Plenary Session Abstracts

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Sunday, September 10, 2017

Common Problems in Peer Review and Scientific Publication

Bias Associated With Conflict of Interest and Peer Review

The Prevalence of Conflict of Interest Disclosures in Biomedical Research

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Objective Conflict of interest disclosures are used to indicate a risk of bias in biomedical research but studies examining their prevalence are out of date or focused on narrow clinical topics. Our aim is to estimate the prevalence of conflict of interest disclosures in biomedical research across disciplines and determine article characteristics associated with higher rates of disclosure.

Design We randomly sampled articles in Medline published from January 1, 2016, to December 31, 2016, in journals following the recommendations of the International Committee of Medical Journal Editors (ICMJE). There were no language restrictions. Non–peer-reviewed articles, including letters and news stories, were excluded. We developed a coding manual to classify the reported conflicts of interest and sources of study funding based on the National Academies of Medicine definition of conflict of interest and the ICMJE disclosure form. Independently, 2 researchers piloted the coding manual on a random sample, resolving discrepancies through verification and discussion.

Results After sampling 1650 articles, 1002 articles met our inclusion criteria. We found that 22.9% (95% CI, 20.3%-25.6%) disclosed a conflict of interest, 63.6% (95% CI, 60.5%-66.6%) disclosed no conflicts, and 13.6% (95% CI, 11.5%-15.7%) did not include a disclosure statement (**Table 1**). Articles focused on drugs, devices, or surgical procedures were significantly more likely to include authors with reported conflicts of interests (71 of 267 [26.6%]) than other empirical articles (64 of 415 [15.4%]) (difference, 11.2%; 95% CI, 3.3%-19.1%). Disclosure statements were inconsistent: we noted 130 different ways of stating there were no conflicts of interest, ranging from "None declared" to "Nothing to declare" to "No relevant conflicts" to statements 63 words long. Furthermore, 90 of 228 articles (39.4%) with statements contained extraneous biographical information not addressing conflicts of interest.

Conclusions Many articles published in journals following the ICMJE recommendations fail to include disclosure statements. Just more than 1 in 5 biomedical articles report a relevant conflict of interest, which is generally consistent with a 2003 review that found that 23% to 28% of academic investigators receive funding from industry, suggesting this may be an underestimate. In current practice, conflict of interest statements are unstructured and inconsistently reported, precluding automatic extraction and analysis of conflict of interest statements.

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Table 1. Prevalence of Author Conflict of Interest (COI) Disclosures

	Author COI Proportion, No. (%) (95% CI by Clopper-Pearson Exact)		
Prevalence	Yes	No	Missing
Empirical articles	135 of 682 (19.8%) (16.9-23.0)	462 of 682 (67.7%) (64.1-71.2)	85 of 682 (12.5%) (10.1-15.2)
Drug-focused	39 of 124 (31.5%) (23.4-40.4)	69 of 124 (55.6%) (46.5-64.6)	16 of 124 (12.9%) (7.6-20.1)
Device-focused	27 of 121 (22.3%) (15.2-30.8)	75 of 121 (62.0%) (52.7-70.7)	19 of 121 (15.7%) (9.7-23.4)
Both drug and device	5 of 22 (22.7%) (7.8-45.4)	16 of 22 (72.7%) (49.8-89.3)	1 of 22 (4.5%) (0.1-22.8)
Neither drug nor device	64 of 415 (15.4%) (12.1-19.3)	302 of 415 (72.8%) (68.3-76.8)	49 of 415 (11.8%) (8.9-15.3)
Commentaries, editorials, and narrative reviews	91 of 290 (31.4%) (26.1-37.1)	150 of 290 (51.7%) (45.8-57.6)	49 of 290 (16.9%) (12.8-21.7)
Systematic reviews and meta-analyses	3 of 30 (10.0%) (2.1-26.5)	25 of 30 (83.3%) (65.3-94.4)	2 of 30 (6.7%) (0.8-22.1)
All articles	229 of 1002 (22.9%) (20.3-25.6)	637 of 1002 (63.6%) (60.5-66.6)	136 of 1002 (13.6%) (11.5-15.9)

Conflict of Interest Disclosures: Dr Bero is a Peer Review Congress Advisory Board Member but was not involved in the review or decision for this abstract.

The Influence of Industry Funding and Other Financial Conflicts of Interest on the Outcomes and Quality of Systematic Reviews

Camilla Hansen,[1,2] Andreas Lundh,[1,3] Kristine Rasmussen,[2] Tove Faber Frandsen,[4] Peter C. Gøtzsche,[2] Asbjørn Hróbjartsson[1]

Objective Funding of systematic reviews by drug and device companies and other financial conflicts of interest among authors may have an impact on how the reviews are conducted. The aim of this study was to investigate if financial conflicts of interest are associated with results, conclusions, and methodological quality of systematic reviews.

Design This is a Cochrane methodology review. We searched PubMed, EMBASE, and the Cochrane Methodology Register as well as the reference lists of included studies and Web of Science for studies citing the included studies. We included observational studies of any design that investigated samples of systematic reviews with and without industry funding or other financial conflicts of interest, published up to November 2016. For studies to be eligible, they had to investigate at least 1 of our outcomes: effect size estimates, statistically favorable results, favorable conclusions, and methodological quality. Two review authors independently extracted data and assessed risk of bias in relation to study inclusion, data extraction, and comparability of the investigated systematic reviews. We reported our findings on effect size estimates qualitatively. We calculated pooled risk ratios (RRs) with 95% confidence intervals for statistically favorable results, favorable conclusions, and methodological quality.

Results Nine observational studies with a total of 983 systematic reviews of drug studies and 15 systematic reviews of device studies were included. Effect size estimates and frequency of statistically favorable results were similar between systematic reviews with and without financial conflicts of interest (**Table 2**). Systematic reviews with financial conflicts of interest more often had favorable conclusions compared with systematic reviews without financial conflicts of interest (RR, 1.96; 95% CI, 1.23-3.13).

Conclusions Systematic reviews with financial conflicts of interest related to drug and device companies more often have favorable conclusions and to some degree lower methodological quality compared with systematic reviews without financial conflicts of interest. It remains unclear whether financial conflicts of interest have an impact on the results.

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Table 2. Systematic Reviews With Financial Conflicts of Interest Compared With Systematic Reviews Without

Outcome	Comparative Risk		Effect Estimate
	Industry n/N (%)	Nonindustry n/N (%)	
Results			
Estimated effect sizes[a]	NA	NA	*z* Score: 0.46 (*P* = .64)
Statistically favorable results	27 of 49 (55)	49 of 75 (65)	RR, 0.84 (95% CI, 0.62-1.14)
Favorable conclusions	163 of 200 (82)	93 of 199 (47)	RR, 1.96 (95% CI, 1.23-3.13)
Methodological quality[b]			
Appropriate search methods	94 of 145 (65)	124 of 157 (79)	RR, 0.72 (95% CI, 0.49-1.06)
Appropriately selected studies	69 of 145 (48)	98 of 157 (62)	RR, 0.68 (95% CI, 0.44-1.06)
Appropriately combined studies	75 of 145 (52)	92 of 157 (59)	RR, 0.90 (95% CI, 0.70-1.14)
Had conclusions supported by the data	40 of 81 (49)	65 of 100 (65)	RR, 0.86 (95% CI, 0.62-1.21)
Assessed risk of bias	56 of 145 (39)	104 of 157 (66)	RR, 0.47 (95% CI, 0.23-0.95)
Interpreted results in light of risk of bias	49 of 127 (39)	69 of 120 (58)	RR, 0.68 (95% CI, 0.53-0.87)

Abbreviations: NA, not applicable; RR, risk ratio.
[a]Measured as pooled *z* score. A *z* score expresses the number of standard deviations a value differs from the mean.
[b]RR < 1 indicates that systematic reviews with financial conflicts of interest have lower methodological quality.

Conflict of Interest Disclosures: Dr Gøtzsche is a Peer Review Congress Advisory Board member but was not involved in the review or decision for this abstract.

Analysis of Uptake and Outcome in Author-Selected Single-blind vs Double-blind Peer Review at *Nature* Journals

Elisa De Ranieri[1]; Barbara McGillivray[2]; Sowmya Swaminathan[3]; Michelle Samarasinghe[4]; Leah Gruen[4]

Objective Double-blind peer review might avoid referee bias. The aims of this study were to analyze the demographics of corresponding authors choosing double-blind peer review and to identify differences in editorial outcome depending on review model.

Design Data include direct submissions and transfers received between March 2015 and February 2017 by 25 Nature-branded journals. The authors chose either single- or double-blind review, and the editors were aware of the choice before taking any decisions. We analyzed direct submissions to study the uptake of double-blind review in relation to gender, country, and institutional prestige of the corresponding author. We analyzed all submissions to study the editorial outcome in relation to review model. The gender (male, female, or not available) of the corresponding authors was determined from their first name using a third-party service (Gender API), discarding results with less than 80%

confidence. The prestige of corresponding author's institutions was measured by normalizing the institution's name using the Global Research Identifier Database (GRID) and dividing institutions in 3 prestige groups using the 2016 Times Higher Education (THE) ranking. We used descriptive statistics for data exploration; we tested our hypotheses using Pearson's χ^2 and binomial tests.

Table 3. Data Concerning the 2 Review Models Based on Several Attributes of the Submission or of the Manuscript's Corresponding Author[a]

Attribute	Double Blind, No. (%)	Single Blind, No. (%)	*P* Value
Direct submissions[b]	12,631 (12)	93,742 (88)	NA
Nature[b]	2782 (14)	17,624 (86)	<2.2e-16
Sister journals[b]	8053 (12)	57,181 (88)	
Nature Communications[b]	3900 (9)	38,914 (91)	
Gender of corresponding author[c]			
Female	1506 (10)	12,943 (90)	.62
Male	7271 (11)	61,536 (89)	
Institution group[d]			
1	240 (4)	5818 (96)	<2.2e-16
2	1663 (8)	19,295 (92)	
3	4174 (13)	27,730 (87)	
Country[e]			
Australia	274 (10)	2366 (90)	<2.2e-16
Canada	259 (9)	2581 (91)	
China	3626 (22)	13,148 (78)	
France	278 (8)	3334 (92)	
Germany	350 (5)	6079 (95)	
India	711 (32)	1483 (68)	
Japan	933 (15)	5248 (85)	
South Korea	643 (12)	3089 (88)	
United Kingdom	509 (7)	6656 (93)	
United States	2298 (7)	30,184 (93)	
Other	2750 (12)	19,574 (88)	
Out to review decision[f]			
Sent	1242 (8)	25,985 (23)	<2.2e-16
Not sent	13,493 (92)	87,734 (77)	
Decision after review[g]			
Accepted	242 (25)	8692 (44)	<2.2e-16
Rejected	732 (75)	11,040 (56)	

[a]When applicable, we show *P* values from hypothesis tests performed to test the null hypothesis that there is no association between review model and each attribute (eg, journal category).

[b]Data set for overall uptake: 106, 373 direct submissions. Sister journals are Nature-branded journals, excluding *Nature* and *Nature Communications*.

[c]Data set for gender analysis: 83,256 direct submissions.

[d]Institution groups are defined to include institutions with a Times Higher Educaion (THE) rank between 1 and 10 (group 1), 11 and 100 (group 2), and above 101 (group 3). Submissions from institutions without a THE ranking are not included. Data set for institutional prestige analysis: 58,920 direct submissions.

[e]The itemized countries are responsible for 80% (85,098) of direct submissions. All other countries are grouped under "Other."

[f]Data set for out-to-review statistics: 128,454 direct submissions and transfers.

[g]Data set for final outcome statistics: 20,706 direct submissions and transfers.

Results Out of 128,454 papers, 106,373 were direct submissions, of which 12% were submitted double-blind review (**Table 3**). We found a small but significant association between journal tier and review type. We had gender information for 50,533 corresponding authors (in 83,256 submissions) and found no statistically significant difference in the distribution of peer-review model between males and females. We had 58,920 records with normalized institutions and a THE rank, and we found that corresponding authors from the less prestigious institutions are more likely to choose double-blind review. In the 10 countries with the highest number of submissions, we found a small but significant association between country and review type. China and the United States had a preference for double- and single-blind review, respectively. The outcome at both first decision and postreview was significantly more negative (ie, a higher likelihood for rejection) for double-blind than single-blind reviewed papers, and we attribute this to differences in the quality of the studies.

Conclusions Authors choose double-blind review more frequently when they submit to more prestigious journals, when they are affiliated with less prestigious institutions, or when they are from specific countries. The double-blind option is also linked to less successful editorial outcomes.

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Conflict of Interest Disclosures: All authors are or have been employed by Springer Nature, which owns and publishes the Nature-branded journals.

Gender and Age Bias in Peer Review in Earth and Space Science Journals

Jory Lerback,[1] Brooks Hanson[2]

Objective The American Geophysical Union (AGU) publishes, 20 journals with approximately 6000 articles and 24,000 reviews annually. We studied the gender differences and dynamics in publishing and reviewing. This has been studied in other disciplines, but these studies have mostly assigned gender to first names (we have self-reported gender), had smaller sample sizes, and/or have not accounted for age.

Design We analyzed membership demographic data and editorial data from the AGU from 2012 to 2016. We analyzed activities in the publications database, looking at demographic data for 23,985 distinct reviewers, 29,927 first authors, 97,120 reviewer suggestions by authors, and 151,484 reviewer invitations by editors. Age is important to include because the proportion of women researchers decreases as age increases; accounting for age is needed to reveal some otherwise hidden gender differences.

Results Female first authors had higher acceptance rates than men across all age cohorts (61 vs 58%; χ^2_1 [n = 29,187] =

Table 4. Proportion of Female Individuals in Peer Review Interactions

Actors	Population Analyzed	% Female of Population (All Ages)	Females in Population Analyzed, No.	Males in Population Analyzed, No.
	Distinct members	29.6	22,570	55,098
	Distinct published first authors	26.9	2661	7248
	Distinct published authors	23.6	5433	17,622
Female first authors	Coauthors	21.7	4069	14,641
Female corresponding authors	Reviewer suggestions	21.5	4616	16,832
Female editor	Reviewer invitations	22.1	5037	17,772
Male first authors	Coauthors	16.0	8811	46,291
Male corresponding authors	Reviewer suggestions	15.8	11,991	63,681
Male editors	Reviewer invitations	17.5	22,474	105,782

20.057). Women make up 27% of first authors (n = 9,909), 24% of all authors (n = 18,710), and 30% of AGU membership (n = 77,668) (**Table 4**). Despite this, women were not utilized as reviewers (21%) as much as expected based on these rates (χ^2_1 first authors = 145.396 [n = 33,395]; $P < .001$; χ^2_1 all authors = 50.958 [n = 47,081] ; $P < .001$; χ^2_1 members = 629.231 [n = 101,694]; $P < .001$, respectively). Although the proportion of female reviewers increased from 2012 to 2016, this gap persisted and was consistent throughout age cohorts of the suggested reviewers. This difference began with authors, who suggested male reviewers more than expected (male authors suggested 16% female reviewers [n=75,672]; female authors suggested 22% (n=21,488). Male editors subsequently invited only 18% female reviewers, whereas female editors invited 22%. This difference in suggestions partly parallels coauthor networks, in which male first authors tend to have other males as collaborators (16% [n= 55,102]), whereas female first authors had collaborators that more closely represented the gender-age distribution of the research population (22% [n=18,710]).

Conclusions We found that women are not being included in activities related to peer review processes as frequently as their male peers in Earth and space journals.

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Conflict of Interest Disclosures: None reported.

Additional Contributions: We thank the American Geophysical Union for providing data.

Bias in Reporting and Publication of Research

Augmenting Systematic Reviews With Information From ClinicalTrials.gov to Increase Transparency and Reduce Bias

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Objective Prospective registration of clinical trials may improve transparency and reduce bias associated with selective reporting. Our objective was to evaluate the impact of access to and integration of information from ClinicalTrials.gov on the conclusions of systematic reviews in 5 clinical areas.

Design Teams of systematic reviewers searched ClinicalTrials.gov for studies relevant to 5 different ongoing systematic reviews: Effectiveness of Treatment Options for the Prevention of Complications and Treatment of Symptoms of Diabetic Peripheral Neuropathy (DPN), Management of Infertility, Omega-3 Fatty Acids and Cardiovascular Disease, Strategies to Improve Mental Health Care for Children and Adolescents, and Tympanostomy Tubes in Children with Otitis Media. A semi-automated approach to matching studies using EndNote was not feasible owing to lack of standardization of format and location of the registry identification number in published reports. Teams compared trials, and information on trials, found from searches of other sources and determined whether information uniquely found in ClinicalTrials.gov changed confidence in evidence and review conclusion.

Results Across all topics, 24% (101 of 419) of all included trials were registered in ClinicalTrials.gov; 38% (95 of 251 total registry records found) did not have results published in peer reviewed literature; and of trials with published and registry reported results, 63% (124 of 198) of outcomes matched in the publication and ClinicalTrials.gov records (**Table 5**) Despite the additional trials found in the searches of ClinicalTrials.gov, the strength of evidence and conclusions in each systematic review were unchanged, primarily owing to missing results of most of the additional trials found.

Conclusions Across topic areas, only 24% (101 of 419) were registered in ClinicalTrials.gov and 38% (95 of 251) of studies did not have results published in peer-reviewed literature. The potential impact of this missing information on the conclusions of systematic reviews is unknown. When there were both ClinicalTrials.gov records and publications, 37% (74 of 198) of outcome measures did not match, raising a concern about bias owing to selective outcome reporting. It appears that prespecification of a primary outcome variable in ClinicalTrials.gov does not inhibit reporting other outcomes in publications. New rules requiring outcome

Table 5. Summary of ClinicalTrials.gov Registration for Published and Unpublished Results in 5 Topic Areas

Review Topic (n trials)	CT.gov Record For Published Trial		CT.gov Registered Trials Without Public Results Reporting		Outcome Measures Reported, No.		
	Yes	No	Results Not Published/Total Studies Found in Registry (y since completion)	Results Not Registered in CT.gov	CT.gov and Publication	CT.gov Only	Publication Only
Effectiveness of treatment options for diabetic peripheral neuropathy (n= 106)	53	53	23/53 ≤ 3 y: 10 >3 y: 13	36	18 outcomes (n=12 studies)	5 outcomes Results: 1 (n=5 studies)	22 (n=16 studies)
Management of infertility (n=24)	12	12	4/94 ≤ 3 y: 2 >3 y: 2	11	11 outcomes	3 outcomes Results: 0 (n= 3 studies)	6 outcomes (n=4 studies)
Omega-3 fatty acids and cardiovascular disease (n=98)	26	72	43/69 ≤ 3 y: 34 >3 y: 9	43	71 outcomes (n=26 studies)	2 outcomes Results: 0 (n=2 studies)	25 outcomes (n=12 studies)
Mental health care for children and adolescents (n=13)	4	9	3/6 All ongoing	NA	Not evaluated	0	13 outcomes (n=12 studies)
Tympanostomy tubes in children with otitis media (n=178)	6	172	22/28 ≤ 3 years: 17 >3 years: 5	20	24 outcomes (n=6 studies)	8 outcomes Results: 0 (n=2 studies)	3 outcomes (n=2 studies)

measure specification and reporting should be considered. Journals and indexing tools could facilitate the inclusion of information from ClinicalTrials.gov into systematic review by adopting a more standardized format for listing the ClinicalTrials.gov identification number.

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Conflict of Interest Disclosures: None reported.

Funding/Support: This project was funded by the Agency for Healthcare Research and Quality.

Role of the Funder/Sponsor: Representatives from the Agency for Healthcare Research and Quality (AHRQ) served as a Contracting Officer's Technical Representative and provide technical assistance during the conduct of the project and provided comments on draft versions of the project. AHRQ did not directly participate in the literature search, determination of study eligibility criteria, data analysis or interpretation.

Disclaimer: The findings and conclusions in this abstract are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ and no statement in this abstract should be construed as an official position of AHRQ or the US Department of Health and Human Service.

Bias Associated With Publication of Interim Results of Randomized Trials: A Systematic Review

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Objective Publication of interim results from ongoing randomized clinical trials may generate substantial interest because they are new and often promising. Final results, however, may not confirm early promise and may receive less attention. Our objective was to describe the publication of interim results from randomized clinical trials and to compare the prominence and consistency with final publications.

Design We conducted a PubMed search (2006-2015) for interim publications of randomized clinical trials, including the terms *interim*, *not mature*, or *immature* in the title or abstract. We used registration numbers and author names to search PubMed, ClinicalTrials.gov, and Web of Science through 2016 for final publications (authors were contacted if none identified) and determined each publication's journal Impact Factor and Altmetric rating (ie, news and social media attention). Two researchers confirmed interim and final publication pairing and abstracted data.

Results Of 1267 publications screened, 613 reported interim results (excluding completed pilot studies, protocols, and cancer trials reporting an interim result for the secondary outcome [overall survival] but with a final primary outcome result [progression-free survival]). Seventy-two percent (442 of 613) of these publications reported on trials stopped early (for benefit [105], harm [67], futility [224], other problems [46]). The remaining 171 ongoing trials reported interim efficacy or safety results. Forty percent (68 of 171) stated the reason for interim publication was a protocol-specified preplanned analysis; a few (6% [10 of 171]) stated other reasons (eg, response to release of results about the same intervention), but most (54% [93 of 171]) stated none. The 171 interim publications were mostly in oncology (28% [48]), surgery (18% [30]), or cardiology (11% [18]); 59% (101) had active controls, and 13% (23) tested noninferiority. The most commonly stated funding sources were solely industry (36% [61]), partly industry (10% [17]), government (18% [30]), and foundation or university (17% [29]). Final results were published for 57% (90) of the 158 trials where sufficient time elapsed for final publication (eg, ≥1 year beyond registry-specified study completion date). Most abstract conclusions

(85% [61]) did not change qualitatively for the 72 pairs of interim and final publications reporting the same primary outcome results, while 15% changed: 8% (6) became weaker (eg, changed from "superior" to "not superior"), and 7% (5) became stronger. Interim and final publications had similar prominence in terms of Impact Factor and Altmetric rating (**Table 6**).

Conclusions Frequent nonpublication of final results may cause bias because true treatment effects often remain unknown. Final publications, when available, have as much journal and media prominence as interim publications but may reach qualitatively different conclusions. Journals should publish fewer interim results (especially when not prespecified) and commit to making the final results known when they do.

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Conflict of Interest Disclosures: Drs Schwartz and Woloshin have served as medical experts in testosterone litigation. No other conflicts were reported.

Table 6. Key Performance Indicators for the 72 Pairs of Interim and Final Publications Both Reporting Primary Outcome Results

Performance Indicator	Interim	Final	*P* value[a]
High impact factor journal (>20)	26% (19 of 72)	29% (21 of 72)	.73
Top 5 impact factor general journals	19% (14 of 72)[b]	14% (10 of 72)	.40
Both in Top 5	NA	35% (5 of 14)	NA
Altmetric-rating median [IQR][c]	7 [2-38]	6 [2-42]	.86

Abbreviations: IQR, interquartile range; NA, not applicable.
[a]*P* values for paired data (McNemar test for dichotomous and sign test for continuous variables).
[b]All published in the *New England Journal of Medicine* or *Lancet*.
[c]Altmetric ratings were only available for 38 interim and 53 final publications.

Identification and Classification of Spin in Clinical Studies Evaluating Biomarkers in Ovarian Cancer: A Systematic Review

Mona Ghannad,[1,2] Maria Olsen,[1,2] Patrick M. Bossuyt[1]

Objective The objective of this systematic review was to document and classify spin or overinterpretation, as well as facilitators of spin, in recent clinical studies evaluating performance of biomarkers in ovarian cancer.

Design We searched PubMed systematically for all studies published in 2015. Studies eligible for inclusion described 1 or more trial designs for identification and/or validation of prognostic, predictive, or diagnostic biomarkers in ovarian cancer. Reviews, animal studies, and cell line studies were excluded. All studies were screened by 2 reviewers. To document and characterize spin, we collected information on the quality of evidence supporting the study conclusions, linking the performance of the marker to outcomes claimed.

Results In total, 1026 potentially eligible articles were retrieved by our search strategy, and 345 studies met all eligibility criteria and were included. The first 200 studies, when ranked according to publication date, will be included in our final analysis. Data extraction was done by one researcher and validated by a second. Specific information extracted and analyzed on study and journal characteristics, key information on the relevant evidence in methods, and reporting of conclusions claimed for the first 50 studies is provided here. Actual forms of spin and facilitators of spin were identified in studies trying to establish the performance of the discovered biomarker. Actual forms of spin identified as shown (**Table 7**) were: (1) other purposes of biomarker claimed not investigated (18 of 50 studies [36%]); (2) incorrect presentation of results (15 of 50 studies [30%]); (3) mismatch between the biomarker's intended clinical application and population recruited (11 of 50 studies [22%]); (4) mismatch between intended aim and conclusion (7 of 50 studies [14%]); and (5) mismatch between abstract conclusion and results presented in the main text (6 of 50 studies [12%]). Frequently observed facilitators of spin were: (1) not clearly prespecifying a formal test of hypothesis (50 of 50 studies [100%]); (2) not stating sample size calculations (50 of 50 studies [100%]); (3) not prespecifying a positivity threshold of continuous biomarker (17 of 43 studies [40%]); (4) not reporting imprecision or statistical test for data shown (ie, confidence intervals, *P* values) (12 of 50 studies [24%]); and (5) selective reporting of significant findings between results for primary outcome reported in abstract and results reported in main text (9 of 50 studies [18%]).

Conclusions Spin was frequently documented in abstracts, results, and conclusions of clinical studies evaluating performance of biomarkers in ovarian cancer. Inflated and selective reporting of biomarker performance may account for a considerable amount of waste in the biomarker discovery process. Strategies to curb exaggerated reporting are needed to improve the quality and credibility of published biomarker studies.

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Conflict of Interest Disclosures: None reported.

Funding/Support: This project has received funding from the European Union's Horizon 2020 research and innovation program under the Marie Sklodowska-Curie grant agreement No. 676207.

Role of the Funder/Sponsor: The funder/sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the abstract.

Table 7. Prevalence of Actual Forms of Spin in Clinical Studies Evaluating Performance of Biomarkers in Overian Cancer

Actual Forms of Spin	All Studies (n=50)	Examples of Actual Forms of Spin
Other purposes of biomarker claimed not investigated	18 (36%)	**Example 1:** Potential use of BM for screening not the aim or investigated in the study. *"With a short analysis time and inclusion of novel markers for early ovarian cancer detection, this platform shows strong promise as a potential point of care screening method for ovarian cancer, where patients could receive results promptly enough to be referred to transvaginal sonography in the same visit. Reduced costs and easier accessibility to results could also assist in longitudinally monitoring biomarker values over time, which has shown some promise in helping detect early stage ovarian cancer."*
Incorrect presentation of results	15 (30%)	**Example 1:** Alternative facts: describe negative association and odds ratio of 0.532 as "protective role." *"In addition to this finding, we observed that rs3814113 on 9p22 may play a protective role from the development of serous histological subtypes of ovarian carcinoma."* **Example 2:** Claim effect despite statistically insignificant results. **Example 3:** Claim effect despite not providing imprecision or statistical test (confidence intervals or *P* values) between different biomarker models tested or patient groups (subgroups).
Mismatch between biomarker's intended clinical application and the population recruited	11 (22%)	**Example 1:** The use of healthy controls for the performance of the BM evaluating diagnostic, prognostic, or predictive treatment response. Similarly recruitment of symptomatic women for the performance of the BM in screening or risk.
Mismatch between intended aim and conclusion	7 (14%)	**Example 1:** Extrapolation of preclinical study results to clinical application. **Example 2:** Use of causal language for BM(s): being assessed despite the use of a nonrandomized design.
Mismatch between abstract conclusion and results presented in the main text	5 (10%)	**Example 1:** Leap from association to genetic risk factor. *"Despite the relatively small sample size of cases and controls, our studies confirmed some of the previously demonstrated GWAS single-nucleotide polymorphisms as genetic risk factors for epithelial ovarian tumors."*
Mismatch between results reported in abstract and results reported in main text	3 (6%)	**Example 1:** The direction of the association in the results is negative, which they interpret as "protective." However, the abstract indicates "significant" association, implying positive. **Example 2:** The reported HRs reported in the abstract does not match the HRs reported in the main text. In main text the HRs for PFS and OS are reported for each quartile. Unclear if what is reported in abstract is the overall HRs.
Other benefits claimed that is not prespecified and/or investigated	2 (4%)	**Example 1:** Reduced costs and easier accessibility to results.

Abbreviations: BM, biomarker; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Spin in Published Biomedical Literature: A Systematic Review

Quinn Grundy,[1] Kellia Chiu,[1] Lisa A. Bero[1]

Objective To explore the nature and prevalence of spin in the biomedical literature.

Design In a systematic review and meta-analysis, we searched MEDLINE, PreMEDLINE, Embase, Scopus, and handsearched reference lists for all articles published between 1946 and 24 November 2016 that included the quantitative measurement of spin in the biomedical literature for at least 1 outcome. Two independent coders extracted data on the characteristics of articles and included studies, methods for assessing spin, and all spin-related results. The data were heterogeneous; results were grouped inductively into outcome-related categories. We had sufficient data to use meta-analysis to analyze the association of industry sponsorship of research with the presence of spin.

Results We identified 4219 articles after removing duplicates and included 35 articles that investigated spin: clinical trials (23/35, 66%);observational studies (7/35, 20%); diagnostic accuracy studies (2/35, 6%); and systematic reviews and meta-analyses (4/35, 11%), with some articles including multiple study designs. The nature and manifestations of spin varied according to study design. We grouped results into the following categories: prevalence of spin, level of spin, factors associated with spin, and effects of spin on readers' interpretations. The highest, but also greatest variability in the prevalence of spin was present in trials (median, 57% of main texts containing spin; range, 19%-100% across 16 articles). Source of funding was hypothesized to be a factor associated with spin; however, the meta-analysis found no significant association, possibly owing to the heterogeneity of the 7 included articles.

Conclusions Spin appears to be common in the biomedical literature, though this varies by study design, with the highest rates found in clinical trials. Spin manifests in diverse ways, which challenged investigators attempting to systematically identify and document instances of spin. Widening the investigation of factors contributing to spin from characteristics of individual authors or studies to the cultures and structures of research that may incentivize or deincentivize spin, would be instructive in developing strategies to mitigate its occurrence. Further research is also needed to assess the impact of spin on readers' decision making. Editors and peer reviewers should be familiar with the prevalence and manifestations of spin in their area of research to ensure accurate interpretation and dissemination of research.

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Conflict of Interest Disclosures: Dr Bero is a member of the Peer Review Congress Advisory Board but was not involved in the review or decision for this abstract.

Summary Effect Sizes in Meta-analyses After Removal of Retracted Studies From the Pool of Primary Studies

Daniele Fanelli,[1] David Moher[2,3]

Objective This study aimed to assess the magnitude and direction of change of summary effect size in meta-analyses (MAs) after retracted papers are removed from the pool of primary studies.

Design We aimed to identify a homogeneous sample of recent MAs that contained, among primary studies, 1 or more studies that were later retracted, to compare pooled odds ratios with and without such studies. On December 16, 2016, we retrieved all retracted publications recorded in the Web of Science (WOS) and then retrieved a list of records that cited these retracted publications. We selected all records containing "meta-analysis" or "systematic review" in the title, abstract, or keywords and then restricted the initial list of potentially relevant titles to records published in 2016. The full text of these studies was retrieved and inspected for selection based on the following exclusion criteria: limited to a systematic review and not a formal MA; not a standard MA (ie, a weighted pooled summary of primary studies, which excludes network MAs, genome-wide association studies, and MAs of functional magnetic resonance imaging, microarray, and genomic data); does not contain primary summary data in the full text (ie, the retracted cited article is not among primary studies of the MA); or does not use odds ratio–convertible metrics (including risk difference, proportion, mean, or other unusual metrics designed for the specific purposes of a study).

Results A total of 3834 records of potentially retracted articles were identified in WOS. We retrieved 83,946 records that cited these potentially retracted publications; from these, we identified 1433 records containing "meta-analysis" or "systematic review" in the title, abstract, or keywords. Of the 109 potentially relevant MAs published in 2016, 17 did not match any exclusion criteria and were included in this study. Each of these MAs had included in its weighted summary 1 retracted study. Three pairs of MAs cited the same retracted study; therefore, the number of distinct retraction events covered in our sample is 14. All MAs had been authored by independent research teams, and only 1 author appeared in 2 MAs. Two MAs were published in the Cochrane Database of Systematic Reviews, and 15 were published in different journals that were classified by WOS in different biomedical fields, from molecular biology to surgery. Additional analyses are ongoing.

Conclusions The 17 MAs included in the study are representative of multiple biomedical research areas and retraction events. For each of these MAs, we will calculate summary effect size with and without the retracted primary study and obtain a ratio of odds ratios across the sample. Pooled results will yield a preliminary estimate of the possible impact that retractions may have on the biomedical literature.

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Conflict of Interest Disclosures: Dr Moher is a member of the Peer Review Congress Advisory Board, but was not involved in the review or decision for this abstract. No other disclosures were reported.

Acknowledgments: Research assistant Julie Wong helped collect the raw data.

Assessing the Outcomes of Introducing a Digital Image Quality Control Review Into the Publication Process for Research Articles in Physiology Journals

Rita Scheman,[1] Christina N. Bennett[1]

Objective To address concerns that American Physiological Society (APS) journals were publishing photographs, mostly Western blots and DNA/RNA gel images, that had inappropriate and/or undeclared modifications, we introduced a postacceptance but prior to early-view publication quality control (QC) procedure in 7 journals using digital image forensic tools to check for image splicing, duplication, extreme contrast, and selective editing. We sought to assess whether the QC check effectively identified and corrected images with modifications prior to publication, and whether corresponding authors we have queried about their images after a QC check have submitted another manuscript without generating another QC query.

Design We assessed the number of QC cases queried per year, image modifications identified, and manuscript outcomes categorized as no revision, revision, corrigendum, rejection, or retraction between 2009 and 2016. We also assessed the number of subsequent submissions of unique manuscripts by corresponding authors involved in initial QC queries and the outcomes of those subsequent QC checks. We report results for 3 time periods: 2009, when no article underwent the QC check unless concerns arose during figure preparation for final publication; 2010 to 2012, when the procedure was introduced in 7 APS journals one at a time; and 2013 to 2016 when all 7 journals used the QC check process.

Results The QC checks were performed on 1.1% of research articles in 2009, 5.9% in 2010 to 2012, and 6.5% in 2013 to 2016. Implementation of the QC check reduced the number of corrigenda published (from 22/25 queries in 2009 to 0/71 in 2016) with a reciprocal increase in the number of revisions prior to publication (3/25 in 2009 to 65/71 in 2016). Since 2009, only 23 of 733 articles contained image modifications serious enough to rescind acceptance or retract the early view version. Since 2013, the proportion of QC queries has decreased 0.7% (95% CI 1.2%-0.3%) each year (P = .03).

Fifty-eight percent (190/326) of corresponding authors who received QC queries from us between 2013 and 2015 submitted another manuscript for publication to one of the journals, and only 8 were involved in a subsequent QC query.

Conclusions Implementing a QC check for review of image modifications in accepted articles has achieved appropriate digital image presentation and publication as measured by a decline in corrigenda and author queries. The yearly decrease in the number of QC queries suggests that returning authors adhere to the journals' image integrity guidelines.

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Conflict of Interest Disclosures: Rita Scheman and Christina N. Bennett are employees of the American Physiological Society, and the data presented herein are derived from American Physiological Society submissions.

Fact Checking Nucleotide Sequences in Life Science Publications: The Seek & Blastn Tool

Jennifer A. Byrne,[1,2] Cyril Labbé[3]

Objective Errors within scientific publications contribute to research irreproducibility. A collection of highly similar cancer research publications (CorpusP) was recently identified, and 38 of 48 of these publications (79%) included nucleotide sequence(s) whose identities, according to blastn analyses, did not match their experimental use (either targeting an identified gene, or serving as a nontargeting control). To expand capacity to identify other studies that may incorrectly describe nucleotide sequence reagents, we aimed to design a semiautomated tool that checks the claimed use of nucleotide sequence reagents with indisputable facts from blastn homology searches; the tool was also tested with other literature claims using Google Scholar searches.

Design From a given publication, seek & blastn, a semiautomated tool, automatically extracts gene identifiers and nucleotide sequences (15 to 90 bases) using named entity recognition techniques (thesaurus and rules). The sentence containing each sequence is automatically analyzed (using finite-state machines) to assign a claimed status (targeting or nontargeting) that is compared with the most likely status according to blastn analysis. Claimed status within the literature can be further assessed by Google Scholar searches. The approach was built using the CorpusP publications and further analyzed using a set of 154 unknown studies (CorpusU) retrieved using studies from CorpusP and the "PubMed similar" functionality.

Results In CorpusP and CorpusU, 48 of 48 (100%) and 111 of 154 (73%) publications included nucleotide sequences that were extracted using seek & blastn. Application of seek & blastn identified the 38 of 48 studies (79%) in CorpusP that appear to have incorrectly employed nucleotide sequence reagent(s). More nontargeting than targeting sequences were accurately predicted to have been used incorrectly (37 of 47 [78.7%] vs 19 of 294 [6.5%]). Furthermore, the analysis of nucleotide sequences flagged by seek & blastn predicted that 30 of 154 CorpusU studies (19%) may have incorrectly employed nucleotide sequence reagent(s). However, the automated use of seek & blastn faces challenges. Overall, 10 of 341 (2.9%) and 11 of 341 (3.2%) sequences in CorpusP were either not extracted or incorrectly extracted, respectively, and claims were not (correctly) identified for 19 of 341 sequences (5.6%). Furthermore, gene identifier variations may complicate the analysis of targeting sequences. Application of seek & blastn therefore currently requires follow-up analyses by life science expert peers.

Conclusions Preliminary use of seek & blastn suggests that the incorrect use of nucleotide sequence reagents may be frequently undetected and represents an underestimated source of error in life science publications. Text mining and text analysis tools such as seek & blastn may therefore provide valuable support to allow peers to identify obvious errors in the published or forthcoming scientific literature.

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Conflict of Interest Disclosures: Springer-Nature is funding a PhD student within the research group of Cyril Labbé. This PhD project is exploring methods to detect automatically generated scientific papers. Funding from Springer-Nature did not support the work described in this abstract.

Types of Research Integrity Issues Encountered by a Specialist Research Integrity Group

Magdalena Morawska,[1] Stephanie L. Boughton[1]

Objective Data on the reasons why articles are retracted exist; however, the types and frequency of research integrity issues faced by editors day to day, particularly before publication, are unclear. Our objective was to categorize and determine the relative frequency of research integrity issues encountered by BioMed Central's Research Integrity Group, which covers approximately 300 journals spanning biological and medical disciplines.

Design We used a retrospective observational study design. We included all new inquiries regarding any aspect of research integrity sent to the Research Integrity Group between January 1, 2015, and December 31, 2016. The study period was chosen because it reflected a period when the structure and remit of the Group remained constant. The inquiries had been sent to the Research Integrity Group by editorial staff for advice and/or investigation of potential research and publication ethics issues following discussion with the journals' editors in chief. They related to submitted manuscripts or published articles and may have been detected by the editors in chief, in-house staff, peer reviewers, or whistle-blowers. Editors in chief and editorial staff are not required to escalate all issues to the Group. We assigned each inquiry to 1 of 6 categories, adapted from the Committee on

Publication Ethics (COPE) Case Taxonomy, covering different research integrity issues: authorship, competing interests, data issues, ethics/consent, peer-review process, and plagiarism/duplicate publication. Inquiries categorized as "ethics/consent" related to questions around ethics approval or consent for research involving human participants or consent for publication of potentially identifiable information (eg, case studies or images). We compared categories and their relative frequency for submitted manuscripts and published articles.

Results During the study period, the Research Integrity Group received 1040 inquiries: 690 (66%) related to submitted manuscripts and 350 (34%) to published articles. **Table 8** shows the breakdown of inquiries by category. The largest category was ethics/consent (35%), and the second largest was plagiarism/duplicate publication (23%). For inquiries relating to submitted manuscripts only, almost half (49%) related to ethics/consent. The largest category for published articles was data issues (41%). These results have been used to inform training needs for both internal staff and external editors. Editorial policies and policy wording have also been revised in line with the results of this study.

Conclusions Category frequency was different before and after publication. The high frequency of prepublication ethics/consent inquiries suggests that such issues can be detected at an early stage and that researchers need training to prevent such issues arising. Data issues were the most common for published articles, suggesting that problems with data may not always be detected by peer review and may only come to light after publication. Future studies could examine issues arising in nonbiomedical journals.

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Conflict of Interest Disclosures: Both authors are employees of Springer Nature. At the time of data collection, Magdalena Morawska was an associate editor and Stephanie Boughton was a medical editor within BioMed Central's Research Integrity Group (part of Springer Nature), the team dealing with the research and publication ethics inquires that were the subject of this study. Both are now part of Springer Nature's Research Integrity Group.

Acknowledgments: We thank the members of BioMed Central's Research Integrity Group and Caroline Black for their helpful feedback on this abstract.

Table 8. Breakdown by Category of All Inquiries Received by the Research Integrity Group Between January 1, 2015, and December 31, 2016

Category	Inquiries, No (%)
Authorship	115 (11)
Competing interests	38 (4)
Data issues	182 (18)
Ethics/consent	362 (35)
Peer-review process	103 (10)
Plagiarism/duplicate publication	240 (23)

Data Sharing

Early Experiences With Journal Data Sharing Policies: A Survey of Published Clinical Trial Investigators

Sara Tannenbaum,[1] Joseph S. Ross,[2,3,4,5] Harlan M. Krumholz,[2,4,5,6] Nihar R. Desai,[2,6] Jessica D. Ritchie,[2] Richard S. Lehman,[2,7] Ginger M. Gamble,[2] Jacqueline Bachand,[8] Sara Schroter,[9] Trish Groves,[9] Cary P. Gross[3,4,10]

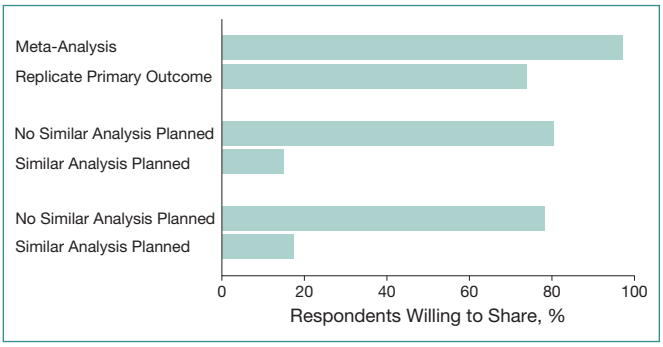
Objective Although the International Committee of Medical Journal Editors (ICMJE) recommendations for trial data sharing have been controversial, little is known about the attitudes and experiences of authors published in journals with existing data sharing policies.

Design We conducted a self-administered online survey of the authors of clinical trials published January 1, 2012, through March 1, 2016, in 3 high-impact journals with policies either requiring all clinical trial authors to share data (*PLOS Medicine*) or publish a statement specifying whether they were willing to share data (*The BMJ* and *Annals of Internal Medicine*). For the latter 2 journals, we only contacted authors who specified that they were willing to share data. We contacted the corresponding author and then an additional author if no response was received. The survey addressed sharing plans, receipt of sharing requests, and effort required to respond to sharing requests. We also asked respondents about willingness to share data in 6 hypothetical scenarios. Each hypothetical request occurred 1 year after publication of the original study but varied by type of request. Survey results are for all respondents unless otherwise indicated.

Results Among the 154 trials for which we contacted authors, 90 responses (58.4%) were received. Respondents and nonrespondents did not significantly differ by journal, year published, region of the corresponding author, or funding source. Half of the respondents had a data sharing plan (n = 49 [54.4%]), and about one-third had received at least 1 sharing request (n = 31 of 89 [34.8%]). Out of the 68 data requests that were received in aggregate, only 4 (5.9%) were denied. Most respondents indicated that they would be willing to share data for a meta-analysis (n = 87 [96.7%]) or for replication of the primary study outcome (n = 66 [73.3%]) 1 year after publication. However, in response to scenarios indicating that data were requested for a secondary outcomes analysis or predictive modeling study, willingness to share was largely influenced by author intent to conduct similar analyses (**Figure 1**). For a secondary outcomes analysis, 70 authors (77.8%) responded that they would share if they had not planned a similar analysis, but 15 authors (16.7%) responded that they would share even if they had planned a similar analysis. Among authors who had granted at least 1 request (n = 25), a median (range) of 18 (3-125) person-hours were spent to prepare data for sharing.

Conclusions Among respondents to a survey of clinical trial authors, we found that data sharing is taking place under

Figure 1. Willingness to Share by Request Type for a Trial Published 12 Months Ago



journal data sharing requirements but that willingness to share data depends on the type of request and intent to publish similar analyses.

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Conflict of Interest Disclosures: Dr Ross, Dr Krumholz, Dr Desai, Ms Ritchie, Dr Lehman, Ms Gamble, and Dr Gross receive research support from Janssen and the Pharmaceutical Companies of Johnson & Johnson, to develop methods of clinical trial data sharing. Dr Ross, Ms Ritchie, and Ms Gamble receive research support from the Blue Cross Blue Shield Association to better understand medical technology evidence generation. Drs Ross, Krumholz, and Desai receive research support from the Centers for Medicare and Medicaid Services to develop and maintain hospital performance measures that are used for public reporting. Dr Ross, Dr Krumholz, and Ms Gamble receive research support from the US Food and Drug Administration to develop methods for postmarket surveillance of medical devices. Dr Ross receives research support from the US Food and Drug Administration to establish the Yale-Mayo Center for Excellence in Regulatory Science and Innovation. Dr Gross receives research funding from 21st Century Oncology and the National Comprehensive Cancer Network-Pfizer. Dr Krumholz chairs a scientific advisory board for United Healthcare. Drs Schroter and Groves are full-time employees at *The BMJ*, and Dr Groves is a member of the Peer Review Congress Advisory Board but was not involved in the review or decision for this abstract. No other conflicts were reported.

Funding/Support: Research reported in this publication was supported by National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health (award No. 5T35DK104689-02).

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the abstract.

Disclaimer: The content is the sole responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Sharing Data Through the Yale University Open Data Access (YODA) Project: Early Experience

Joseph S. Ross,[1,2,3,4] Jessica D. Ritchie,[1] Stephen Bamford,[5] Jesse A. Berlin,[5] Karla Childers,[5] Nihar Desai,[1,6] Ginger M. Gamble,[1] Cary P. Gross,[2,3,7] Richard S. Lehman,[1,8] Peter Lins,[5] Sandra A. Morris,[5] Joanne Waldstreicher,[5] Harlan M. Krumholz[1,3,4,6]

Objective To describe early experience with sharing clinical research data through the Yale University Open Data Access (YODA) Project.

Design Cross-sectional analysis of all submitted proposals by investigators to use clinical research data being made available by Johnson & Johnson (J & J) through the YODA Project, since the inception of the initiative in October 2014, including approval, data access, and publication status.

Results Of the clinical trials conducted by J & J, to date, 189 trials have been reviewed by J & J and determined to be available for sharing with external investigators, most commonly of therapies used for the treatment of bipolar disorder and schizophrenia. In addition to 1 medical device trial and 188 pharmaceutical trials, J & J continues to review trials for eligibility, and additional trials can be made available on request, including trials of consumer products. As of June 2017, the YODA Project had received 73 proposals from external investigators to use data from 159 trials; the median number of trials requested was 3 (interquartile range [IQR], 1-9; maximum, 50). Among the 73 proposals, 65 (89.0%) have been approved by an independent review panel and 2 (2.8%) are under review; 6 (8.2%) were withdrawn or closed owing to patient privacy concerns, unavailability of needed data elements, or lack of research proposal clarity. The most common study purposes proposed were to address secondary research questions (n = 39), combine data as part of larger meta-analyses (n = 35), and/or validate previously published studies (n = 17). Of the 65 approved proposals, 50 researchers have access to the data and are working on their projects (median duration of access, 43.7 weeks; IQR, 21.0-71.5), 8 are awaiting execution of their Data Use Agreement or data preparation, and 5 have completed their projects, 2 of which resulted in publications in the peer-reviewed literature, and 3 of which have submitted a manuscript for publication. In both cases, the final publication represented the originally proposed research. The authors of the remaining 2 proposals did not pursue their projects.

Conclusions Early experience sharing data through the YODA Project has demonstrated a demand for shared clinical research data as a resource for investigators. As trial funders and investigators increasingly share data, and make use of shared data, it is essential to understand best practices and incentives to ensure success.

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Conflict of Interest Disclosures: Drs Ross, Desai, Gross, Lehman, and Krumholz and Mss Ritchie and Gamble receive research support from Janssen, the Pharmaceutical Companies of Johnson & Johnson, to develop methods of clinical trial data sharing. Dr Ross and Mss Ritchie and Gamble receive research support from the Blue Cross Blue Shield Association (BCBSA) to better understand medical technology evidence generation. Drs Desai, Ross, and Krumholz receive research support from the Centers for Medicare and Medicaid Services to develop and maintain hospital performance measures that are used for public reporting. Drs Ross and Krumholz and Ms Gamble receive research support from the US Food and Drug Administration (FDA) to develop methods for post-market surveillance of medical devices. Dr Ross and Ms Ritchie receive research support from the FDA to establish the Yale-Mayo Center for Excellence in Regulatory Science and Innovation. Dr Gross receives research funding from 21st Century Oncology and the National Comprehensive Cancer Network–Pfizer. Dr Krumholz chairs a scientific advisory board for United Healthcare. Drs Berlin, Morris, and Waldstreicher, Ms Childers, and Messrs Bamford and Lins are employees of Johnson & Johnson.

Funding/Support: This research was the direct result of experience gained from a research agreement through Yale University from Johnson & Johnson (Janssen) to develop methods of clinical trial data sharing.

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the abstract.

Disclaimer: The authors assume full responsibility for the accuracy and completeness of the ideas presented.

Statements About Intent to Share Individual Participant Data at ClinicalTrials.gov

Annice Bergeris,[1] Tony Tse,[1] Deborah A. Zarin[1]

Objective Following recent calls for clinical trialists to declare their plans to share individual participant data (IPD) prior to study initiation, ClinicalTrials.gov added 2 optional data elements in December 2015: (1) Plan to Share IPD (submitted at study initiation) and (2) Available Study Data/Documents (submitted after study completion). We sought to characterize responses to ClinicalTrial.gov's IPD sharing–related questions.

Design We summarized responses to IPD sharing–related questions for all interventional studies initially registered in 2016 and for the subset of trials registered by "high-volume data providers," defined as organizations that registered 10 or more records. Organizations were categorized by key funder type, ie, were categorized as "NIH" if at least 1 National Institutes of Health institute was listed as a sponsor or collaborator, as "industry" if not classified as NIH and at least 1 company was listed as a sponsor or collaborator, and as "other" for all remaining records. Because of considerable heterogeneity in responses among the high-volume data provider subsample, we further characterized responses for trials registered by the top 10 high-volume data provider organizations within each key funder type.

Results Of 21,310 trial records analyzed by May 10, 2017, 14,523 (68.2%) included a response to the question about plans to share IPD; 1930 records (13.3%) indicated yes, 3821 (26.3%) indicated undecided, and 8772 (60.4%) indicated no. Proportions within each key funder type varied among the 10,894 records from high-volume data providers (**Table 9**). Among the top 10 organizations within each key funder type, the percentage of records indicating that plans exist for sharing IPD ranged from 0% to 24% for NIH-funded studies, 0% to 63% for industry-funded studies, and 0% to 28% of studies with other funding. Among 131 records indicating that documents were available for sharing, 76 specified the study protocol would be shared, 52 specified other documents (eg, information leaflets), 32 specified informed consent forms, 16 specified the clinical study report, and 14 specified the individual participant data set. Five of 14 records (36%) specifying availability of IPD listed no plans for sharing IPD.

Conclusions Sixty-eight percent of trial registrants responded to an optional question about plans to share IPD. Among those respondents, 13% said they would share data and another 26% were undecided. Of the 131 records indicating availability of documents for sharing, only 14

Table 9. Responses to Trial Registration Question About Plan to Share Individual Participant Data Among High-Volume Data Providers[a]

Summary Statistics	Total	Key Funder Type		
		NIH	Industry	Other
Organizations (trial records), No.	429 (10,894)	23 (484)	69 (2031)	337 (8379)
≥1 Response (records, No. [%])	404 (6802 [62.4])	18 (178 [36.8])	52 (566 [27.9])	335 (6058 [72.3])
% Yes, median (range)	6 (0-92)	8 (0-36)	0 (0-88)	7 (0-92)
% Undecided, median (range)	14 (0-100)	6 (0-64)	0 (0-100)	17 (0-87)
% No, median (range)	43 (0-100)	18 (0-69)	6 (0-100)	45 (0-100)
≥1 Missing response (records, No. [%])	401 (4092 [37.6])	22 (306 [63.2])	63 (1465 [72.1])	316 (2321 [27.7])
% No response, median (range)	25 (0-100)	57 (0-100)	73 (0-100)	23 (0-100)

Abbreviation: NIH, National Institutes of Health.

[a]High-volume data providers defined as organizations that registered 10 or more trial records.

indicated that IPD were available. Considerable cultural and scientific changes will be necessary before the sharing of IPD and associated documents becomes part of routine practice by clinical researchers.

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Conflict of Interest Disclosures: All authors work for ClinicalTrials.gov. Dr Zarin is a member of the Peer Review Congress Advisory Board but was not involved in the review or decision for this abstract.

Funding/Support: Supported by the Intramural Research Program of the National Library of Medicine, National Institutes of Health.