, morbidity, mortality, function, patient/staff satisfaction, service utilization, cost, care disparities)	7-9

Text section; Item number and name	*Section or Item description*	
Outcomes (continued)	iii. Considers benefits, harms, unexpected results, problems, failures iv. Presents evidence regarding the strength of association between observed changes/improvements and intervention components/context factors v. Includes summary of missing data for intervention and outcomes	
Discussion	*What do the findings mean?*	
14. Summary	a. Summarizes the most important successes and difficulties in implementing intervention components, and main changes observed in care delivery and clinical outcomes b. Highlights the study's particular strengths	9
15. Relation to other evidence	Compares and contrasts study results with relevant findings of others, drawing on broad review of the literature; use of a summary table may be helpful in building on existing evidence	9-11
16. Limitations	a. Considers possible sources of confounding, bias, or imprecision in design, measurement, and analysis that might have affected study outcomes (internal validity) b. Explores factors that could affect generalizability (external validity), for example: representativeness of participants; effectiveness of implementation; dose-response effects; features of local care setting c. Addresses likelihood that observed gains may weaken over time, and describes plans, if any, for monitoring and maintaining improvement; explicitly states if such planning was not done d. Reviews efforts made to minimize and adjust for study limitations e. Assesses the effect of study limitations on interpretation and application of results	11
17. Interpretation	a. Explores possible reasons for differences between observed and expected outcomes b. Draws inferences consistent with the strength of the data about causal mechanisms and size of observed changes, paying particular attention to components of the intervention and context factors that helped determine the intervention's effectiveness (or lack thereof), and types of settings in which this intervention is most likely to be effective c. Suggests steps that might be modified to improve future performance d. Reviews issues of opportunity cost and actual financial cost of the intervention	
18. Conclusions	a. Considers overall practical usefulness of the intervention b. Suggests implications of this report for further studies of improvement interventions	11 -12
Other information	*Were other factors relevant to conduct and interpretation of the study?*	
19. Funding	Describes funding sources, if any, and role of funding organization in design, implementation, interpretation, and publication of study	18