Conclusion While the numbers in each category are small, and therefore do not warrant statistical analysis and should be interpreted with caution, apart from plagiarism and unethical editorial decisions, which appear to have increased, we observed no clear patterns in the types of problems presenting to COPE since 1997.

[1]*Lancet*, London, UK; [2]Committee on Publication Ethics (COPE); [3]Sideview, 19 Station Rd, Princes Risborough, HP27 9DE UK, e-mail: liz@sideview.demon.co.uk

FRIDAY, SEPTEMBER 11

Publication Pathways

Predictors of Time to Publication of Manuscripts Rejected by Major Biomedical Journals

Kirby Lee,[1] Nicholas Lehman,[2] I'Alla Brodie,[3] and Lisa Bero[1]

Objective To evaluate publication rates and predictors of time to publication for manuscripts rejected by major biomedical journals.

Design Cohort study of 1008 manuscripts reporting original research submitted for publication and subsequently rejected at 3 major biomedical journals (*BMJ*, *Lancet*, and *Annals of Internal Medicine*) during 2003-2004. Our main predictor of publication was statistical significance of results ($P < .05$) reported for the primary outcome. We also abstracted manuscript characteristics including study design, sample size, funding source, and whether the manuscript was outright rejected vs rejected after external peer review. The primary outcome of our study was subsequent publication of the rejected manuscripts. We determined publication status and time from rejection to publication in the medical literature by searching PubMed, Cochrane Library, and the Cumulative Index for Nursing and Allied Health Literature through June 30, 2008 (minimum follow-up time of 4.3 years). Predictors of time to publication were analyzed using multivariable Cox proportional hazards regressions. All analyses were planned a priori.

Results Seventy-six percent (767) of manuscripts were published (median, 1.25 years, range, 0.01-5.32 years). The majority of manuscripts were published in specialty journals (85%, 654/767) with lower impact factors than the original rejecting journal. Manuscripts were more likely to be published if they had larger sample sizes and less likely if they did not disclose a funding source or did not report results using statistical tests for comparisons, particularly after 1.25 years from initial rejection (**Table 6**).

Conclusions A quarter of manuscripts initially rejected by major biomedical journals remained unpublished. Although some methodological characteristics and disclosing the funding source were associated with publication, articles with statistically significant results were not more likely to be published.

[1]University of California, San Francisco, Clinical Pharmacy, 3333 California St, Suite 420, San Francisco, CA 94118, USA, e-mail: leek@pharmacy.ucsf.edu; [2]Colby College, Waterville, ME, USA; [3]San Diego State University, San Diego, CA, USA

Table 6. Multivariable Predictors of Time to Publication (N = 902)[a]

Characteristic	Hazard Ratio (95% CI)	*P* Value
Statistical significance of results (early, < 1.25 years after rejection)		
Statistically significant	Reference	
Not statistically significant	1.27 (0.92-1.76)	.15
No statistical tests[b]	1.01 (0.77-1.32)	.96
Statistical significance of results (late, > 1.25 years after rejection)		
Statistically significant	Reference	
Not statistically significant	0.74 (0.49-1.12)	.16
No statistical tests[b]	0.68 (0.51-0.91)	.008
Study design		
All other designs	Reference	
RCT	1.08 (0.85-1.37)	.55
Systematic review	1.77 (0.91-3.45)	.095
Sample size		
< 100	Reference	
101-703	1.08 (0.89-1.30)	.44
>703	1.28 (1.06-1.54)	.011
Outright rejection, no external peer review from initial journal		
Yes vs no	0.91 (0.76-1.08)	.28
Funding source		
Nonindustry	Reference	
Any industry	0.87 (0.69-1.10)	.25
Not disclosed	0.66 (0.55-0.78)	<.001

[a]106 manuscripts did not report a sample size. Statistical significance of results estimated for early and late time periods due to nonproportionality.
[b]Studies reporting no formal statistical tests, descriptive statistics only, or qualitative research.

Publication of Research Reports After Rejection by the *New England Journal of Medicine* in 2 Time Periods

Michael Bretthauer, Pam Miller, Edward W. Campion, and Jeff Drazen

Objective In the past 2 decades, the number of peer-reviewed medical journals that publish original research reports has increased. We compared the subsequent publication of original research manuscripts after rejection at a major general medical journal, the *New England Journal of Medicine*, with an acceptance rate of less than 10%. Data were obtained for both 1995 and 2003.

Design All original research manuscripts rejected after external peer review at the index journal during the calendar years 1995 and 2003 were identified from our electronic databases. All manuscripts were tracked for subsequent publication in a medical or scientific journal by searching for similar titles and authors in PubMed. Searches were performed between November 25, 2008, and January 30, 2009, for the 1995 manuscripts. For the 2003 manuscripts, searches were completed in the first week of February 2009. Descriptive statistics were computed by the use of SPSS 15.0.

Results Of 1423 manuscripts rejected in 1995, we identified 1273 that were subsequently published (89.5%), as compared to 1040 of 1205 (86.3%) for those in 2003. The manuscripts were published in 384 different journals in 1995, as compared to 319 in 2003. The median time from rejection by the index journal to eventual publication in another journal was 437 days (interquartile range [IQR]: 313-652 days) in 1995 vs 398 days (IQR: 286-564 days) in 2003. **Table 7** shows the 5 types of journals that published the papers after rejection at the index journal for the 2 time periods.

Table 7. Eventual Publication by Other Journals After Initial Rejection

	1995	2003
Type of Journal	No. of Reports (%)	No. of Reports (%)
General medical journals	205 (16.1)	189 (18.2)
General pediatric journals	46 (3.6)	33 (3.2)
Basic science journals	39 (3.2)	21 (2.0)
Specialty journals	146 (11.5)	101 (9.6)
Subspecialty journals	837 (65.8)	696 (66.9)
Total	1273 (100)	1040 (100)

Conclusions The vast majority of research manuscripts that are rejected by a general medical journal after peer review are published elsewhere. However, there is substantial delay in this process. The time from rejection at the index journal to publication elsewhere declined only slightly from 1995 to 2003.

New England Journal of Medicine, 10 Shattuck St, Boston, MA 02115-6094, USA; e-mail: mbretthauer@nejm.org

An Evaluation of Time to Publication for Randomized Trials Submitted to the *BMJ*

Sara Schroter,[1] Douglas G. Altman,[2] and John P. A. Ioannidis[3]

Objective To evaluate the publication fate of randomized controlled trials (RCTs) submitted to the *BMJ* and to understand how many and which trials remain unpublished a long time after submission.

Design We evaluated all 660 reports of RCTs submitted to the *BMJ* between January 1, 1998, and December 31, 2001. We identified the published articles or, if we could not locate any published reports, we contacted the authors.

Results We found that 602 of 660 RCTs (91%) were published: 150 (23%) in the *BMJ* and 452 (68%) in other journals. All except 6 of the trials published elsewhere were in journals with lower impact factor than *BMJ* (median, 2.13; interquartile range [IQR], 1.53-3.03). The median time from submission to publication was 1.36 years (IQR, 0.89-2.15; and 1.30, IQR, 0.87-1.91, excluding the 40 unpublished trials). About 25% of the RCTs submitted to the *BMJ* remained unpublished for 2 or more years after submission. Excluding the *BMJ*-published papers, a higher impact factor was associated with more rapid publication (HR, 1.08 per point, P = .002). Unpublished trials were significantly less likely to go to external review, have external reviews returned, and reach the *BMJ* editorial "hanging" committee than published trials but were not significantly different in their country of origin. Of the 18 unpublished trials for which authors replied to our survey, 3 authors were still trying to get their paper published, at least half were said to have significant results, 3 said that negative results were perceived as a main reason for nonpublication, and 8 were discouraged by rejections.

Conclusions Results of all RCTs should be publicly available since they are level I evidence. The large majority of the trial reports submitted to the *BMJ* get published in time, but about 25% remained unpublished after 2 years. Among those remaining unpublished, negative results are not perceived as a prime reason for failure to publish.

[1]BMJ Editorial, BMA House, Tavistock Square, London WC1H 9JR, UK, e-mail: sschroter@bmj.com; [2]Centre for Statistics in Medicine, Wolfson College Annexe, Oxford, UK; [3]Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece

Complexity of Peer Review Evaluations: Twelve-Year Prospective Study on 424 Submitted Papers to a Specialized Journal

Francine Kauffmann,[1,2] Klaus Rabe,[3] Béatrice Faraldo,[1,2] Hélène Tharrault,[1,2] Jean Maccario,[1,2] and Alan R. Leff[4]

Objective To classify reviewer scores and assess whether scores predict the career of a manuscript, beyond the initial decision of acceptance or rejection.

Design Included manuscripts were edited by 1 associate editor between 1994 and 1999. Subsequent publication through December 2008 was searched for rejected manuscripts. For all published papers, citations were assessed from their publication date through December 2008. Outcomes studied were publication (initial journal [n = 173] or another journal [n = 187]), impact factor for the year of publication, citations (Web of Science). Reviewer scores (1-5) regarding "originality," "scientific importance," "adequacy of methods," "brevity/clarity," and "adequacy of interpretation" were analyzed as predictors. Analyses on citation rates (geometric mean = 26, range, 1-441) conducted on 329 papers were adjusted for duration of follow-up after publication (9.9±1.6 years; P < .001) and impact factor (66 journals, 3.6±1.7; P < .0001).

Results Principal component analysis on reviewer scores separated "science" (methods, interpretation) and "journalism" (originality, importance). Two hundred fifty-one papers were rejected (43 without a reject recommendation of at least 1 reviewer) and 173 accepted (13 with a reject recommendation of 1 reviewer). For acceptance or rejection, tree discriminant analysis was performed as all scores were highly predictive of outcome: "interpretation" was the first criteria, followed by "methods" and "scientific importance." Discriminant analyses showed that every publication after rejection (75%) was driven by "originality" and early (within 2 years after rejection, n = 140 [75%]) vs late publication by "methods." Reviewer "scientific importance" score was the major determinant for all citations (P = .01), in the first 2 years (P < .01), and after (P = .02). In the first 2 years, poor "interpretation" increased citations (P = .03). Results were similar when restricting the analysis to the 173 accepted papers.

Conclusions Peer review evaluation can capture various aspects regarding submitted papers, which differentially predicts acceptance, publication of rejected papers, and citations rates. This is an issue relevant for authors, reviewers, editors, and readers.

[1]INSERM U780, 16 avenue PV Couturier, Villejuif, 94807 France, e-mail: francine.kauffmann@inserm.fr; [2]Université Paris-Sud, IFR69, Villejuif, France; [3]Department of Pneumology, Leiden University Medical Center, Leiden, the Netherlands; [4]Department of Medicine, University of Chicago, Chicago, IL, USA

Publication Bias

Testing for the Presence of Positive-Outcome Bias in Peer Review: A Randomized Controlled Trial

Gwendolyn B. Emerson,[1] Richard A. Brand,[2] James D. Heckman,[3] Winston J. Warme,[1] Fredric M. Wolf,[4] and Seth S. Leopold[1]

Objective To the extent positive-outcome bias exists, it risks undermining evidence-based medicine. We designed a stratified randomized block design trial to test the hypothesis that a significantly greater percentage of peer reviewers for 2 orthopedic journals would recommend publication of a "positive" outcome report compared with a "no-difference" outcome report of an otherwise identical fabricated randomized controlled trial (RCT).

Design We fabricated 2 versions ("positive" and "no difference") of a well-designed, CONSORT-conforming, amply-powered, multi-institutional, blinded RCT including 3308 patients evaluating dosage and timing of perioperative antibiotics. The versions were identical except for the direction of the finding on the principal study endpoint (fewer surgical site infections in the "positive" version; no difference in surgical site infections in the "no-difference" version). Both versions were sent to peer reviewers by *Journal of Bone and Joint Surgery (JBJS)* and *Clinical Orthopaedics and Related Research (CORR)*. The 209 reviewers were randomly allocated to either "positive" or "no-difference" versions, with randomization stratified by journal. Reviewers were informed that a study was ongoing but were not informed of the research question nor that they were reviewing the "test" manuscript.

Results At *JBJS*, the "positive" manuscript was significantly more likely to be recommended for publication than the "no-difference" manuscript (98% vs 71%; odds ratio [OR], 20.4; 95% confidence interval [CI], 2.6-161.7). At *CORR*, the difference was not statistically significant (97% of "positive" manuscripts recommended for publication vs 90% of "no difference" manuscripts; OR, 3.4; 95% CI, 0.6-18.2).

Conclusions Results suggest positive-outcome bias is variably present during peer review of orthopedic manuscripts submitted for publication, as it was present for 1 journal but not the other. Many of the 209 reviewers have regularly reviewed for both journals; we speculate the difference between journals may relate to historical perceptions about the 2 journals. Journal editors may consider providing reviewers with more explicit guidelines for review of "no-difference" manuscripts.

[1]Department of Orthopaedics and Sports Medicine, University of Washington, Box 356500, 1959 NE Pacific St, Seattle, WA 98195, USA, e-mail: leopold@u.washington.edu; [2]*Clinical Orthopaedics and Related Research*, Philadelphia, PA, USA; [3]*Journal of Bone and Joint Surgery*, Needham, MA, USA; [4]Department of Medical Education and Biomedical Informatics, University of Washington, Seattle, WA, USA

Composite Outcomes Can Be Misleading

Gloria Cordoba,[1] Lisa Schwartz,[2] Steven Woloshin,[2] Harold Bae,[2] and Peter Gøtzsche[1]

Objective A composite outcome combines several individual outcomes into 1 main outcome. It increases statistical power but can be misleading since the result may be driven by less important components. We compared the composite outcome to the most clinically important outcome.

Design Systematic review of parallel-group randomized clinical trials published in 2008 reporting a binary composite primary outcome. Two independent coders abstracted the data and a third observer, blinded to the results, selected the most important component.

Results Of 43 eligible trials, 36 were included (3 were excluded because no component was clearly most important, 4 because of insufficient or inconsistent data). Twenty-seven trials (75%) were about cardiovascular topics, and 25 trials (69%) were either entirely or partly industry funded. Composite outcomes had a median of 3 components (range, 2-9). Death (or cardiovascular death) was the most important component in 30 trials. There were 15,531 events (14% of patients) for the composite outcome and 4,513 (4%) for the most important component. The point estimate for the risk ratio for the composite outcome was equally often lower as larger than that for the important component, and it differed by more than 20% from it in 14 trials (39%). Statistically significant results were reported in 11 trials for only the composite outcome; in 2 trials for only the most important outcome (death or cardiovascular death); and in 1 trial for both but in opposite directions, as the effect was beneficial for the composite of death or nonfatal myocardial infarction and harmful for death.

Conclusions Composite outcomes may exaggerate perceptions of how well interventions work and, conversely, can hide effects on mortality. The pivotal assumption that the effect of the intervention should be similar for each of the components is often not met.

[1]Nordic Cochrane Centre, Rigshospitalet, Blegdamsvej 9, Dept 7112, DK-2100 Copenhagen, Denmark, e-mail: pcg@cochrane.dk; [2]Dartmouth Institute for Health Policy, Dartmouth Medical School, Hanover, NH, USA

Reporting Biases and Publication Strategy for Off-Label Indications: A Potent Mix

S. Swaroop Vedula,[1] Ilyas Rona,[2] Palko Goldman,[2] Thomas Greene,[2] and Kay Dickersin[1]

Objective To describe reporting practices in clinical trials sponsored by Parke-Davis/Pfizer in the context of their use of a "publication strategy" to market gabapentin for off-label indications.

Design One of us (K.D.) was provided internal company documents by plaintiffs' lawyers as part of legal action against Pfizer. We compared protocols with internal research reports and publications to identify reporting biases. We also examined internal company marketing assessments to identify whether a "publication strategy" or an "indication strategy" (ie, obtaining Food and Drug Administration approval) was recommended. One author (S.V.) extracted data relevant to reporting biases and another (K.D.) verified. K.D. signed an agreement in August 2008 agreeing to be bound by a protective order entered in pending litigation against Pfizer, which limits disclosure of confidential discovered information unless such information is ordered unsealed by the court, or the claim of confidentiality is waived by the claiming party. Through communications with counsel involved in the litigation occurring between August and October 2008, Pfizer agreed to waive any confidentiality claims concerning documents reviewed as part of K.D.'s expert report. As a result, all of the documents reviewed for this study have had their confidentiality claims waived.

Results We examined 20 clinical trials of gabapentin for 4 off-label indications included as part of the legal action: migraine prophylaxis (n = 3), bipolar disorders (n = 3), neuropathic pain (n = 8), and nociceptive pain (n = 6). Marketing assessments for 3 indications recommended a "publication strategy," and the fourth recommended multiple strategies. Each trial was associated with 1 or more reporting biases, including failure to publish efficacy results in full (11/20). In the 12 published trials, we also observed selective publication of primary (7/12) and secondary (11/12) outcomes, analyses in selected populations (5/12), possible ghost authorship (3/12), citation bias (5/12), possible time-lag bias (5/12), and a positive "spin" of the findings (8/12) (ie, a discrepancy between results and conclusions).

Conclusions Combining "publication strategy," used as a marketing tool, with biased reporting of results represents a potent mix that can create a false perception of a drug's efficacy. We propose that existence of a publication strategy should be revealed by the trial sponsor to trial participants, investigators, editors, and peer reviewers at appropriate time points, and publicly at trial registration.

[1]Johns Hopkins Bloomberg School of Public Health, Mailroom W5010, 615 N Wolfe St, Baltimore, MD 21205, USA, e-mail: svedula@jhsph.edu; [2]Greene LLP, Boston, MA, USA

Rhetoric

"Spin" in Reports of Randomized Controlled Trials With Nonstatistically Significant Primary Outcomes

Isabelle Boutron,[1,3] Susan Dutton,[1] Philippe Ravaud,[2] and Douglas G. Altman[1]

Objective The objectives of this study were to identify the nature and frequency of "spin" (ie, manipulation of the content and rhetoric of reporting to convince the reader of the likely truth of a result) in published reports of randomized controlled trials (RCTs) with nonstatistically significant primary outcome(s).

Design The Cochrane Highly Sensitive Search Strategy was used to identity reports of RCTs with a primary publication indexed in PubMed in December 2006. Articles were included if the study was a 2-arm RCT with a clearly identified primary outcome that was not statistically significant (ie, $P \geq .05$). To systematically evaluate "spin" in reports, 2 readers appraised each selected article using a pretested standardized data abstraction form developed in pilot testing performed on another sample. We used the following preliminary classification scheme to investigate the main text and abstract to assess whether authors (1) interpreted nonstatistical outcomes as if the trial were an equivalence trial; (2) emphasized nonstatistically significant outcomes showing the benefit of treatment (linguistic "spin" or other method); (3) focused on other statistically significant results such as within-group comparisons, secondary outcomes, subgroup analyses, and modified population analyses; and (4) overinterpreted safety. Any other strategies used to influence readers were also collected. All discrepancies were discussed to achieve consensus and a third reader resolved any disagreements.

Results Of the 1735 PubMed citations retrieved, 616 reports of RCTs were selected based review of the title and abstract. After screening the full text, 74 reports of 2-arm parallel trials with a primary outcome clearly identified and nonstatistically significant were selected. The full results will be presented during the Congress.

Conclusion These results will provide information on the prevalence and nature of "spin" in a representative sample of published reports of RCTs with nonstatistically significant outcomes.

[1]Centre for Statistics in Medicine, University of Oxford, Oxford UK; [2]Hôpital Bichat, Paris, France; [3]Groupe Hospitalier, Bichat-Claude Bernard, Departement d'Epidemiologie, 46 rue Henri Huchard, Paris, Cedex 18 75877 France, e-mail: isabelle.boutron@bch.ap-hop-paris.fr

Rhetoric Used in Reporting Research Results

Lisa Bero and Yolanda Cheng

Objective To identify rhetoric used to frame research results reported in drug studies and to determine if statistically significant numerical data support the claims about a drug.

Design In this observational study, we evaluated 35 published randomized controlled trials for language about a drug's effect(s). The 35 articles from 24 journals were publications of trials that had been submitted in New Drug Applications (NDAs) where there were discrepancies in conclusion between the published literature and the NDA trial report that favored the drug. For each publication, we assessed the results and conclusion sections for rhetoric that suggested that the drug was more effective or safer than the comparator. An initial group of keywords (eg, significance, statistical, clinical, more, less, effective, safe/well-tolerated) guided the extraction of rhetoric. Additionally, the statistically significant result (eg, *P* value, 95% confidence interval) was recorded if it was presented in text, tables, or figures. The rhetoric statements were grouped according to 6 categories of effect: increase/positive, decrease/negative, equivalence/consistency, safety, clinical importance, and qualifying/ambiguity. For each statement, we noted the accompanying use of the term "significance" and a statistical test.

Results The articles were published between 1993 and 2004, with 30 of 35 published after 2000. Seven of the articles had no sponsorship statement. Three of the 24 journals had an impact factor greater than 10 (range, 0-17.6). For the 35 papers assessed, 695 rhetoric statements were extracted. Forty-nine percent (338/695) of the statements of effect made were not accompanied by any mention of a statistically significant result. Fifty-one percent (357/695) of the rhetoric statements included the term "significance," where 72% (258/357) were supported by a statistical test result. The majority of the rhetoric statements were classified as increase/positive effect statements, with 84% (142/169) of them having an associated statistical test. Rhetoric regarding the safety of a drug was rarely supported by a statistical result (**Table 8**).

Table 8. Categorization of Rhetoric Statements

Category	No. of Rhetoric Statements	No. of Times "Significance" Used with Statement	No. of Occurrences of Statistical Test Accompanying Statement
Increase/Positive	317	169	142
Decrease/Negative	167	117	64
Equivalence/Consistency	65	10	6
Safety	96	2	1
Clinical Importance	55	36	11
Qualifying/Ambiguity	60	5	2

Conclusions Rhetoric used to frame research results in drug studies overstates the effectiveness of a drug. A limitation of our study is that we did not obtain original data and conduct our own statistical analysis. The text of result and conclusion sections should align more closely with the numerical results.

Department of Clinical Pharmacy, University of California, San Francisco, 3333 California St, Suite 420, Box 0613, San Francisco, CA 94118, USA, e-mail: berol@pharmacy.ucsf.edu

A Propaganda Index for Screening Manuscripts and Articles

Eileen Gambrill

Objective The propaganda index is designed to serve as a complement to methodological filters such as CONSORT in reviewing manuscripts and published literature. Propaganda regarding problems addressed promotes the medicalization of behaviors and feelings and hinders empirical investigation of well-argued alternative views. Predictions were as follows: (1) reading a definition of propaganda will not facilitate propaganda spotting skills, (2) use of a propaganda index will facilitate this task, and (3) methodological quality is not correlated with a measure of propaganda.

Method A propaganda index consisting of 32 items was created based on related literature. Items concerned medicalization, use of vague terms, lack of documentation for claims made, and hiding controversy. Twenty articles describing randomized controlled trials (RCTs) regarding social anxiety were selected via an Internet search. Twenty PhD-level consumers of the literature were asked to read 5 articles with authors' names and journal titles removed and to identify propaganda using a definition of propaganda as "encouraging beliefs and actions with the least thought possible." They next applied the index to each article and returned this information. One week later they were to again rate the same 5 articles using the index.

Results Review of the 5 articles by the author revealed a high rate of propaganda: 78 out of 110 opportunities. This review served as the criterion. Preliminary results for 8 participants showed that they detected between 0 and 17 indicators over all 5 articles with an average of 5 before using the index. Percentage agreement of participants with the criterion ratings on the propaganda index for all 5 articles ranged from 57% to 88% with an average of 74%. Further data regarding predictions will be presented at the conference.

Conclusion Preliminary data suggest that, without prompting, many forms of propaganda remain undetected in reports of RCTs and that detection can be increased by use of a propaganda index.

University of California at Berkeley, School of Social Welfare, 120 Haviland Hall #7400, Berkeley, CA 94720-7400, USA, e-mail: gambrill@berkeley.edu

Trial Registration

Frequency and Nature of Changes in Primary Outcome Measures

Deborah A. Zarin, Tony Tse, and Rebecca J. Williams

Objective Prespecification of outcome measures forms the basis of most statistical analyses of clinical trials. Trial registration allows for the tracking of changes to outcome measures from study initiation to eventual publication. Changes may occur any time after study initiation, though there is no standard for distinguishing important vs unimportant changes. The objective of this study was to determine the frequency and type of changes in primary outcome measures (POMs) between entries in ClinicalTrials.gov and associated publications and between initial and current registry entries.

Design We identified 75 sequential MEDLINE citations with ClinicalTrials.gov entries, generating "registry-publication pairs." Study 1 (50 pairs) compared the registry POM to outcomes in the publication. Study 2 (25 pairs) compared the publication POM to the registered outcomes. Study 3 examined changes over time for all 75 registry POMs. Each outcome measure was coded for "principality" (primary, secondary, or unspecified), domain (eg, depression), specific measure (eg, HAM-D), and time frame. Pairs were considered matches if the domain was the same. If either specific measure or time frame were not consistent, pairs were "substantively different."

Results Sixty-two of the 75 registry-publication pairs were consistent, though differences in level of specificity within pairs were observed (**Table 9**). One publication POM had been registered as a secondary outcome measure. Eight of 50 Study 1 pairs and 3/25 Study 2 pairs had substantive differences. Six of 75 Study 3 POMs changed substantively after initial registration. Forty-eight of 75 of the ClinicalTrials.gov entries were initially registered more than 3 months after the start date, with some delayed by years.

Table 9. Results of 2 Studies Characterizing Primary Outcome Measures (POMs)

	Study 1 Registry POM (n = 50)	Study 2 Publication POM (n = 25)
Index POMs Without Corresponding Outcome Measures	1	1
Index POMs With a Match[a]	49	24
Principality: Registry → Article		
Primary → Primary	38	
Primary → Secondary	0	
Primary → Unspecified	3	
Principality: Article → Registry		
Primary → Primary		20
Primary → Secondary		1
Specific Measure and Time Frame Consistent	41	21
≥1 Component Not Consistent	8	3
Specific Measure Not Consistent	4	1
Time Frame Not Consistent	5	2

[a]Two POMs were considered a match if they had the same domain (eg, pain).

Conclusions The taxonomy enabled us to categorize POM pairs. Most POM pairs were consistent based on our criteria. Our ability to detect inconsistencies was limited at times by vague registry entries or substantially delayed initial registrations. This taxonomy could be used to develop consensus criteria for tracking and communicating outcome measure changes.

National Library of Medicine, National Institutes of Health, 8600 Rockville Pike, Bldg 38A, Room 75705, Bethesda, MD 20892, USA, e-mail: dzarin@mail.nih.gov

Trial Registration Can Be a Useful Source of Information for Quality Assessment: A Study of Randomized Trial Records Retrieved From the World Health Organization Search Portal

Ludovic Reveiz,[1] An-Wen Chan,[2] Karmela Krleža-Jerić,[3] Carlos Granados,[4] Mariona Pinart,[5] Itziar Etxeandia,[6] Diego Rada,[7] Monserrat Martinez,[8] and Andres Felipe Cardona[9]

Objective We evaluated empirically whether trial registries provide useful information to evaluate the quality of randomized controlled trials (RCTs).

Methods We compared methodological characteristics of a random sample of ongoing RCTs registered in 6 World Health Organization (WHO) primary registries and ClinicalTrials.gov in 2008. As 90% of trials were provided from ClinicalTrials.gov, we ensured adequate representation across registries by including a representative sample of each registry. We assessed the reporting of relevant domains from the Cochrane Collaboration's "Risk of Bias" tool and other key methodological aspects. Two reviewers independently assessed each record.

Results A random sample of records of actively recruiting RCTs was retrieved from 7 registries using the WHO International Clinical Trials Registry Platform (ICTRP) search portal. Weighted overall proportions in the ICTRP search portal for adequate reporting of sequence generation, allocation concealment, and blinding (patient-reported outcomes and objective outcomes) were 5.23% (95% confidence interval [CI], 2.55-7.91), 1.37% (95% CI, 0%-2.76%), 8.58% (95% CI, 5.8-11.36), and 8.69% (95% CI, 5.29-12.09), respectively. Most items had insufficient or no information to permit judgment (**Table 10**). Significant differences in the proportion of adequately reported RCTs were found between registries that had specific methodological fields for describing methods of randomization and allocation concealment compared to registries that did not (random sequence generation, 74% vs 2%, $P < .001$; allocation concealment, 53% vs 0%, $P < .001$). Concerning other key methodological aspects, weighted overall proportions of RCTs with adequately reported items were as follows: eligibility criteria (81%), primary outcomes (66%), secondary outcomes (46%), follow-up duration (62%), description of the interventions (53%), and sample size calculation (1%). Final results will be presented at the Congress.

Table 10. Adequate Reporting of Sequence Generation and Allocation Concealment From the WHO ICTRP Search Portal From January 1 to December 12, 2008, by Source Registry

Registry	Random Sequence Generation, No. (%)	Allocation Concealment, No. (%)	Both (Adequate Sequence Generation and Allocation Concealment Reporting), No. (%)
Australian New Zealand Clinical Trials Registry	38/49 (78)	27/49 (55%)	26/49 (53)
Clinical Trials Registry of India	18/21 (86)	13/21 (62)	11/21 (52)
ClinicalTrials.gov	2/81 (3)	0/81 (0)	0/81 (0)
ISRCTN	2/63 (3)	0/63 (0)	0/63 (0)
Chinese Clinical Trial Register	0/6 (0)	0/6 (0)	0/6 (0)
German Clinical Trials Register	0/5 (0)	0/5 (0)	0/5 (0)
Netherlands National Trial Register	0/40 (0)	0/40 (0)	0/40 (0)
Total in the sample	60/265 (23)	40/265 (15)	37/265 (14)
Total in the ICTRP search portal (weighted)	5.23%	1.37%	

Conclusions Registries with specific methodological fields obtained more relevant quality information than those with general or coded fields. Critical appraisal of RCTs should include a search for information on trial registries as a complement to journal publications. However, the usefulness of the information will vary across registries due to variable content.

[1]Research Institute, Sanitas University Foundation, Cochrane Collaboration Branch, Av Calle 127 #21–60 cons 221, Bogota, Colombia, e-mail: lreveiz@yahoo.com; [2]Mayo Clinic, Rochester, MN, USA; [3]Knowledge Synthesis and Exchange Branch, Canadian Institutes of Health Research, Ottawa, Ontario, Canada; [4]Research Institute, National University of Colombia; [5]Department of Dermatology Research Unit for Evidence-based Dermatology, Hospital Plató,

Barcelona, Spain; [6]Clinical Epidemiology Unit, Cruces Hospital, & Osteba-Basque Office for HTA, Department of Health-Basque Country, Spain; [7]Department of Physiology, University of the Basque Country (UPV/EHU), Spain; [8]Institut de Recerca Biomèdica de Lleida (IRBLLEIDA)-Universitat de Lleida, Catalonia, Spain; [9]Grupo Oncología Médica, Instituto Catalán de Oncología, Hospital Universitario Germans Trias i Pujol, Badalona, Spain

Registration Completeness and Changes of Registered Data From ClinicalTrials.gov for Clinical Trials Published in ICMJE Journals After September 2005 Deadline for Mandatory Trial Registration

Mirjana Huic,[1,2] Matko Marušić,[2,3] and Ana Marušić[2,3]

Objective After September 2005, journals represented by the International Committee of Medical Journal Editors (ICMJE) were to publish clinical trials that are timely and adequately registered in approved registries. We assessed how well ICMJE member journals followed their own registration requirement policy.

Design We identified all reports of clinical trials with ClinicalTrials.gov registration number published by ICMJE journals from September 13, 2005, to April 24, 2008 (n = 438). For a random subset of 102 reports (*Annals of Internal Medicine* = 12/36, *BMJ* = 12/29, *Croatian Medical Journal* = 5/5, *CMAJ* = 1/1, *JAMA* = 16/100, *Lancet* = 14/88, *New England Journal of Medicine* = 42/179), we used the Archive section of ClinicalTrials.gov to analyze the completeness of minimal registration dataset and changes to the registration data elements relevant for the quality of trial reporting .

Results Of 102 trial reports, 73 were registered before and 29 after the September 2005 deadline, and 24 were registered before trial start date. At the time of registration, a number of trials had missing or misplaced data in the 20-item minimal dataset, such as specified key secondary outcomes, primary outcome, or target sample size; this number decreased at the last registration change before publication. The completeness of the registration data improved over time for most journals. Individual studies underwent changes in the registry from initial registration to publication (range, 1-38, median, 4; 95% confidence interval, 3-5 for 87 studies with 1 or more changes). A considerable number of published reports (23-78 of 102) had data items different (information either disclosed or changed) from those declared in the registration dataset (TABLE 11).

Conclusions ICMJE journals have not always fully adhered to their own registration policy. Registration quality assurance is needed for full policy implementation and transparency of clinical trials reporting in journals.

[1]Agency for Quality and Accreditation in Health Care, Zagreb, Croatia; [2]*Croatian Medical Journal*, Croatia; [3]University of Split School of Medicine, Soltanska, Split, 21000 Croatia, e-mail: marusica@mef.hr

Table 11. International Committee of Medical Journal Editors Journals With Missing Data or Information Different From Registry Data

Minimal dataset item	No. of RCTs with missing data (No. of RCTs with data provided in other registry field)[a]		No. of published RCTs with information different from registry data (n = 102)[c]
	At initial registration (n = 102)	Last change before publication (n = 85)[b]	
10. Official scientific title of the study	17	6	70
13. Intervention(s)	3 (3)	2 (3)	63
14. Key inclusion or exclusion criteria	3	2	54
15. Study type	0	0	23
16. Anticipated trial start date	17 (1)	4 (1)	31
17. Target sample size	38 (18)	32 (12)	78
19. Primary outcome	49 (40)	33 (28)	45
20. Key secondary outcomes	53 (27)	36 (24)	69

[a]Numbers in parentheses indicate the registrations where specific information from the missing field was provided in another registry field ("Detailed Description").
[b]17 trials had a single registration entry before publication.
[c]Difference from the last registration data or first registration data if there was a single registration. The difference was either disclosure of the data item missing in the registry or change in the specific content of the register record. For example, only the drug code in the "Intervention(s)" registration field was found for 7 RCTs at initial registration and for 6 RCTs at last change before publication; generic names of the drugs were disclosed in published reports.

Is Protocol Information Recorded in ClinicalTrials.gov Useful for Systematic Reviewers Relying on Conference Abstracts?

Roberta Scherer,[1] Ann Ervin,[1] JaKeisha Taylor,[2] and Kay Dickersin[1]

Objective Trial registration records could provide key protocol information on trials published only as abstracts for systematic reviewers. The Association for Research in Vision and Ophthalmology (ARVO) required trial registration for abstracts describing controlled clinical trials (RCTs) starting in 2007. The objective of this study was to evaluate the proportion of 2007, 2008, and 2009 ARVO abstracts of RCTs that had been registered and compare information provided in "registered" abstracts with that in ClinicalTrials.gov.

Design We identified abstracts either describing an RCT or providing registration information. For 2007 RCT abstracts with a valid ClinicalTrials.gov registration number, we abstracted information on study participants, intervention, sample size, and primary outcome, and compared it to similar information abstracted from ClinicalTrials.gov. We plan to include similar information from 2008 and 2009 abstracts.

Results About two-thirds of identified RCTs claimed registration (108/174 [62%] in 2007; 103/153 [67%] in 2008; and 124/170 [73%] in 2009). Fifty-two percent (56/108) of 2007 abstracts claiming registration had a valid, unique ClinicalTrials.gov registration number; 3 not registered as an RCT in ClinicalTrials.gov were excluded from further analyses. There was good agreement between the abstract and ClinicalTrials.gov record in the description of participant characteristics. Reported sample size was concordant for 6 trials, lower in 20 abstracts, and higher in 11 (37 RCTs had sample size recorded in both sources). Agreement on intervention was 77% (41/53). The primary outcome reported in the abstract matched 1 or more

primary outcomes reported in the ClinicalTrials.gov "primary outcome" field for 26 of 34 trials with an entry in that field.

Conclusions When authors fail to identify, register, and fully publish RCTs, then no protocol information beyond the abstract is available for systematic reviewers. Even if registered, information in ClinicalTrials.gov may disagree with that in the abstract. Protocols and amendments should be available at study inception to assist systematic reviewers.

[1]Johns Hopkins Bloomberg School of Public Health, Mailroom W5010, 615 N Wolfe St, Baltimore, MD 21205, USA, e-mail: rscherer@jhsph.edu; [2]Delta State University School of Nursing, Cleveland, MS, USA