QUALITY OF TRIALS

Impact of a Systematic Review on Subsequent Clinical Research: The Case of the Prevention of Propofol Injection Pain

Céline Habre,[1] Nadia Elia,[1,2,4] Daniel M. Pöpping,[3] Martin R. Tramèr[1,4]

Objective In 2000, a systematic review identified intravenous lignocaine, administered with venous occlusion, as the most efficacious intervention for the prevention of propofol injection pain. We set out to determine whether, after the publication of the review, the number of trials on this issue had decreased over time and whether authors of subsequently published trials referred to that review and used it to design their study (ie, to justify the choice of a comparator intervention or to estimate study size).

Design We systematically searched (MEDLINE, Cochrane Central Register of Controlled Trials, EMBASE, and related bibliographies) for all randomized trials testing interventions to prevent propofol injection pain, published since 2002 (ie, 2 years after the publication of the review). We extracted information based on the year of publication, experimental and control interventions, whether the review was cited, and whether authors explicitly declared having used it to design the study. Lignocaine injection with venous occlusion was regarded as the gold standard. Study designs comparing any experimental intervention with the gold standard were regarded as appropriate. Main outcomes were the number of published trials over time, number (percent) of trials citing the review, using it to design the study, and with appropriate study designs.

Results Between January 2002 and 2013, 136 trials (19,778 patients) were published, without a clear decreasing trend over time. Ninety-nine (72.8%) authors cited the review, but only 21 (15.4%) declared using it to design the study. Designs were appropriate in 34 (25%) trials and inappropriate in 102 (75%). Of the 21 trials in which authors declared using the review to design their study, 18 (86%) had appropriate designs. Of the 115 trials in which authors did not use the review to design their study, only 16 (14%) had appropriate designs.

Conclusions A large number of trials have been published since the publication of the systematic review. Most authors cited the systematic review; however, only a minority used it as a rational basis for the design of their study. Trials designed on the basis of the review were more likely to be appropriate, thus suggesting that the knowledge of systematic reviews in study design should be encouraged.

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Conflict of Interest Disclosures Nadia Elia is associate editor and Martin Tramèr is editor in chief, *European Journal of Anaesthesiology*. No other disclosures reported.

Publication of Randomized Controlled Trials That Were Discontinued: An International Multicenter Cohort Study

Benjamin Kasenda,[1] Erik von Elm,[2] Anette Blümle,[3] Yuki Tomonaga,[4] John You,[5] Mihaela Stegert,[1] Theresa Bengough,[2] Kelechi Kalu Olu,[1] Matthias Briel,[1,5] for the DISCO Study Group

Objective Our aim was to determine the prevalence of discontinuation of randomized controlled trials (RCTs) for different reasons, the publication history of discontinued RCTs, and differences between industry- and investigator-initiated RCTs with respect to discontinuation and publication.

Design We established a multicenter cohort of RCTs based on protocols approved by 6 research ethics committees (RECs) from 2000 to 2003 in Switzerland, Germany, and Canada. We extracted data on RCT characteristics and planned recruitment. We determined completion status of RCTs by using information from REC files, publications identified by literature search, and by surveying investigators. We used multivariable logistic regression to investigate the following risk factors for nonpublication of RCTs: trial discontinuation (vs completion), trial initiation by industry (vs investigators), national setting (vs international), sample size below median (vs above), and single-center study (vs multicenter).

Results We included 894 protocols of RCTs involving patients. Of those, 574 (64.2%) were completed (ie, attained >90% of target sample size), 250 (28.0%) discontinued for any reason, and for 70 (7.8%) the status remained unclear. Reasons for discontinuation were poor recruitment (100/250, 40.0%), futility (37/250, 14.8%), administrative reasons (36/250, 14.4%), harm (25/250, 10.0%), benefit (9/250, 3.4%), and other (43/250, 17.2%). Industry-initiated RCTs (n=538 [60.2%]) were completed in 71.9%, whereas investigator-initiated RCTs (n=356 [39.8%]) were completed in 52.5% of cases. Funding sources of discontinued investigator-initiated RCTs (n=136) were public (n=32 [23.5%]), industry (n=26 [19.1%]), charity (n=15 [11.0%]), public and industry (n=11 [8.1%]), and public and charity (n=2 [1.5%]); 35 (25.7%) discontinued investigator-initiated RCTs had no external funding, and for 15 (11.0%) the funding source remained unclear. Of all discontinued and completed RCTs, 114 (45.6%) and 416 (72.5%) were published as full journal articles, respectively. Discontinued industry-initiated RCTs (n=114) were published in 43.9% and discontinued investigator-initiated RCTs (n=136) in 47.1% of cases. Independent risk factors for nonpublication were trial discontinuation and single-center study (**Table 10**).

Conclusions Discontinued RCTs are common, in particular when they are investigator-initiated, and often not published. Our results may raise journal editors' and researchers' awareness of existing determinants of RCT nonpublication and the prevalence of unpublished discontinued RCTs.

Table 10. Factors Associated With Nonpublication of Randomized Controlled Trials (RCTs) Based on 815 RCTs With Complete Data

	Univariable			Multivariable		
Risk Factors	OR	95% CI	*P* value	OR	95% CI	*P* value
RCT discontinued (vs completed)	3.17	2.32-4.32	<.001	3.00	2.16-4.16	<.001
Initiated by industry (vs investigator)	0.75	0.57-0.99	.039	1.41	0.98-.02	.064
National (vs international)	2.22	1.67-2.95	<.001	1.33	0.86-2.05	.191
Study size below median[a] (vs above median)	2.10	1.59-2.78	<.001	1.39	0.98-1.97	.063
Single-center study (vs multicenter)	2.42	1.69-3.47	<.001	1.71	1.03-2.85	.038

[a]The median study size was 250.

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Terminated Trials in ClinicalTrials.gov: Characteristics and Evaluation of Reasons for Termination

Katelyn DiPiazza,[1] Rebecca J. Williams,[2] Deborah A. Zarin,[2] Tony Tse[2]

Objective Early termination of clinical trials raises a broad range of scientific, ethical, and resource issues. Prior research on the topic has focused on specific therapeutic areas and problems related to participant recruitment, but little is known about the reasons for termination across the clinical research enterprise. This study aims to determine the number and characteristics of trials that terminated within a cohort of trials registered at ClinicalTrials.gov. It also examines reasons for termination and the amount and type of results data available from such trials.

Design In February 2013, we determined the status of all registered interventional studies initiated in 2006 and summarized the characteristics of terminated trials using the registration data elements. We also examined terminated trials with results posted on ClinicalTrials.gov and categorized the explanations for why the study stopped by whether the reason was based on scientific data accumulated from the trial (eg, interim efficacy data) or not (eg, low enrollment). We also summarized the publication status and the type and amount of results data available for a subset of these trials.

Results Of the 7,852 registered trials initiated in 2006 and verified in the 2 years (if ongoing), 84% (n=6,622) had ended 6 years later and, of these, 12% (n=789) were terminated. In the sample of 917 terminated trials with results posted on ClinicalTrials.gov, 21% (n=193) were categorized as ending prematurely based on scientific data accumulated from the trial (**Table 11**) and, as of April 2013, 21% (n=193) were published in journals indexed by PubMed. In a subset of terminated trials with posted results (n=861), approximately 71% (n=612) of the trials had summary results data for at least 1 participant in the primary outcome measure.

Conclusions Terminated studies frequently end prematurely for reasons other than scientific data accumulated from the trial. Because many terminated studies are not published, ClinicalTrials.gov is a unique resource for data from such trials.

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Conflict of Interest Disclosures Rebecca Williams is assistant director, Deborah Zarin is director, and Tony Tse is program analyst for ClinicalTrials.gov.

Table 11. Categorization of Reasons for Termination for 917 Trials With Results Posted to the ClinicalTrials.gov Results Database as of February 2013

Termination Category	Trials No. (%)
Termination based on scientific data from trial interim efficacy (positive, negative, inconclusive) or safety and toxicity data	193 (21)
Termination not based on scientific data from trial	631 (69)
Insufficient accrual rate	356 (39)
Unspecified business decision/strategic reason	77 (8)
Trial administration or conduct (eg, issues with protocol, investigators, site)	56 (6)
External information (eg, results from other trials, competing trials, or changes in standard care rendering trial irrelevant)	52 (6)
Funding issues	35 (4)
Product withdrawn from market	19 (2)
Other (eg, uninformative response, misuse of data element)	19 (2)
Lack of drug supply	17 (2)
Termination reason not provided	93 (10)

Funding/Support No external funding outside of the employer of the 3 authors (NLM/NIH).

QUALITY OF REPORTING TRIALS

A Review of Registration and Reporting of "Continuish" Outcomes in Randomized Trials

Steven Woloshin,[1] Lisa M. Schwartz,[1] Allison Hirst,[2] Ly-Mee Yu,[3] Alice Andrews,[1] Gary Collins,[3] Rose Wharton,[3] Milensu Shanyinde,[3] Susan J. Dutton,[3] Omar Omar,[3] Sally Hopewell,[3] Joshua Wallace,[3] Jackie Birks,[3] Nicola Williams,[3] Eric Ohuma,[4] Douglas G. Altman[3]

Objective True continuous and ordinal measures, visual analog scales, scores, and counts—"continuish" measures—can be analyzed in many ways: means, medians, and percent above cutoff. Because of this flexibility, investigators can select an approach based on statistical significance. We examined how continuish primary outcomes measures are reported in randomized controlled trials (RCTs), and compared them with trial registry entries meant to avoid data-driven analyses.

Design Review of 2-arm parallel-group RCTs of treatment published in the PubMed Core Clinical Journals in 2010 (n=568) for explicit continuish primary outcomes in the abstract. Pairs of reviewers extracted data using a standardized form.

Results Of the 337 trials with a continuish outcome in the abstract, 99 (30%) never specified a primary outcome. We analyzed a random sample of 180 trials from the remainder. Most measures were true continuous like weight (64%); scores (21%); or pseudocontinuous-like visual analog scales (9%). Continuish primary outcomes were reported as mean (69%), percent above cutoff (11%), median (8%), relative change (7%), and other (6%). In 76 (43%) articles, the primary measure was analyzed multiple ways, with consistent statistical significance in 8 (11%). The clinical importance of the difference in the primary continuous outcome was discussed for only 59% of the 90 positive trials. Of eligible articles, 134 of 180 (74%) were registered; in the current registry records, primary outcomes were missing for 6 (4%); 83 (62%) only mentioned the domain or unit without specifying the metric or summary statistic (**Table 12**). All 5 pri-

Table 12. Missing and Changed Information Within the Registry and Between the Registry and Journal Article

	Initial and Current Registry (n=116 Trials[a])		Current Registry and Article (n=134 Trials)	
Primary Outcome Specification	Missing in Initial Registry No. (%)	Changed in Current Registry No. (%)	Missing in Current Registry No. (%)	Changed in Journal Article No. (%)
Domain (eg, depression)	23 (20)	7 (6)	20 (15)	20 (15)
Time frame (eg, 1-year)	31 (27)	11 (10)	33 (25)	25 (19)
Unit (eg, Hamilton scale)	55 (47)	0 (0)	61 (46)	4 (3)
Metric (eg, change from baseline)	68 (59)	1 (1)	86 (64)	2 (2)
Summary statistic (eg, mean)	80 (69)	0 (0)	103 (77)	1 (1)
Any change	…	16 (14)	…	42 (31)

[a]Only includes registries that archive changes.

mary outcome specifications were identical in the current trial registry and the published journal article for only 9 (7%) of 134 trials.

Conclusions Most journal articles of RCTs with continuish outcomes inadequately specify the primary outcome and analyze it in multiple ways with inconsistent statistical significance. Trial registries need to enforce stricter requirements to ensure that analyses of treatment effects are truly prespecified.

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Reporting of Crossover Trials on Medical Interventions for Glaucoma

Tsung Yu,[1] Tianjing Li,[1] Barbara Hawkins,[1,2] Kay Dickersin[1]

Objective Crossover trials are clinical experiments in which participants are randomly assigned to receive sequential treatments with the intent of estimating differences within individual rather than at the group level. We aim to describe the methodological and reporting issues in 83 crossover trials testing medical interventions for glaucoma and assess their usefulness in meta-analysis.

Design As part of a large network meta-analysis, we identified 526 eligible randomized controlled trials testing medical interventions for glaucoma through our comprehensive literature search (searched in November 2009). We abstracted data on the design, analysis, and reporting of 83/526 (15.8%) that used a crossover design.

Results Seventy-two trials (72/83; 86.7%) studied 2 interventions altogether, and the others studied 3 or more. Only 33/83 trials (39.8%) reported that there was a washout period before a participant crossed over to the next intervention. The description of statistical methods was variable and unclear in most cases. In the trial reports, only 19/83 (22.9%) mentioned the concept of period effect and 25/83 (30.1%) mentioned carryover effect. Eighty-two trials (82/83; 98.8%) used data from more than one period for analysis, but 53/82 (64.6%) did not report if and how they accounted for the paired participants in a crossover design. Seventy-one trials (71/83, 85.5%) presented the results as if the data arose from a parallel-group trial. Only 25/83 trials (30.1%) reported an estimate of treatment effect and associated variability using within-participant differences, and 14/83 (16.9%) reported results at the end of first period that can also be meta-analyzed. Altogether, 36/83 trials (43.4%) reported quantitative data with sufficient details to be included in a meta-analysis.

Conclusions In our sample, most crossover trials did not adequately report important methodological considerations and had few useful data, making meta-analyses difficult. Inability to integrate trial data into systematic reviews wastes resources and the time of study participants. Peer reviewers should seek advice from those who understand the methods when evaluating manuscripts for publication. We urge the CONSORT group to develop and publish an extension for crossover design to guide and improve the reporting of such trials.

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Characterization of Trials Designed Primarily for Marketing Purposes Rather Than Addressing Genuine Clinical Questions: A Descriptive Study

Virginia Barbour,[1] Druin Burch,[2] Fiona Godlee,[3] Carl Heneghan,[4] Richard Lehman,[4] Joseph Ross,[5] Sara Schroter[3]

Objective Clinical trials designed to promote drugs, as opposed to address scientific objectives, have been infrequently identified through access to internal industry documents but are frequently suspected. Such trials can be hard to identify and have the potential to distort the medical literature by misleading readers. Our objective is to define characteristics of trials that appear to be primarily marketing driven and estimate their prevalence.

Design We are conducting a 3-phase study examining drug trials published in 6 general medical journals in 2011. In phase 1, 6 investigators independently reviewed all trial publications to reach consensus on likely marketing trials. We did not have fixed criteria but used expert consensus, based on our understanding of previously described seeding trials. In phase 2, we are identifying predictors of categorization, using blinded researchers to extract trial information (eg, role of manufacturer in design, data analysis, and reporting, average number of patients recruited per center in relation to rarity of the disease, clinical relevance of findings, use of surrogate and composite outcomes, and extent to which conclusions focused on secondary outcomes). To develop a model of independent predictors, we will use multivariate logistic regression to estimate the adjusted odds ratios (and 95% CIs) for studies deemed to be marketing trials. A sensitivity analysis will be performed for the manufacturer-funded trials only. Phase 3 will involve in-depth descriptive research around a subgroup to determine the context in which they appear—within the journal, and in relation to information on the drug's licensing and marketing.

Results To date, 25/207 trials (12%) were rated by at least 4 independent investigators as very likely marketing trials and 121 (58%) as very unlikely. After consensus discussion, 41 (20%) trials were considered very likely marketing trials and 14 (7%) as possibly so. Phase 2 and 3 analyses are under way.

Conclusions Our findings suggest that a fifth of all drug trials published in the highest impact general medical journals in 2011 were designed primarily for marketing purposes. This study will highlight characteristics for editors, reviewers, and readers to be aware of when assessing published trials.

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Conflict of Interest Disclosures Fiona Godlee is editor of the *BMJ* and Virginia Barbour is chief editor of *PLOS Medicine*, but they were excluded from evaluations of papers published in these journals. Virginia Barbour is chair of COPE, which contributed a research grant to the study. She was not involved in the committee that awarded the grant. Sara Schroter is an employee of the *BMJ* and regularly undertakes research into the publishing process. The other authors reported no conflicts of interest.

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REPORTING GUIDELINES

Consensus-Based Case Report Guidelines Development: CARE Guidelines

Joel J. Gagnier,[1,2] Gunver Kienle,[3] Douglas G. Altman,[4] David Moher,[5,6] Harold Sox,[7] David Riley,[8] and the CARE Group

Objective Case reports have helped identify effects from interventions and recognize new or rare diseases. Data from case reports—increasingly published in indexed medical journals—is beginning to be systematically collected and reported. However, the quality of published case reports is uneven. One study evaluated 1,316 case reports from 4 emergency medicine journals and found that more than half failed to provide information related to the primary treatment. Case reports, written without reporting guidelines (with the exception of harms), are insufficiently rigorous to guide clinical practice, inform research design, or be aggregated for data analysis. This analysis was conducted to develop and implement systematic reporting guidelines for case reports

Design We followed published recommendations for guideline development using a modified Delphi process with (1) a literature review and interviews generating guidelines items, (2) an October 2012 face-to-face consensus meeting to draft reporting guidelines, and (3) postmeeting feedback and guideline finalization.

Results Recommendations for the reporting of case reports are listed in **Table 13**.

Conclusions The CARE guidelines have been developed in a consensus-based process and represent essential information necessary to improve the quality of case reports. These guidelines are generic and will need extensions for specific specialties and purposes. Feedback from use of the guidelines in 2013, though positive, is limited. The analysis of systematically aggregated information from patient encounters may provide scalable, data-driven insights into what works for which patients transforming how we think about "evidence" and its creation, diffusion, and use.

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Conflict of Interest Disclosures Joel Gagnier, University of Michigan, and David Riley, Global Advances in Health and Medicine, organized this consensus-based guideline development project. No honoraria were paid; however, conference expenses were reimbursed. The volunteer steering committee consisted of Joel J. Gagnier, Gunver Kienle, David Moher, and David Riley.

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Poor Description of Nonpharmacological Interventions: A Remediable Barrier to Use in Practice?

Tammy Hoffmann, Chrissy Erueti, Paul Glasziou

Objective To evaluate the completeness of intervention descriptions in randomized trials of nondrug interventions, identify the most frequently missing elements, and assess whether missing details can be obtained from trial report authors.

Design We assessed all reports of randomized trials of nonpharmacological interventions published in 2009 in 6 leading general medical journals; 133 reports met inclusion criteria. As 4 had evaluated 2 nonpharmacological interventions, we evaluated descriptions of 137 interventions. Based on the primary report and its references, and any appendices or websites, 2 independent raters assessed whether the intervention description had sufficient detail to allow replication (CONSORT item 5) for each element of an 8-item checklist. Differences between assessments were resolved through discussion. For reports with missing details, questions were e-mailed to corresponding authors and, if authors replied, the raters reassessed relevant items.

Results Of 137 interventions, 53 (39%) were adequately described. Using the 63 responses from 88 contacted authors (71% response rate), the number of interventions described adequately increased to 81 (59%) (**Figure 7**). Among the checklist items that scored worst in primary reports was "intervention materials" (47% complete), but it improved the most following author response (92%). Some authors (27/70) were able to send materials or provide further information; other authors (21/70) could not, with reasons including copyright or intellectual prop-

Table 13. Items to Be Included in Case Reports

The Narrative: A case report tells a story in a narrative format that includes the presenting concerns, clinical findings, diagnoses, interventions, outcomes (including adverse events), and follow-up. The narrative should include a discussion of the rationale for any conclusions and any takeaway messages.		
Section	Item Number	Item Description
Title	1	The words "case report" (or "case study") should be in the title along with phenomenon of greatest interest (eg, symptom, diagnosis, test, intervention).
Key Words	2	The key elements of this case in 2-5 words.
Abstract	3	(a) Introduction: What does this case add? (b) Case presentation The primary symptoms of the patient The primary clinical findings The primary diagnoses and interventions The primary outcomes (c) Conclusion: What were the main "takeaway" lessons from this case?
Introduction	4	Brief background summary of this case referencing relevant medical literature
Patient Information	5	(a) Demographic information (eg, age, gender, ethnicity, occupation) (b) The presenting symptoms of the patient (his/her chief complaints) (c) Medical, family, and psychosocial history, including diet, lifestyle, and genetic information whenever possible, and details about relevant comorbidities including past interventions and their outcomes
Clinical Findings	6	Describe the relevant physical examination (PE) findings.
Timeline	7	Depict important dates and times in this case (table or figure).
Diagnostic Assessment	8	(a) Diagnostic methods (eg, PE, laboratory testing, imaging, questionnaires) (b) Diagnostic challenges (eg, financial, language/cultural) (c) Diagnostic reasoning including other diagnoses considered (d) Prognostic characteristics (eg, staging) where applicable
Therapeutic Intervention	9	(a) Types of intervention (eg, pharmacologic, surgical, preventive, self-care) Administration of intervention (eg, dosage, strength, duration) Changes in intervention (with rationale)
Follow-up and Outcomes	10	(a) Summarize the clinical course of all follow-up visits including Clinician- and patient-assessed outcomes Important follow-up test results (positive or negative) Intervention adherence and tolerability (how this was assessed) Adverse and unanticipated events
Discussion	11	(a) The strengths and limitations of the management of this case (b) The relevant medical literature (c) The rationale for conclusions (including assessments of cause and effect) (d) The main "takeaway" lessons of this case report
Patient Perspective	12	The patient should share his or her perspective or experience whenever possible.
Informed Consent	13	Did the patient give informed consent? Please provide if requested.

erty concerns, not having the materials or intervention details, or not aware of the importance of providing such information. Although 46 interventions (34%) had a relevant website containing further information or materials, many websites were not mentioned, not freely accessible, or no longer functioning.

Conclusions The omission of essential information about interventions is a substantial, yet remediable, obstacle to the replication and use of treatments evaluated in clinical trials. Reducing this loss will require action by funders, researchers, and editors at multiple stages, and long-term repositories of materials linked to publications.

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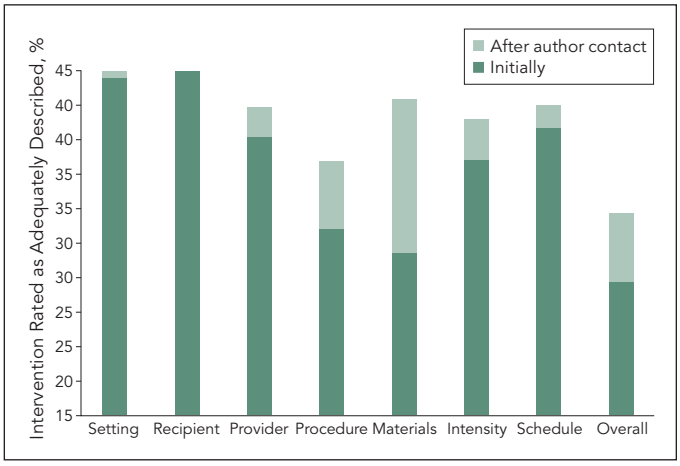
Figure 7: Interventions Checklist Items Rating as Adequately Described, Initially and After Authors' Reply



Impact of Adding a Limitations Section in Abstracts of Systematic Reviews on Reader Interpretation: A Randomized Controlled Trial

Amélie Yavchitz,[1,2] Philippe Ravaud,[1,3,4,5,6] Sally Hopewell,[1,5,7] Isabelle Boutron[1,3,4,5]

Objective We aimed to assess the impact of a Limitations section in abstracts of systematic reviews on reader interpretation.

Design In a 2-arm parallel-group randomized controlled trial, we compared abstracts with and without a Limitations section and selected a sample of abstracts of systematic reviews evaluating the effects of health care interventions with conclusions favoring the beneficial effect of the experimental treatment. We modified the selected abstracts by (1) removing the original Limitations section (when it existed) and (2) adding a Limitations section written according to specific guidance. The Limitations section was written by 1 researcher and evaluated independently by another. The created Limitations section focused on the limitations of evidence as recommended in the PRISMA for Abstract checklist (item 9). All abstracts were standardized, with the treatment name, authors, and journal masked. Study acronyms were also deleted. The same abstract, with or without the Limitations section, randomly assigned to 300 corresponding authors of clinical trials published between 2010 and 2012 and indexed in PubMed. Participants were invited by e-mail to connect to a secure website to complete the survey and were blinded to the study hypothesis. The primary outcome was the participants' confidence in the results of the study based on the information reported in the abstract. Secondary outcomes were the reader's perception of the quality and the validity of the systematic review.

Results Three hundred participants were randomized; 150 assessed an abstract with a Limitations section and 150 an abstract with no Limitations section. There was no statistically significant difference for the assessment of abstracts with Limitations section vs without Limitations section on the confidence in the results (scale 0-10, mean [SD] = 4.4 [2.3] vs 4.6 [2.5], P=.5); the confidence in the validity of the conclusion (scale 0-10, mean [SD] = 4.0 [2.3] vs 4.1 [2.5], P=.8); and the benefit of the experimental intervention to patients (scale 0-10, mean [SD] = 4.3 [2.3] vs 4.4 [2.6], P=.6).

Conclusion Adding a Limitations section in abstract on the quality of evidence of systematic review did not impact readers' interpretation.

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Beyond STARD: Characterizing the Presence of Important Elements in Diagnostic Test Accuracy Reports

Natasha Cuk,[1] Carmen C. Wolfe,[2] Douglas G. Altman,[3] David L. Schriger,[1] Richelle J. Cooper[1]

Objectives STARD, by specifying a minimum content for diagnostic test accuracy papers, is aimed at improving reporting. Our experience as editors leads us to believe that there are several topics for which STARD is insufficiently demanding: clarity of hypothesis statements (what test characteristics are considered acceptable performance); sample size considerations; determination of cut points for continuous tests; sensible use of receiver operating characteristic (ROC) curves; and handling of clustered data. We sought to describe the current reporting of diagnostic accuracy studies with respect to these issues.

Design We identified 20 journals (6 general medicine, 7 major specialties, and 7 randomly selected subspecialties) that publish original clinical research and were ranked high in Impact Factor. For each journal, we randomly sampled up to 10 articles published in 2008-2012 that assessed diagnostic tests (identified by title, abstract, or main analysis reporting test characteristics or ROC curve). We developed, piloted, and revised a standardized form used by trained independent raters to capture the elements needed to assess the aforementioned items.

Table 14. Characteristics of 186 Diagnostic Accuracy Studies

Power and Conclusions (N=186)		
Authors state objective threshold for determining test's utility	9%	
Sample size prespecified	22%	
Precision (eg, sensitivity must have 95% CI ≤+5%)		7/41
Comparison (eg, lower limit of CI for sensitivity ≥98%)		20/41
Other (power for modeling, difference in proportions)		12/41
Unclear		2/41
Enough information to replicate sample size calculation	66%	27/41
Authors make judgment about test's utility	98%	
Sample Enrollment and Spectrum bias (N=186)		
Enrollment dates (start and stop) provided[a]	81%	
Enrollment naturalistic (not separately for cases/controls)	80%	
Enrolled sample for whom test would be applied	81%	121/149
If not: Was spectrum bias considered in analyses?	18%	5/28
Were caveats re: spectrum bias discussed?	54%	15/28
Presentation of Results (N=186)		
Presents table contrasting index and gold standard results[a]	48%	
Presents basic performance measures (sensitivity...)[a]	92%	
Presents CIs for all basic measures reported	56%	96/172
Handling of Continuous Outcomes (N=110)		
Distribution of index test result shown by gold standard result	47%	
Explanation of choice of cut points[a]	52%	
Loss function described (relative value of false positive vs false negative)	6%	
ROC curves provided	66%	
ROC curve is square	68%	50/73
ROC curve shows key cutpoints	16%	12/73

ROC indicates receiver operating characteristics.

[a]Item is in STARD checklist.

Results We identified 186 articles in 20 journals (1 journal had no diagnostic papers, and 1 journal only had 6 in the 5-year period). In only 40% of cases was the title sufficient to identify the article. Only 10 of these 20 journals' Instructions for Authors refer to STARD. Data for selected key findings are shown in **Table 14**.

Conclusions While only 9% of articles stated an a priori success threshold, 98% made claims about the utility of the test. This is akin to stating that a randomized trial was positive or demonstrated efficacy without specifying a clinically important difference. We have identified areas for which the conduct and reporting of studies of diagnostic test performance could be improved. These data could be used by the STARD group when revising the guideline. Reporting could also be improved by convincing journals to endorse and follow STARD, since half of these high-impact journals have not yet done so.

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Identifying Barriers to Uptake and Implementation of CONSORT

Larissa Shamseer,[1,2] Laura Weeks,[3] Lucy Turner,[1] Sharon Straus,[4] Jeremy Grimshaw,[1,2] David Moher[1,2]

Objective To describe the development of a behavior-change intervention to improve implementation of the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Design A systematic approach to intervention development, accounting for theory, evidence, and practical issues, was employed. Development consisted of the following steps: (1) Identify the problem and stakeholders to be targeted. (2) Determine which barriers and facilitators need to be addressed through a series of semistructured interviews with trial authors and journal editors and a survey of journal editors. Thematic content analysis was used to group interview data into the 12 domains of the theoretical domains framework (TDF); survey data were summarized using descriptive statistics. (3) Identify intervention components (mapped relevant theoretical domains to established behavior change techniques guided by evidence and experts).

Results Six editors of journals that endorse CONSORT, 1 editor of a nonendorsing journal, and 10 authors of trials submitted to *Implementation Science* and the *Canadian Medical Association Journal* were interviewed. Seventy-eight journal editors (27.6% response rate) completed the survey. Only 13% of CONSORT-endorsing journals (n=56) require that peer reviewers check for CONSORT adherence, and only 35.3% indicate using CONSORT to determine whether a trial should be published. Eighty-one percent of editors expressed support for an electronic CONSORT tool, and 59% wanted educational tutorials about CONSORT. Based on our findings, the following TDF domains and behavior change strategies have been identified as key target areas moving forward: knowledge: provision of CONSORT documents and evidence of CONSORT impact; skills: development of training materials and webinars about how to use CONSORT; beliefs about consequences and environmental context and resources: development of an electronic tool to facilitate compliance by authors and for editors/reviewers; motivations and goals: providing assessments on the completeness of trial reporting at individual journals to demonstrate need for improvement; social influence: use of social media to connect with and recruit key stakeholders to disseminate CONSORT information.

Conclusions A more active approach than previously used is needed to ensure CONSORT implementation by authors and journal editors and peer reviewers. The identified interventions should be developed, implemented, and evaluated.

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WebCONSORT Impact of Using a Web-Based Tool to Improve the Reporting of Randomized Trials: A Randomized Controlled Trial

Sally Hopewell,[1,2] Isabelle Boutron,[2] Douglas G. Altman,[1] David Moher,[3] Victor Montori,[4] Virginia Barbour,[5] David Schriger,[6] Philippe Ravaud[2]

Objective The CONSORT statement is an evidence-based guideline for reporting clinical trials. In addition, a number of extensions have been developed that specify additional information for more complex trials. The aim of this study is to evaluate if a simple web-based tool (WebCONSORT, which incorporates a number of these different extensions) improves the completeness of reporting of randomized trials published in biomedical publications.

Design We are conducting a multicenter randomized trial. Journals (n=435) that endorse the CONSORT statement (ie, referred to in Instruction to Authors) but do not actively implement it (ie, require authors to submit a completed CONSORT checklist) have been invited to participate. Authors of participating journals are requested, at the manuscript revision stage, to use the web-based tool to improve the reporting of their randomized trial. Authors (n=302) registering to use the tool are randomized (using centralized computer generated randomization) to intervention or control. Authors and journal editors are blinded to the allocation. In the intervention group, authors are directed to the WebCONSORT tool. The tool allows authors to obtain a customized CONSORT checklist and flow diagram specific to their trial design (eg, noninferiority trial, pragmatic trial, cluster trial) and type of intervention (eg, pharmacological or nonpharmacological). The checklist items and flow diagram should then be reported in the manuscript and the completed checklist submitted to the journal along with the revision. In the control group, authors are directed to a different version of the WebCONSORT tool. This version of the tool includes the flow diagram but not the main checklist or elements relating to CONSORT extensions. The flow diagram should then be

reported in the manuscript and submitted to the journal along with the revision. The main outcome measure is the proportion of poorly reported CONSORT items (initial and extensions) reported in each article.

Results Randomization commenced on March 25, 2013, and, as of June 13 2013, 59 journals have agreed to participate.

Conclusion This randomized trial is still open to recruitment and prelimentary findings will be presented.

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POSTPUBLICATION ACCESS, DISSEMINATION, AND EXCHANGE

Stability of Internet References in General Medical Journals

Paula A. Rochon,[1,2] Wei Wu,[2] Jerry H. Gurwitz,[3] Sunila R. Kalkar,[4] Joel Thomson,[5] Sudeep S. Gill[2,6]

Objective To evaluate the stability of Internet references over time that were used in leading general medical journals.

Design We identified all original contributions published in 5 leading peer-reviewed general medical journals published in print and online (*Annals of Internal Medicine, BMJ, JAMA, Lancet,* and *New England Journal of Medicine*) and a leading online-only general medical journal (*PLOS Medicine*) published at 2 time points (January 2005 and January 2008). We followed the sample prospectively and determined the number and percent of the Internet references that remained accessible after 5 years (from November 2008 to March 2013).

Results We identified 68 Internet references in the 2005 publications (n = 89) and 86 Internet references in the 2008 publications (n=76) (**Table 15**). Over a 5-year period, the rate of functional Internet references decreased from 51% to 37% in articles published in 2005 and decreased from 78% to 44% in articles published in 2008. We also evaluated the overall sample (2005 and 2008 articles) in 2013; the rate of functional Internet references was 37% for the 5 journals published in print and online and 59% for the online-only journal (*P*=.03). Among the Internet references cited in the Methods section, only 30% (95% CI: 20%-43%) remained accessible. The Internet references in other sections (Introduction, Results, or Discussion/Comment) had a significantly higher accessibility rate (47%, 95% CI, 37%-57%, *P* =.04). Commercial Internet references also had a higher accessibility rate (61%, 95% CI, 41%-78%), compared to government Internet references (39%, 95% CI, 27%-52%) and noncommercial organization Internet references (36%, 95% CI, 27%-48%).

Conclusions The use of Internet references in medical journals has increased, while the stability of Internet references has deceased substantially over time. This decline was most pronounced in the Methods section of articles, where retention of the exact information on study methodology as originally cited may be most crucial to permit subsequent confirmation.

Table 15. Description of Internet References

Characteristic	No. (%)		
	January 2005	January 2008	Overall
Original investigations	89	76	165
Total No. of references	2510	2662	5172
Internet reference identification			
Internet reference found from the reference list	52	66	118
Internet reference embedded in the text	16	20	36
Total Internet references	68 (2.7)	86 (3.2)	154 (3.0)
Section of the article when Internet references cited			
Introduction	26(38)	23(27)	49(32)
Methods	18(26)	38(44)	56(36)
Results	6(9)	5(6)	11(7)
Discussion	17(25)	17(20)	34(22)
Type of Internet reference			
Government	17(25)	37(43)	54(35)
Noncommercial organization	38(56)	39(45)	77(50)
Commercial	13(19)	10(12)	23(15)
Type of journal			
Journals published in print and online	58(85)	67(78)	125(81)
Online-only journal	10(15)	19(22)	29(19)
Accessibility of Internet reference			
Accessible in November 2008 [time between publication and assessment]	35(51) [4 years]	67(78) [1 year]	102(66)
Accessible in July 2009 [time between publication and assessment]	35(51) [5 years]	61(71) [2 years]	96(62)
Accessible in February 2011 [time between publication and assessment]	31(46) [6 years]	49(57) [3 years]	80(52)
Accessible in February 2012 [time between publication and assessment]	30(44) [7 years]	42(49) [4 years]	72(47)
Accessible in March 2013 [time between publication and assessment]	25(37) [8 years]	38(44) [5 years]	63(41)

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Electronic Culling of the Clinical Research Literature: Filters to Reduce the Burden of Hand Searching

Nancy L. Wilczynski, K. Ann McKibbon, R. Brian Haynes

Objective To facilitate the transfer of new, valid, relevant knowledge into clinical practice, research staff in the Health Information Research Unit (HiRU) at McMaster University have created a health knowledge refinery (HKR). The HKR begins with critical appraisal of original and review studies in 122 top clinical journals and leads to the creation of the McMaster PLUS (MacPLUS) database. The time and resources to critically appraise the literature are substantial. We determined if Clinical Queries search filters for large bibliographic databases could be modified to electronically cull the clinical research literature to reduce the burden of hand searching.

Design The Clinical Queries (search filters available for use in PubMed) were modified to include only text words and a NOT string to exclude irrelevant content. A retrospective database of all content indexed in the 122 journals was created by searching MEDLINE via PubMed for a 17-month period. We tested the modified Clinical Queries in this retrospective database to determine if articles contained in the MacPLUS database were retrieved by the modified Clinical Queries.

Results A total of 66,939 articles were downloaded from PubMed for the 122 journals over 17 months of publishing, May 1, 2010, to September 30, 2011. This is the number of articles that HiRU staff would need to review over 17 months (average of 3,938 articles per month—at a time estimate of 92 hours per month). Of these 66,939 articles 3,701 (5.5%) met our criteria for the MacPLUS database; 53 articles were missed. Review of the content of the 53 missed articles showed that the research evidence was redundant and/or of limited relevance for clinical application. Given prior validation of the search filters, results are shown in **Table 16** using all articles rather than showing the results for the development and validation data sets. Use of the new filters reduced manual processing time by 55%.

Conclusion Search filters can be used to electronically cull the clinical research literature to reduce the burden of hand searching.

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Letters and Comments Published in Response to Research: Whither Postpublication Peer Review?

Margaret A. Winker

Objective To describe features of postpublication peer review published in journals, comparing frequency, features, and accessibility of letters and comments.

Design The first 20 research articles published in 2012 in each of the 8 ICMJE member journals published in English plus *PLOS Medicine* were evaluated to determine whether letters or comments had been published; access, characteristics, and interval to publication; and whether links to other types of postpublication peer review were provided.

Results Eight journals permitted letters and 4 permitted comments on all article types (**Table 17**). Five journals published any letters and 3 published any comments in response to the articles. Three journals published no letters or comments in response to any of the articles. Of the 8 journals that permitted letters, 31 (19%) of 160 articles had any letters published. Of the 5 journals that published any letters, 31 (31%) of 100 articles had any letters published. Of the 4 journals that permitted comments, 23 (29%) of 80 articles had any comments. Of the 3 journals that published any comments, 23 (38%) of 60 research articles had comments. Eighty percent (144 of 180) of articles had no letters or comments posted. The mean time from publication of the article to letters was 15 weeks; comments were

Table 16. Results of Filtering the Content of 122 Top Clinical Journals

No. of Articles to Review Prior to Filtering (17-mo Total –per mo)	Time to Review Before Filtering (hr/mo)	No. of Articles to Review After Filtering (17-mo total – per mo)	Time to Review After Filtering (hr/mo)	No. of PLUS Articles Found (17-mo total)	No. of PLUS Articles Missed (17-mo total)
66,939 3,938	92.0	30,174 1,775	41.5	3,701	53

Table 17. Postpublication Peer Review Frequency, Features, and Accessibility for 8 Journals

Characteristics	*Ann Intern Med*	*BMJ*	*Chin Med J*	*JAMA*	*Lancet*	*NEJM*	*N Z Med J*	*PLOS Med*	*Rev Chil Med*
Permits letters	X	X	X	X	X	X	X		X
Permits comments on all articles	X	X						X	
No. (%) articles with any journal PPPR	8 (40)	14 (70)	0 (0)	9 (45)	3 (15)	7 (35)	0 (0)	4 (20)	0 (0)
Time from article to PPPR publication (mean unless otherwise specified)	letters: 21/wk; 1 d - 5 mo	letters: 6/wk; comments: 1 d - 6 mo	NA	15 wk	17 wk	12 wk	NA	3 d - 6 wk	NA
Author replies to PPPR, no. (%)	letters: 7 (100%); comments: 4 (80)	letters: 3 (50%); comments: 4 (31)	NA	letters: 9 (100)	letters: 3 (100)	letters: 7 (100)	NA	comments: 1 (25)	NA
Article links to journal PPPR		X	NA		X	X	NA	X	NA
Access rules same for article and PPPR		X	NA			X	NA	X	NA
Article links to nonjournal PPPR								X	

NA indicates not applicable; PPPR, postpublication peer review.

published from 1 day to 6 months after the article was published. All journals publishing letters or comments included conflict of interest disclosures. Letters were more likely than comments to include author responses. All letters and some comments included references. Four journals linked articles to journal-based postpublication peer review; for 3 journals that did not link to related letters, letters could be identified only via journal or PubMed search. Three journals had different access rules for articles and letters. One journal linked articles to nonjournal postpublication peer review.

Conclusions Most research articles had no postpublication peer review letters or comments published in the journal. Some journals did not link to postpublication peer review letters or comments from the article; only 1 journal linked to nonjournal postpublication peer review. Some journals used different access rules for articles and postpublication peer review. Postpublication peer review needs to be substantially improved to live up to its potential for helping readers assess study quality and impact.

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Likes, Shares, and Tweets: The Growing Role of Social Media at a General Medical Journal

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Objective Many medical journals now have a presence on Facebook and Twitter, yet the experience of a general medical journal with these social media sites has yet to be described in the literature.

Design We sought to characterize the interactions of Facebook and Twitter users with a large, weekly general medical journal, the *New England Journal of Medicine* (*NEJM*). We obtained data from NEJM.org, the *NEJM* Facebook webpage, and the *NEJM* Twitter feed for usage between January 1, 2012, and December 31, 2012.

Results Facebook has become sixth among all websites as a source of referrals to NEJM.org with a total of 206,191 visits referred during 2012. As of December 31, 2012, 359,006 unique Facebook users had "Liked" the *NEJM* Facebook page, representing a combined network of 83 million friends. During the course of 2012, *NEJM* posted 727 times on its Facebook wall, and these posts were seen by 32,660,674 users. Medical quizzes received the most comments (mean, 130 vs 55 for all other posts; $P<.001$), but journal content posts received higher numbers of shares and likes. Posts containing images received more comments than those without images (65 vs 27, $P<.001$) as well as more shares (68 vs 31; $P<.001$) and more likes (242 vs 123; $P<.001$). However, posts without images actually directed more traffic to the NEJM.org site than those with images (142 vs 23 click-throughs; $P<.001$). *NEJM* Twitter followers doubled from 47,500 to 93,000 over the course of 2012. By December 2012, Twitter ranked tenth overall in sources of web traffic to NEJM.org, bringing more than 16,000 visitors that month. Tweets about research study results were retweeted more often than other types of tweets (29.9 vs 19.3, $P<.0001$).

Conclusions Facebook and Twitter have proven to be important outlets for dissemination of journal content to a large, worldwide audience. The reach of *NEJM* through these outlets has grown substantially over the past year, and both are driving additional traffic to the journal's website. Further research will explore how medical journals can use Facebook, Twitter, and other sources of social media to connect more effectively with readers in the digital age.

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