

RESEARCH

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Ask a simple question, but can you find the answer?

Doctors systematically explore a patient's story. They hunt for red flag symptoms, review body systems, and explore hidden agendas. They use various sources—for example, they might glean a collateral history, review notes, or read letters. With the full clinical picture they can help to answer a patient's query. When information is missing—maybe because the patient has cognitive impairment, or notes are incomplete—doctors will be able to identify with the feelings of frustration and potential for making the wrong decision.

It is similar for researchers and missing data. And implications of missing research reach down from the ivory towers to the heart of interactions with patients. Research contributes to the evidence based medicine summaries, patient information leaflets, guidelines and policies we read and use from day to day. If information is missing, and some conclusions are incorrect, medicine has a problem. Three papers in this issue give doctors a flavour of the problems researchers face.

There are mistakes in how trials are labelled on Medline, an important source for researchers searching for

trials. Susan Wieland and colleagues describe the differences between correctly and incorrectly labelled randomised controlled trials on Medline (p 17). Beate Wiesler and colleagues look at three documents related to clinical trials including the journal publication, and measure whether they contain the information researchers need (p 18). And Beth Hart and colleagues explore whether the conclusions of existing systematic reviews change when unpublished studies are included in meta-analyses (p 13).

Is there anything researchers can do? Options have increased in recent years, according to a linked Research Methods and Reporting article from An-Wen Chan (p 19). Trial registries, protocols, some pharmaceutical companies, and regulatory authorities all have unpublished data that can help. But this is not a cause for complacency because “the current situation is a disservice to research participants, health systems, and the whole endeavour of clinical medicine,” Richard Lehman and Elizabeth Loder write in their linked editorial (p 1). Better systems are needed.

Where have all the trials gone?

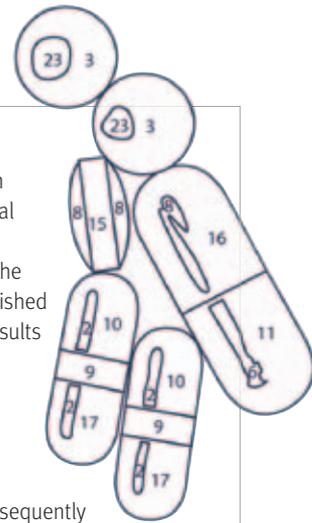
Back in 1986, oncologist and epidemiologist R John Simes called for prospective registration of all clinical trials in a publicly accessible registry (<http://jco.ascopubs.org/content/4/10/1529.abstract>). This, he argued, would aid discovery of ongoing and unpublished trials and would reduce the bias towards positive results in the evidence base.

In 2000 the US National Library of Medicine, as a result of the FDA (Food and Drug Administration) Modernization Act 1997, launched what is now the world's biggest publicly accessible registry, ClinicalTrials.gov. Many other registries opened subsequently round the world. But registration was voluntary and patchy until the influential International Committee of Medical Journal Editors (ICMJE) ruled in 2005 that clinical trials had to be registered prospectively to qualify for publication in one of its member journals. There were then 12 members, including the *BMJ*, and now there are 14 (www.icmje.org/about.html).

The ICMJE rules greatly increased rates of trial registration, but other journals following the committee's uniform requirements for manuscripts didn't have to adopt the rules, and most trialists were still off the hook. Then in 2007 the FDA Amendments Act (FDAAA) made prospective registration at ClinicalTrials.gov mandatory for all clinical trials of drugs, devices, or biological agents with at least one site in the United States (excluding phase I studies and early feasibility trials of devices). The act also required the posting of basic results within one year of the completion of each trial that was registered and ongoing in September 2007, and brought in fines of \$10 000 per infringement. So the act had teeth.

Or did it? Andrew Prayle and colleagues' analysis of ClinicalTrials.gov and the US database of FDA approved drugs, Drugs@FDA, found that only 22% of eligible registered drug trials had results posted at the registry (p 15). Studies funded solely by the drug industry complied better than the rest (40% v 9%) but, as Prayle and colleagues put it, “if the reporting rate does not increase, the laudable FDAAA legislation will not achieve its goal of improving the accessibility of trial results.”

Furthermore, the act requires posting only of “basic results” of eligible registered trials. So Joseph Ross and colleagues searched to see if trials funded by the US National Institutes of Health, registered at ClinicalTrials.gov, and completed at least 30 months earlier had been published yet in peer reviewed journals indexed in Medline (p 14). They found publications for fewer than half overall. And, a median of 51 months after trial completion, a third of trials remained unpublished.



Research online: See www.bmj.com/research



S. GSCHEINER/SPL

Identifying women with suspected ovarian cancer in primary care

Julia Hippisley-Cox and Carol Coupland derive and validate an algorithm to estimate the absolute risk of having ovarian cancer in women with and without symptoms.

Timing of onset of cognitive decline Results from the Whitehall II prospective cohort study show evidence of cognitive decline in UK men and women at all ages between 45 and 70, report Archana Singh-Manoux and colleagues.

Effect of reporting bias on meta-analyses of drug trials: reanalysis of meta-analyses

Beth Hart,¹ Andreas Lundh,² Lisa Bero¹

EDITORIAL by Lehman and Loder

¹Department of Clinical Pharmacy, Institute for Health Policy Studies, University of California, San Francisco, 3333 California St, Suite 420, San Francisco, CA 94118, USA

²Nordic Cochrane Centre, Rigshospitalet and University of Copenhagen, Copenhagen, Denmark

Correspondence to: L Bero
berol@pharmacy.ucsf.edu

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STUDY QUESTION

What effect does inclusion of unpublished trial outcome data obtained from the Food and Drug Administration (FDA) have on the results of meta-analyses of drug trials?

SUMMARY ANSWER

In general, the effect of including unpublished FDA trial outcome data varies by drug and outcome.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

When unfavourable results of drug trials are not published, meta-analyses and systematic reviews that are based on only published data may overestimate the efficacy of drugs. Addition of unpublished trial outcome data to published meta-analyses changed their results; the direction of the effect varied by drug and outcome.

Selection criteria for systematic reviews

We identified eligible systematic reviews containing at least one meta-analysis by searching Medline, Embase, and the Cochrane Library in November 2010. We included systematic reviews that were done after FDA approval of drugs with unpublished FDA outcome data, were published in English, had outcomes and comparators that were the same as for the trials with unpublished outcomes, and had participants' characteristics consistent with the FDA approved indications for the drug. We excluded systematic reviews in which included trials were not referenced or that combined trials across mul-

iple drug classes. We also excluded systematic reviews that used non-standard meta-analytic techniques (such as Bayesian or network meta-analyses) or that used inappropriate or invalid methods for calculation of summary statistics (such as unweighted pooled analyses).

Primary outcome(s)

The main outcome was the effect of including unpublished FDA trial data on the summary estimates of meta-analyses of drug trials.

Main results and role of chance

We reanalysed 42 meta-analyses (41 efficacy outcomes, one harm outcome) for nine drugs across six drug classes. Overall, addition of unpublished FDA trial data caused 46% (19/41) of the summary estimates from the meta-analyses to show less efficacy of the drug (range 1-53% change in summary estimate), 7% (3/41) to show identical drug efficacy, and 46% (19/41) to show greater drug efficacy (2-166% change in summary estimate).

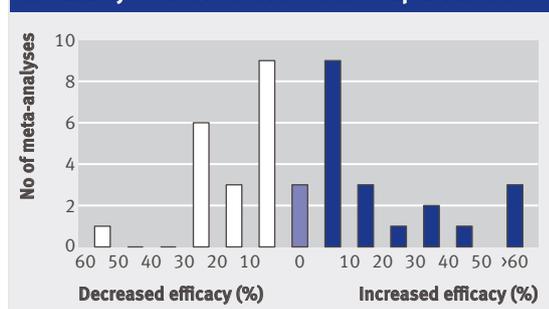
Bias, confounding, and other reasons for caution

We were able to identify systematic reviews for only nine of the 24 drugs for which unpublished FDA trial outcome data were available. One reason for the lack of relevant systematic reviews may be that reviewers are unaware of unpublished outcomes and so do not include these outcomes in their protocols. Therefore, selective reporting of FDA trial outcomes could affect systematic reviews by influencing the research questions that are asked, as well as the data included in the analysis. Another limitation of the study was that we did not do a review of all safety data that were submitted to the FDA. Although our findings suggest that inclusion of unpublished FDA trial outcome data changes the results of meta-analyses of efficacy outcomes, we cannot determine the overall effect of unpublished data on the safety of drugs or on the risk-benefit ratio of each included drug.

Study funding/potential competing interests

This work was supported by a grant from the Doris Duke Charitable Foundation to the University of California, San Francisco, to fund clinical research fellow BH.

Meta-analyses of drug efficacy (n=41): percentage change in summary statistics after inclusion of unpublished data



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Publication of NIH funded trials registered in ClinicalTrials.gov: cross sectional analysis

Joseph S Ross,^{1,2} Tony Tse,³ Deborah A Zarin,³ Hui Xu,⁴ Lei Zhou,⁴ Harlan M Krumholz^{2,5,6}

EDITORIAL by Lehman and Loder

¹Section of General Internal Medicine, Department of Medicine, Yale University School of Medicine, New Haven, CT, USA

²Center for Outcomes Research and Evaluation, Yale-New Haven Hospital, New Haven, CT

³Lister Hill National Center for Biomedical Communications, National Library of Medicine, National Institutes of Health, Bethesda, MD, USA

⁴Fuwai Hospital and Cardiovascular Institute, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

⁵Robert Wood Johnson Clinical Scholars Program and Section of Cardiovascular Medicine, Department of Medicine, Yale University School of Medicine, New Haven, CT

⁶Section of Health Policy and Administration, Yale University School of Epidemiology and Public Health, New Haven, CT

Correspondence to: J S Ross, Section of General Internal Medicine, Yale University School of Medicine, PO Box 208093, New Haven, CT 0520, USA
joseph.ross@yale.edu

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Listen to a podcast interview with Joseph Ross at bmj.com/multimedia

STUDY QUESTION

How many clinical trials funded by US National Institutes of Health (NIH) and registered within ClinicalTrials.gov are published in peer reviewed biomedical journals indexed by Medline and how long is the time lag before publication?

SUMMARY ANSWER

Fewer than half of NIH funded trials are published in a peer reviewed biomedical journal indexed by Medline within 30 months of trial completion, and, at a median of 51 months after trial completion, a third of trials remained unpublished. There were, however, improvements in timely publication among trials completed in 2007 or later.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Between 25% and 50% of clinical trials remain unpublished even several years after completion. In this study of clinical trials funded by US NIH, fewer than half of those registered after September 2005 within ClinicalTrials.gov and completed by December 2008 were published in a peer reviewed biomedical journal indexed by Medline within 30 months of trial completion and a third remained unpublished.

Participants and setting

635 NIH funded clinical trials registered within ClinicalTrials.gov, a trial registry and results database maintained by the US National Library of Medicine, after 30 September 2005 and updated as having been completed by 31 December 2008, allowing at least 30 months for publication after completion of the trial.

Design

Cross sectional analysis.

Primary outcome

Publication and time to publication in the biomedical literature, as determined through Medline searches, the last of which was performed in June 2011.

Main results and the role of chance

Among the included trials, 294 (46%) were published in a peer reviewed biomedical journal indexed by Medline within 30 months of trial completion. The median period of follow-up after trial completion was 51 months (25th-75th centiles 40-68 months) and 68% (n=432) were published overall. Among the published trials, the median time to publication was 23 months (14-36 months). Trials completed in either 2007 or 2008 were more likely to be

published within 30 months of study completion compared with trials completed before 2007 (54% (196/366) v 36% (98/269), respectively; P<0.001).

Bias, confounding, and other reasons for caution

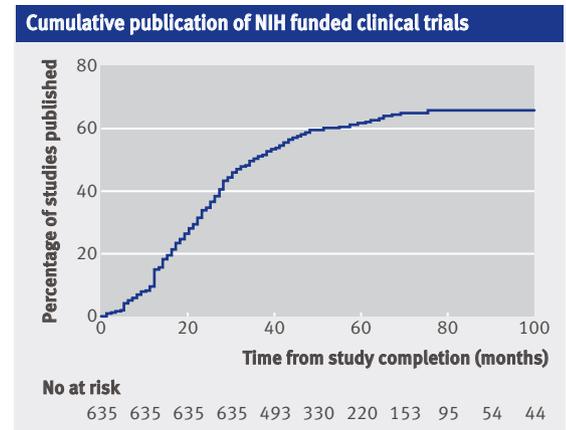
We focused our search for relevant publications from NIH funded research on peer reviewed biomedical journals indexed by Medline and did not search other databases, such as Embase or research conference proceedings (abstracts). This paper highlights the importance of ensuring the timely dissemination of publicly funded research so that data from all those who volunteer are available to inform future research and practice. Although there might be many reasons for lack of publication, the results database at ClinicalTrials.gov offers a complementary method of providing timely public access to study results. The peer reviewed literature, however, is likely to remain the principal method of communicating with clinicians and policy makers.

Generalisability to other populations

Our study was limited to NIH funded trials and cannot be generalised to other international government agencies that fund clinical trial research.

Study funding/potential competing interests

The study was funded by the National Library of Medicine, Department of Health and Human Services. JSR and HMK receive support from Medtronic and from the Centers of Medicare and Medicaid Services; JSR is supported by the National Institute on Aging and the American Federation for Aging Research; DAZ and TT are supported by the Intramural Research Program of the National Institutes of Health, National Library of Medicine; HMK is supported by a National Heart Lung Blood Institute Cardiovascular Outcomes Center Award.



Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: cross sectional study

Andrew P Prayle, Matthew N Hurley, Alan R Smyth

EDITORIAL by Lehman and Loder

University of Nottingham, Division of Child Health, School of Clinical Sciences, Queens Medical Centre, Nottingham NG7 2UH, UK

Correspondence to: A P Prayle andrew.prayle@nottingham.ac.uk

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STUDY QUESTION

Do studies comply with the requirements of the Food and Drug Administration Amendments Act (2007) (FDAAA) by reporting summary results on ClinicalTrials.gov?

SUMMARY ANSWER

At the time of the search, many trials that should have published data on ClinicalTrials.gov had not done so.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The FDAAA mandates publication of a results summary on ClinicalTrials.gov within a year of completion for trials of drugs approved by the FDA, biological agents, or devices, with the aim of reducing bias in the literature. Only 22% of trials that should have reported results had done so.

Selection criteria for studies

We searched ClinicalTrials.gov for all intervention trials that completed between 1 January and 31 December 2009. We excluded trials that were not under the jurisdiction of the FDAAA—namely phase 0/I trials and trials that did not have a site in the United States. We then identified trials that were subject to mandatory reporting, because they were of an FDA approved drug, by cross referencing with Drugs@FDA.

Primary outcome(s)

The main outcome was reporting of results on ClinicalTrials.gov within one year of the primary completion date (the date of the last clinical trial visit of the last patient enrolled in the trial).

Main results and role of chance

We identified 738 trials subject to mandatory reporting. Of these, 163 (22%) had reported results. Studies not subject to mandatory reporting reported results less frequently (76/727; 10%). Industry funded trials were more likely to report than were other trials (126/317 industry *v* 37/421 non-industry; $P=2.2 \times 10^{-16}$; 95% confidence interval for difference between proportions

Number of trials subject to mandatory reporting that had reported results, by phase and funder of study

Characteristic of trial	No (%) with results
Phase:	
II	34/329 (10)
III	73/229 (32)
IV	56/180 (31)
Funder:	
Industry	126/317 (40)
Mixed	25/265 (9)
NIH/government	4/48 (8)
Other	8/108 (7)
Total	163/783 (22)

NIH=National Institutes of Health.

24.7% to 37.3%). Later phase of study was associated with increased reporting of results ($P=4.4 \times 10^{-11}$).

Bias, confounding, and other reasons for caution

Our primary dataset consisted of those studies considered to be under FDAAA jurisdiction and subject to mandatory reporting according to available summary data of ClinicalTrials.gov and Drugs@FDA. We were not able to identify studies that had exemption from reporting. For a minority of studies, determining whether a particular drug formulation was covered by a previous FDA approval was difficult. On these few occasions, we took an inclusive approach. A subgroup analysis including only trials of non-generic drugs with FDA approval (so eliminating the considerations of formulation) showed that 96/347 (28%) of these had reported results. This is also supported by the subgroup analysis including only phase IV trials (by definition FDA approved), of which 56/180 (31%) had reported results.

Study funding/potential competing interests

The study was not directly funded. APP is funded by the National Institute for Health Research, and MNH is funded by the Wellcome Trust. ARS has provided consultancy to drug companies and has registered trials on ClinicalTrials.gov.

Assessment of publication bias, selection bias, and unavailable data in meta-analyses using individual participant data: a database survey

Ikhlaaq Ahmed,¹ Alexander J Sutton,² Richard D Riley³

EDITORIAL by Lehman and Loder

¹MRC Midlands Hub for Trials Methodology Research, School of Health and Population Sciences, University of Birmingham, Birmingham B15 2TT, UK

²Department of Health Sciences, University of Leicester, Leicester LE1 7RH, UK

³School of Health and Population Sciences, University of Birmingham
Correspondence to: R D Riley
r.d.riley@bham.ac.uk

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STUDY QUESTION

What is the potential for publication bias, data availability bias, and reviewer selection bias in recently published meta-analyses that use individual participant data, and do authors of such analyses acknowledge these issues?

SUMMARY ANSWER

Publication, availability, and selection biases are often a potential concern for meta-analyses of individual participant data, but many reviewers neglect to examine or discuss them.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Publication related biases hide relevant trials and their results, and potentially lead to meta-analyses being biased toward favourable treatment effects. Our survey shows that this problem is rarely considered in meta-analyses that use individual patient data, but that publication bias, data availability bias, and reviewer selection bias are often potential concerns.

Selection criteria for studies

Using an existing database of 383 meta-analyses of individual participant data that were published between 1991 and March 2009, we surveyed the 31 most recent meta-analyses of randomised trials that examined whether an intervention was effective.

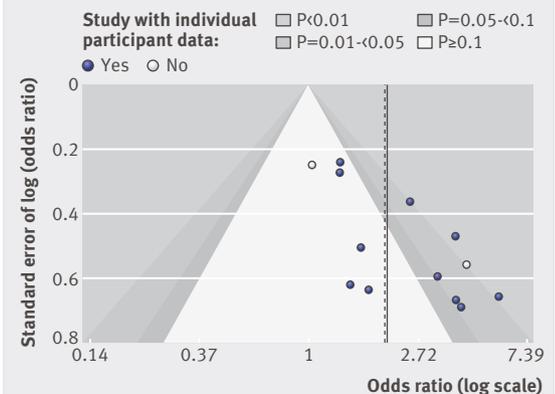
Primary outcome(s)

We investigated the potential for publication bias (for example, were unpublished studies included?), data availability bias (such as, did all studies supply their individual participant data?), and reviewer selection bias (such as, did the authors request individual participant data from all studies identified by a systematic review?)

Main results and role of chance

Only nine (29%) of the 31 meta-analyses included individual participant data from “grey literature” (such as unpublished studies) in their primary meta-analysis, and the potential for publication bias was discussed or investigated in just 10 (32%). Sixteen (52%) of the 31 meta-analyses did not obtain all the individual participant data requested, yet five of these (31%) did not mention this as a potential limitation, and only six (38%) examined how trials without individual participant data might affect the conclusions. In nine (29%) of the meta-analyses reviewer selection bias was a potential issue, as the identification

Funnel plot for 11 trials included in a meta-analysis of individual participant data plus two trials lacking individual participant data



P values correspond to a trial's treatment effect
Solid line indicates summary result from meta-analysis of just individual participant data trials (odds ratio 2.06); dotted line indicates result from meta-analysis of individual participant data combined with aggregate data from two studies lacking individual participant data (odds ratio 2.02)

of relevant trials was either not stated or based on a more selective, non-systematic approach.

In four meta-analyses that included ≥ 10 trials we could extract data to investigate funnel plot asymmetry, and one showed significant asymmetry ($P < 0.1$) consistent with publication bias (figure). To investigate availability bias, we managed to extract odds ratios for two trials not providing individual participant data. Including them alongside the other 11 studies had a minimal impact of the summary odds ratio estimate (shifting it from 2.06 (95% CI 1.48 to 2.86) to 2.02 (1.45 to 2.81)) but increased the extent of between-trial heterogeneity, leading to the 95% prediction interval for the odds ratio in an individual clinical setting shifting from 1.03 to 4.89 (indicating significant improvement with treatment) to an interval that includes 1 (0.85 to 4.81), implying treatment may not be superior in every clinical setting.

Bias, confounding, and other reasons for caution

Our survey contained only a modest sample of 31 meta-analyses of individual participant data and, as we did not question review authors directly, methodological deficiencies identified in the meta-analyses are impossible to disentangle from their reporting standards.

Study funding/potential competing interests

IA is funded by the MRC Midlands Hub for Trials Methodology Research, at the University of Birmingham.

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Understanding why evidence from randomised clinical trials may not be retrieved from Medline: comparison of indexed and non-indexed records

L Susan Wieland,^{1,2} Karen A Robinson,^{3,4} Kay Dickersin²

● EDITORIAL by Lehman and Loder

¹University of Maryland School of Medicine, Center for Integrative Medicine, Baltimore, MD 21201, USA

²US Cochrane Center, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

³Department of Medicine, School of Medicine, Johns Hopkins University, Baltimore, MD, USA

⁴Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

Correspondence to: L Susan Wieland ls Wieland@gmail.com

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STUDY QUESTION

Are there differences between Medline records of randomised controlled trials (RCTs) that are indexed with RCT [pt] (publication type), and records that are not?

SUMMARY ANSWER

Medline records of randomised controlled trials that were not indexed with RCT [pt] were more likely than indexed records to be focused on trial information other than main results.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Indexing with RCT [pt] aids in retrieval of randomised trial reports from Medline. Reports of randomised trials that are not indexed with this publication type are more likely than indexed reports to describe trial design and methods, baseline characteristics of participants, long term follow-up, and secondary and observational data analyses, making this type of information more difficult to identify from Medline. Researchers and healthcare decision makers relying on using RCT [pt] may be missing important evidence in their searches.

Selection criteria for records

The Cochrane Collaboration worked with the US National Library of Medicine from 1994 to 2006 to add the RCT [pt] indexing term (“retag”) records of randomised controlled trials that were not indexed with RCT [pt]. We compared randomised controlled trial records identified through the Cochrane retagging project that met our inclusion criteria (entered into Medline in 2005, had undergone indexing, included an abstract, contained the word “random” or a variant in the title or abstract) and were not indexed with RCT [pt] with a random sample of records meeting our inclusion criteria that were indexed with RCT [pt].

Primary outcomes

Comparisons between tagged and untagged records by type of trial information, and examination of untagged records for other types of clinical trial indexing.

Main results and the role of chance

We confirmed that 572/591 (97%) of untagged records and 578/594 (97%) of tagged records contained information from randomised controlled trials. Most tagged reports (526/578; 91%, 95% confidence interval 89% to 93%) described main results. Untagged reports were more likely than tagged reports to contain information on design and methods, baseline characteristics, long term follow-up, secondary analyses, and observational analyses using trial data. Crossover designs were more commonly seen in untagged than in tagged reports of main results (36% v 10%; difference 25%, 95% confidence interval 19% to 32%). The Medical Subject Heading “Randomized Controlled Trials” was the most common clinical trial term applied to untagged reports, although more than half of untagged reports had no trial related indexing. Since the Cochrane retagging project ended in 2006, researchers and healthcare decision makers relying on RCT [pt] may be missing important evidence in their searches. Based on our identification of over 500 randomised controlled trial records added to Medline in 2005 and not tagged with RCT [pt], we estimate that at least 3000 records describing randomised controlled trials but not indexed as such may have been entered into Medline between 2006 and 2011. Use of validated search strategies, as opposed to dependence on publication types, should help searchers identify all relevant trial reports.

Bias, confounding, and other reasons for caution

Our sample of untagged records was based on what we retrieved after searching and application of our eligibility criteria; thus we may have missed untagged records that could have altered our findings. In addition, we based our assessment on the title and abstract rather than the full text, although we referred to the full text in cases of uncertainty.

Generalisability to other populations

Although we did not limit our examination by study question or journal, the US National Library of Medicine indexes some records more quickly than others, and our sample of untagged records excluded records for which indexing had not been completed. It is possible that our results may not be applicable to records from journals that are indexed more slowly.

Study funding/potential competing interests

This study was not funded. We have no competing interests.

Types of information contained in untagged and tagged reports of randomised controlled trials indexed by US National Library of Medicine

Information	No (%) of untagged records (n=572)	No (%) of tagged records (n=578)	% difference (95% CI)
Main results	234 (41)	526 (91)	-50 (-45 to -55)
Design and methods	87 (15)	8 (1)	14 (11 to 17)
Baseline data	14 (2)	1 (<1)	2 (1 to 4)
Secondary analysis	111 (19)	28 (5)	15 (11 to 18)
Observational data	93 (16)	5 (1)	15 (12 to 19)
Long term follow-up	33 (6)	10 (2)	4 (2 to 6)

Impact of document type on reporting quality of clinical drug trials: a comparison of registry reports, clinical study reports, and journal publications

Beate Wieseler, Michaela F Kerekes, Volker Vervoelgyi, Natalie McGauran, Thomas Kaiser

EDITORIAL by Lehman and Loder

Institute for Quality and Efficiency in Health Care, Dillenburg
Strasse 27, 51105 Cologne,
Germany

Correspondence to: B Wieseler
beate.wieseler@iqwig.de

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STUDY QUESTION

To what extent do three types of document for reporting clinical trials (reports posted in trial results registries, clinical study reports submitted to regulatory authorities, and journal publications) provide sufficient information on methods and outcomes to enable trial evaluation?

SUMMARY ANSWER

Registry reports and journal publications insufficiently report clinical trials but may supplement each other. Clinical study reports largely provide complete information to enable trial evaluation, but they are generally not publicly available.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Poor reporting of clinical trials methods and outcomes is a major problem in clinical research, and our analysis shows that this particularly affects registry reports and journal publications. In addition to adhering to standards for journal publications, reporting could be improved by implementing worldwide mandatory reporting standards for results registries (for new studies) and by making clinical study reports publicly available (for older studies).

Design and data sources

We performed a retrospective analysis of three types of document for reporting clinical trials: registry reports, (clinical) study reports, and (journal) publications. We analysed all primary studies and corresponding documents from 16 health technology assessments of drugs conducted by the German Institute for Quality and Efficiency in Health Care (IQWiG) between 2006 and February 2011.

Data analysis and outcomes

We assessed reporting quality for each study and each available document for six items on methods and six on

outcomes (see table for details), and dichotomised them as “completely reported” or “incompletely reported.” For each document type, we calculated the proportion of studies with complete reporting for methods and outcomes, per item and overall, and compared the findings.

Main results

We identified 268 studies. Publications, study reports, and registry reports were available for 192 (72%), 101 (38%), and 78 (29%) studies, respectively. Reporting quality was highest in study reports, which overall provided complete information for 90% of items (1086/1212) (table). By contrast, registry reports and publications provided complete information for only 51% (477/936) and 46% (1052/2304) of items, respectively. Registry reports provided more complete information on outcomes than on methods (overall 330/468 (71%) v 147/468 (31%)); the same applied to publications (594/1152 (52%) v 458/1152 (40%)). In the matched pairs analysis, reporting quality was poorer in registry reports than in study reports for overall methods and outcomes ($P < 0.001$ in each case). Compared with publications, reporting quality was poorer in registry reports for overall methods ($P < 0.001$), but better for outcomes ($P = 0.005$).

Limitations

Our sample covered only a limited number of medical indications and interventions. Moreover, the registry reports included were prepared by a limited number of companies, with most reports being produced by three companies. The registry reports included were not prepared according to the new requirements of the Food and Drug Administration Amendments Act or the upcoming European regulation. Future reports in ClinicalTrials.gov may be of better quality. Moreover, our sample of studies was restricted to randomised controlled trials investigating drugs, so we cannot comment on other study designs or studies of non-drug interventions.

Study funding/potential competing interests

This work was supported by IQWiG. All authors are employees of IQWiG. In order to produce unbiased health technology assessment reports, the institute depends on access to all of the relevant data on the topic under investigation. The authors therefore support the mandatory worldwide establishment of trial registries and study results databases as well as the implementation of reporting standards for clinical trials.

Completeness of information on study methods and outcomes by document type

Information	No of items with complete information/total No of items in sample		
	Study report* (n=101)	Registry report† (n=78)	Journal publication (n=192)
Study methods‡	533/606 (88%)	147/468 (31%)	458/1152 (40%)
Study outcomes§	553/606 (91%)	330/468 (71%)	594/1152 (52%)
All items	1086/1212 (90%)	477/936 (51%)	1052/2304 (46%)

*Clinical study reports submitted to regulatory authorities during drug approval.

†Reports posted in trial results registries.

‡Items are randomisation, allocation concealment, blinding, sample size estimation, definition of intention to treat dataset, and no of patients in intention to treat dataset.

§Items are primary end point, withdrawals, reasons for withdrawal, patients with adverse events, patients with serious adverse events, and patients withdrawn due to adverse events