

BMJ Open Peer Reviewed Evaluation of Registered End-Points of Randomised Trials (the PRE-REPORT study): a stepped wedge, cluster-randomised trial

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ABSTRACT:

Objective To test whether providing relevant clinical trial registry information to peer reviewers evaluating trial manuscripts decreases discrepancies between registered and published trial outcomes.

Design Stepped wedge, cluster-randomised trial, with clusters comprised of eligible manuscripts submitted to each participating journal between 1 November 2018 and 31 October 2019.

Setting Thirteen medical journals.

Participants Manuscripts were eligible for inclusion if they were submitted to a participating journal during the study period, presented results from the primary analysis of a clinical trial, and were peer reviewed.

Interventions During the control phase, there were no changes to pre-existing peer review practices. After journals crossed over into the intervention phase, peer reviewers received a data sheet describing whether trials were registered, the initial registration and enrolment dates, and the registered primary outcome(s) when enrolment began.

Main outcome measure The presence of a clearly defined, prospectively registered primary outcome consistent with the primary outcome in the published trial manuscript, as determined by two independent outcome assessors.

Results We included 419 manuscripts (243 control and 176 intervention). Participating journals published 43% of control-phase manuscripts and 39% of intervention-phase manuscripts (model-estimated percentage difference between intervention and control trials = −10%, 95% CI −25% to 4%). Among the 173 accepted trials, published primary outcomes were consistent with clearly defined, prospectively registered primary outcomes in 40 of 105 (38%) control-phase trials and 27 of 68 (40%) intervention-phase trials. A linear mixed model did not show evidence of a statistically significant primary outcome effect from the intervention (estimated difference between intervention and control = −6% (90% CI −27% to 15%); one-sided p value = 0.68).

Conclusions These results do not support use of the tested intervention as implemented here to increase agreement between prospectively registered and published trial outcomes. Other approaches are needed to improve the quality of outcome reporting of clinical trials.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Highly innovative study that uses a stepped wedge design to evaluate an intervention aimed at improving peer review.
- ⇒ The 13 participating high-impact journals are diverse with respect to medical specialty, journal size, location and peer review practices.
- ⇒ The intervention is simple and was deployed via pragmatic methods that could potentially be automated for scalability.
- ⇒ Pairing the tested intervention with an educational programme for editors and reviewers detailing specific recommendations for the assessment of registry information might have increased the intervention's effectiveness.

Trial registration number ISRCTN41225307.

INTRODUCTION

Clinical trial registries were developed more than 20 years ago, in large part to facilitate the unbiased reporting of results from clinical trials.^{1 2} To further support this goal, in 2005, the International Committee of Medical Journal Editors (ICMJE) mandated the registration of all clinical trials before the start of enrolment as a condition of publication in ICMJE-member journals.³ Shortly afterwards, the WHO also called for the prospective registration of all trials, and trial registration is now endorsed or required by many regulators, funding organisations and other stakeholders.^{4–9} While trial registries have proven to be a valuable tool for identifying and quantifying some forms of reporting biases within the biomedical literature, evidence shows that biased reporting persists.^{10–12} Specifically, discrepancies between prespecified trial outcomes and outcomes reported in published manuscripts are frequently

observed, indicating the presence of selective outcome reporting.^{11–16}

In theory, publicly available trial registries should allow for the identification and correction of selective outcome reporting during peer review. In practice, however, the continued high prevalence of selective outcome reporting indicates that registries have not fulfilled this potential. Several possible barriers exist, which may limit the effective use of registries during peer review. These barriers include the absence of clear policies at some journals identifying specific individuals responsible for reviewing registry entries and lack of familiarity among some reviewers and editors with registration requirements and available registry resources, including audit trails showing changes made to registry entries over time.^{17 18} Most reviewers are also volunteers with limited time available to devote to their reviews, and they may not feel that they have enough time to seek out registry information themselves. Additionally, because registry entries often include the names of trial investigators and sponsors, some reviewers may hesitate to access these sites in order to preserve blinded peer review.

This study was designed to test a solution to these barriers by pushing relevant trial registry information to peer reviewers assigned to evaluate clinical trial manuscripts. We hypothesised that providing manuscript reviewers with information about relevant registration requirements, the trial's registration status and the list of prospectively defined primary outcomes would improve clinical trial reporting by increasing the consistency between prospectively registered and published trial outcomes.

METHODS

Study design

This was a stepped wedge, cluster-randomised trial testing the impact of providing peer reviewers with registry information for the clinical trials they were reviewing on consistency between registered and published trial outcomes. The rationale and detailed description for the study methods have been published previously (online supplemental appendix).¹⁹ Clusters consisted of all eligible clinical trial manuscripts sent for peer review during the study period by an individual participating journal. This study was prospectively registered at the ISRCTN Registry on 24 October 2018.

JOURNAL SELECTION

We emailed the editors-in-chief at journals across a broad range of medical specialties to assess eligibility, feasibility and interest in study participation. Journals were approached for possible participation if they published an average of at least 10 clinical trial manuscripts per year and had endorsed the ICMJE requirement for prospective trial registration as a condition for publication. In order to participate, each journal's editor-in-chief had

to determine that there was an opportunity to improve on existing practices with respect to the use of registry information during peer review. To minimise the risk of a change in behaviour on behalf of submitting authors or peer reviewers due to participation in the study (ie, Hawthorne effect), we did not publicly disclose the identities of participating journals prior to study completion, and journals were asked not to provide reviewers with specific details about the purpose of the study. Additionally, in order to maintain the confidentiality of all relevant stakeholders and to encourage journal participation, we agreed not to publicly release outcome data identifying individual manuscripts or individual participating journals. Thirteen journals agreed to participate in the study (online supplemental table 1).

Manuscript eligibility

Manuscripts reporting results from a clinical trial were eligible for inclusion if they were submitted to a participating journal between 1 November 2018 and 31 October 2019 and were sent for external peer review. We defined clinical trials according to the definition used by the WHO and ICMJE: any research study that prospectively assigned human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.^{3 20} Manuscripts were not eligible if they described a study protocol without reporting trial results, or if they stated that the manuscript was not intended to report on the trial's primary outcome (ie, manuscripts describing only secondary analyses, secondary outcomes or reanalyses). Manuscripts were also ineligible if they had previously been peer reviewed by one of the other participating journals.

Screening procedures for eligible manuscripts were individualised for each participating journal in order to accommodate confidentiality requirements as well as existing editorial and peer review processes. At some participating journals, journal staff members screened submissions for manuscript eligibility before alerting Peer Reviewed Evaluation of Registered End-Points of Randomised Trials (PRE-REPORT) investigators to a potentially eligible submission; at others, the PRE-REPORT investigators directly screened all submitted manuscripts for eligibility via the journal's electronic manuscript management system.

Registry data abstraction

An investigator with expertise in the use of trial registries reviewed each included manuscript for a trial registration number or other evidence of trial registration. When manuscripts did not contain registration information, the investigator then performed a keyword and title search of ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform search portal and relevant national or regional registries to identify a matching registry entry. We assessed potential matches between registry entries and manuscripts by comparing the study title, interventions, sample sizes, enrolment dates, investigator names

and trial locations between the registry and manuscript. When this initial search failed to identify a match, a second investigator performed an additional registry search. If the second search also failed to identify a matching registry entry, the trial in question was labelled unregistered. After identifying the registry record for an included trial, we recorded the date of trial registration, enrolment dates and all registered outcomes as defined when enrolment began.

Randomisation

We used a stepped wedge, cluster-randomised design to control for potentially confounding factors at the journal level, including characteristics of submitted manuscripts and existing peer review processes.^{21 22} All participating journals began the 12-month study in the control phase and then crossed over into the intervention phase between months 3 and 10 after study initiation according to a randomisation schedule created by the study statistician using computer-generated random numbers. Manuscript screening and data collection processes did not change between the control and intervention phases.

Interventions

For journals in the control phase, there was no change to the instructions or information provided to peer reviewers as part of each journal's usual peer review practices. For eligible manuscripts submitted for peer review during the intervention phase, a PRE-REPORT investigator completed a registry data form (Supplementary Methods) which described whether the submitted trial was registered, the timing of registration relative to study enrolment and a description of the registered primary outcome(s) at the time study enrolment began. In some cases, registries are amended after enrolment has commenced to change the listed primary outcome. When this occurred, the primary outcome listed in the registry when enrollment began was the outcome included in the data form. These registry data forms were then distributed to all peer reviewers who accepted an invitation to review the included manuscript. For each journal, the method of distribution of data forms was determined by the editor-in-chief based on existing peer review processes and consisted of either incorporating this form into the downloadable version of the manuscript available to reviewers (six journals) or directly emailing the registry data form to reviewers through the journal's online manuscript tracking system within 24 hours of accepting the invitation to review (seven journals). We were not able to determine whether individual reviewers actually accessed the registry data forms. The data forms also included a reminder of the ICMJE requirements for prospective clinical trial registration as a condition of publication, though they did not include recommended actions in order to promote case-by-case decision-making by reviewers and editors having expertise specific to the content of each manuscript.

Outcome assessment

We tracked each submitted manuscript throughout the editorial process until the journal editors reached a final publication decision. For accepted manuscripts, we recorded the published definitions of all primary and secondary trial outcomes. Outcomes were classified as primary if they were described as such by study authors within the published abstract or manuscript. If the manuscript did not contain an explicitly identified primary outcome but did include a sample size calculation, we classified the outcome used for this calculation as the published primary outcome. If no primary outcome was explicitly identified and no sample size calculation was performed, the published primary outcome was considered undefined.

Our primary outcome for each included trial was the presence of a clearly defined, prospectively registered primary outcome consistent with the primary outcome in that trial's published manuscript. Trials were considered prospectively registered if a primary outcome was recorded on ClinicalTrials.gov or any of the Primary Registries in the WHO Registry Network (<http://www.who.int/ictrp/network/primary/en/>) prior to enrolment of the trial's first participant (or prior to 13 September 2005 for trials beginning before 1 July 2005). We classified an outcome as being clearly defined if it provided sufficient information to reasonably allow its identification on review of the study results and to allow an independent investigator to replicate the study. In most cases, this required the registry to include both a clearly defined time period for assessment and an outcome variable specifying a general domain (eg, 'pain'), specific measurement (eg, '11-point visual analogue scale') and specific metric (eg, 'change from baseline').²³

Outcomes were considered consistent if every primary outcome described in the registry was reported as a primary outcome in the manuscript, and every primary outcome reported in the manuscript was described as a primary outcome in the registry. We characterised outcome inconsistencies using the following classification: registered primary outcome is reported as secondary in the publication; registered primary outcome not reported in the publication; published primary outcome was described as secondary in the registry; published primary outcome was not registered; timing of primary outcome assessment differs between the registry and publication.^{15 24} By definition, trials which were not prospectively registered were considered to have introduced new primary outcomes in the publication.

Two investigators, who were blinded to whether manuscripts were in the control or intervention phase, independently evaluated all registered and published outcomes for clarity and consistency using a standardised assessment form. Before beginning the evaluation process, these outcome assessors participated in a series of training sessions focused on our standardised framework for performing outcome evaluations. Both outcome assessors could access relevant registry data

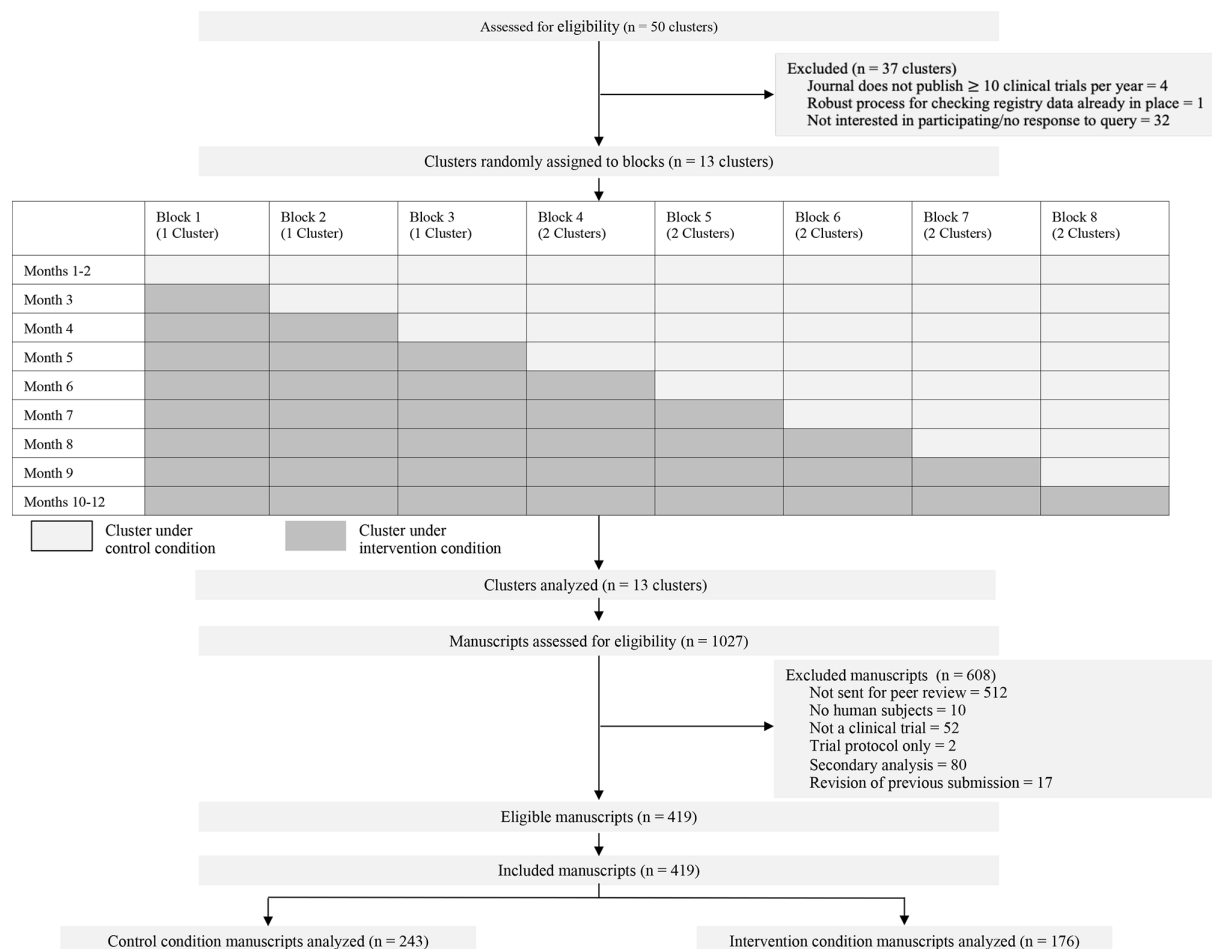


Figure 1 Flow diagram of eligible and included trials.

and a version of the published manuscript from which all submission and publication dates had been redacted. Dates were redacted in order to preserve blinding given the trial's stepped wedge format. After performing their initial independent evaluations, the assessors discussed all outcome discrepancies until a consensus was reached for each included trial. We measured inter-rater agreement with respect to both outcome clarity and consistency using Cohen's kappa.

Secondary outcomes of our study included the rates of acceptance for included manuscripts, the disclosure of a primary outcome change within the published version of the manuscript and time elapsed between initial manuscript submission and publication. As another secondary analysis involving those trials that were registered prospectively but without a clear primary outcome definition, we determined whether the vaguely defined registered outcome was broadly consistent with the published primary outcome. When possible, we also recorded the implications of primary outcome discrepancies for statistical significance of the primary outcome reported in the published manuscript. Discrepancies in secondary outcomes between prospectively completed registry entries and publications will be reported in a future manuscript.

Sample size

We used Qaqish's conditional linear family approach to generate 2000 simulated data sets with correlated binary outcomes corresponding to the trial's stepped wedge design in order to estimate power for the primary outcome.²⁵ Based on data from a prior systematic review, we expected that 33% of published manuscripts would have inconsistent outcomes during the control phase, and based on 2017 data, we assumed that the participating journals would accept for publication, on average, two trial manuscripts per month.¹⁰ We further assumed that responses from manuscripts from the same journal in the same phase would have an intraclass correlation of no more than 0.50 (ICC1), and that responses from manuscripts from the same journal but from different phases would have an ICC of at least 0.05 (ICC2). Under these assumptions, enrolling eight journals would provide at least 80% power to detect a 26% absolute reduction (80% relative reduction) in outcome inconsistency using a one-sided test at the 0.05 significance level. We recruited an additional five participating journals, for a total of 13, in order to accommodate a lower magnitude impact of the intervention, lower rates of manuscript publication or the possibility of journals dropping out of the study.

ANALYSIS

All manuscripts were analysed based on the study phase of the relevant journal at the time of manuscript submission, in keeping with an intention-to-treat approach. For our primary outcome, we used a linear mixed model to compare observations between intervention and control phases. This approach was used rather than logistic regression to allow for the estimation of differences in proportions between intervention-condition and control-condition trials, as the cluster-randomised, stepped wedge design limits the utility of comparing raw differences in proportions. The model included fixed effects for study phase (control or intervention) and study month as well as journal-specific random effects that allow for different levels of correlation depending on whether manuscripts are reviewed in the same month or in different months. We prespecified the use of a one-sided test at the 5% level based on the assumption that the intervention would be very unlikely to increase the publication of manuscripts with primary outcome inconsistencies and estimated 90% CIs to be consistent with this one-sided 5% level. We used a similar linear mixed model for the secondary outcome of acceptance of submitted manuscripts; however, for this outcome, we report a two-sided test and 95% CI because the expected intervention effect was less clear. Because most of the remaining secondary outcomes were based on observations within a subset of the published trials, there were not sufficient data to support fitting a statistical model for these outcomes.

We also performed a post hoc exploratory analysis involving all included trials regardless of publication status in which we classified trials according to whether: (1) the manuscript was published without a primary outcome that matched a clearly defined, prospectively registered primary outcome or (2) the trial was either unpublished or was published with a primary outcome matching a clearly defined, prospectively registered primary outcome. The same linear mixed model as used for the primary outcome was also applied to this exploratory outcome.

Patient and public involvement

Patients or the public were not involved in the design, conduct, analysis or reporting of this research.

RESULTS

Thirteen journals initially agreed to participate in the trial, one of which dropped out after the enrolment of one control-condition manuscript, which was not accepted for publication, leaving 12 journals which contributed manuscripts that were eventually published. From the participating journals, we assessed 1027 submitted manuscripts for eligibility, and 419 manuscripts were included in the trial (figure 1). Of these included manuscripts, 243 were submitted to journals in the control phase of the study, and 176 were submitted to journals in the intervention phase.

Table 1 Characteristics of included trials

Trial characteristics	Control condition (n=243)	Intervention condition (n=176)
Number of participants; median (IQR)	78 (35–172)	75 (42–149)
Trial phase; n (%)		
Phase 0-II	44 (18%)	41 (23%)
Phase III	26 (11%)	19 (11%)
Phase IV	27 (11%)	25 (14%)
Other/undefined	146 (60%)	91 (52%)
Funding source; n (%)*		
Industry	66 (27%)	55 (31%)
Federal government	79 (33%)	46 (26%)
Foundation	54 (22%)	25 (14%)
Other/self-funded	74 (30%)	65 (37%)
*Total adds to more than 100% because trials could have multiple funding sources.		

Analyses of all included trials

The control and intervention groups were similar with respect to study size and funding characteristics (table 1). Thirty-three trials (8%) were unregistered at the time of manuscript submission, 135 (32%) were registered retrospectively, and 251 (60%) were registered prospectively. Of the 419 included manuscripts, 173 (41%) were published by the participating journal and 246 (59%) were not.

Forty-three per cent (n=105) of manuscripts submitted to journals in the control phase were published, and 39% (n=68) of manuscripts submitted to journals during the intervention phase were published (linear mixed model-estimated percentage difference between intervention and control trials=–10%, 95% CI –25% to 4%) (online supplemental figure 1). Prospectively registered trials were more likely to be accepted for publication (117/251, 47%) than unregistered trials (7/33 trials, 21%; model-estimated difference=29% (95% CI 10% to 47%)). Among retrospectively registered trials, 49/135 (36%) were accepted for publication; the model-estimated difference between prospectively and retrospectively registered trials was 9% (95% CI –1% to 20%) (table 2).

Analyses of published trials

We evaluated our primary outcome among each of the 173 published trials by assessing for the presence of a clearly defined, prospectively registered primary trial outcome that matched the primary outcome reported in the publication. Forty of 105 (38%) control-condition trials and 27 of 68 (40%) intervention-condition trials met this standard. The linear mixed model did not show evidence of a statistically significant effect from the intervention (model-estimated difference between the proportions of intervention-condition and control-condition

Table 2 Timing of registration relative to trial initiation

Registration timing	Total 419	Published* n=173	Not published* n=246
Registered before enrolment began; n (%)	251	117 (68%)	134 (54%)
Registered after enrolment began; n (%)	135	49 (28%)	86 (35%)
Registered up to 6 months after enrolment began; n (%)	66	31 (18%)	35 (14%)
Registered 6–12 months after enrolment began; n (%)	20	6 (3%)	14 (6%)
Registered over 12 months after enrolment began; n (%)	49	12 (7%)	37 (15%)
Unregistered; n (%)	33	7 (4%)	26 (11%)

*Refers to publication within the participating journal.

trials meeting the primary outcome =−6% (90% CI −27% to 15%); one-sided p value=0.68) (figure 2). Most trials in both the control and intervention arms which failed to meet criteria satisfying our primary outcome did so because they were not prospectively registered (table 3). Among the trials which were prospectively registered with a clearly defined primary outcome, 36 (21%) had discrepancies between the registered and published primary outcomes (online supplemental table 2). We did not observe a notable difference in the proportion of trials with outcome discrepancies between the control (n=21, 20%) and intervention (n=15, 22%) groups. Cohen's kappa revealed substantial interrater agreement with respect to both whether registered primary outcomes were clearly defined (k=0.88, p<0.001) and consistency between registered and published primary outcomes (k=0.74, p<0.001).

When primary outcome discrepancies were present, the discrepancy resulted in promotion of a new primary outcome in the publication that was statistically significant or demotion of a registered primary outcome that was not statistically significant in 11 cases (7/21 (33%) control; 4/15 (27%) intervention). Four outcome changes did not result in promotion of a statistically significant outcome or demotion of a non-significant outcome. In 21 cases, we were unable to determine the impact of the outcome discrepancy on the statistical significance of outcomes in the published manuscript. Among trials with discrepancies between a clearly registered

primary outcome and a published primary outcome, the published manuscript disclosed or explained discrepancies between registered and published outcomes for one trial in the control group (5%) and three trials in the intervention group (20%).

The median time elapsed between submission and publication did not differ substantially between submissions made during the control phase (182 days, IQR 112–248) and the intervention phase (188 days, IQR 147–285).

Sensitivity analysis

There were 14 published trials (10 control and 4 intervention), which were prospectively registered, but had registered primary outcomes that were not clearly defined. Three of these trials (two control and one intervention) had published outcomes that were consistent with the available outcome information in the registry, though in each of these cases, the registered trial record was ambiguous such that published outcomes could have been measured and reported in multiple ways while still broadly matching the primary outcome as defined in the registry. We performed a sensitivity analysis in which we considered these three trials to have met criteria for our primary outcome. In this analysis, 42 of 105 published trials in the control condition (40%) and 28 of 68 published trials in the intervention condition (41%) were prospectively registered with matches between all registered and published primary outcomes (model-estimated difference between proportions of intervention-condition and control-condition trials=−3% (90% CI −23% to 18%); one-sided p value=0.58).

Post hoc analysis

A post hoc exploratory analysis involving all of the included trials regardless of publication status did not show evidence that the tested intervention increased the proportion of trials that were either rejected by the journal or published with a primary outcome matching a clearly defined, prospectively registered primary outcome (control=178/243 (73%), intervention=135/176 (77%); model-estimated difference between intervention-condition and control-condition trials=−1% (95% CI −13% to 10%), one-sided p value=0.58).

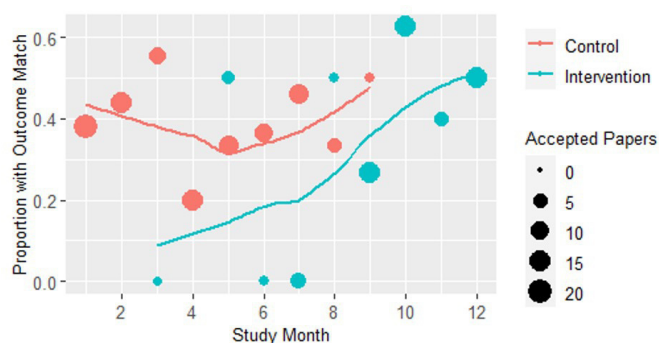


Figure 2 Proportion of accepted papers with clear, prospectively registered primary outcomes that match the published primary outcomes, by intervention phase and study month. Includes loess smoothing lines.

Table 3 Registration and outcome data for trial manuscripts published in the index journal

Outcomes for included trials	Control trials (n=105)	Intervention trials (n=68)
Prospectively registered; n (%)	71 (68%)	46 (68%)
Prospectively registered with clear primary outcome; n (%)	61 (58%)	42 (62%)
Prospectively registered with clear primary outcome that matches published primary outcome; n (%)	40 (38%)	27 (40%)

DISCUSSION

This stepped wedge, cluster-randomised trial included manuscripts sent for peer review over a 1-year period at a diverse group of biomedical journals to test whether pushing information from trial registries to peer reviewers would decrease the incidence of inconsistencies between prospectively registered and published primary outcomes. Fewer than 40% of the manuscripts accepted for publication had published primary outcomes that matched clearly defined, prospectively registered primary outcomes. The tested intervention did not decrease the incidence of inconsistencies between registered and published outcomes.

In contrast to the critical role that peer review plays in the dissemination of findings from biomedical research, relatively few studies have been performed to test innovations aimed at improving current peer review processes.^{26–34} Furthermore, the majority of trials which have tested interventions related to peer review are limited in their generalisability because they were performed at a single journal.^{33–34} No prior randomised trials have examined interventions to ensure consistency between registered and published outcomes.³⁴ Our finding that fewer than half of the included trials had published primary outcomes matching prospectively registered primary outcomes emphasise the urgent need to identify interventions that are effective at increasing the quality of prospective trial registration, reducing post hoc outcome switching and improving trial reporting.^{35–36} Although the current trial did not show evidence that the tested intervention was beneficial, it does demonstrate the feasibility of testing peer review interventions using rigorous methodology, and offers a potential framework for similar trials in the future. Specifically, applying a stepped wedge design with clusters defined by the participating journals allowed us to control for journal-specific confounders while balancing logistical considerations involved in integrating the intervention into existing editorial workflows at each journal.

Several lessons from the implementation of this study may increase the likelihood of ascertaining a benefit when testing future peer review-based interventions. First, in order to limit the risk that trial participation itself, rather than the intervention, might be responsible for changing reviewer behaviour (ie, risk of a Hawthorne effect), we deployed the intervention at participating journals without notifying peer reviewers about the study and without providing educational material to reviewers explaining the importance of trial registration

and the scope or implications of outcome switching. In retrospect, these educational efforts could have taken place without disclosing the existence of the trial and would likely be incorporated into a roll-out of this type of intervention outside the context of a trial. Therefore, it would have been reasonable to include such efforts as part of the tested intervention. Additionally, among our participating journals, those that published the largest number of clinical trials were randomly assigned to cross into the intervention condition towards the end of the study period. Although it is unlikely that this impacted the study findings in this case, it did decrease the power of our trial to identify a beneficial treatment effect. Future trials randomising at the journal level should consider employing stratified randomisation based on the anticipated number of included manuscripts. Finally, we observed that 40% of the included trials which were published were either unregistered, registered retrospectively or registered with a vague primary outcome. In these cases, intervention at the time of peer review might prevent publication of such a trial in the participating journal, thereby aligning that specific journal with the guidance from the WHO and ICMJE requiring prospective registration as a condition of publication. Intervention during peer review, however, does not solve the more fundamental problem that unregistered or retrospectively registered trials, or trials with vaguely defined primary outcomes, are often conducted and regularly published. Instead, solving this problem will require interventions further upstream in the trial process, before trial enrolment is initiated in the first place. For example, we recommend that Institutional Review Boards confirm the timely and clear registration of clinical trials prior to granting study approval.³⁷

This study has a number of strengths which should increase confidence in the validity of these findings. First, we included more than 400 clinical trials from a group of well-respected journals that represent a diverse range of clinical specialties. This group included journals published in both the USA (n=9) and Europe (n=4), and participating journals were also heterogeneous with respect to editorial and peer-review processes, number of trials published and impact factor, thereby increasing the external validity of these findings. The use of a cluster design, as opposed to randomisation of individual submitted manuscripts, helped minimise the risk that peer reviewers and decision editors assessing control-phase manuscripts would be contaminated by exposure to the intervention. Additionally, the stepped wedge

design allowed us to control for potentially confounding characteristics unique to each participating journal by facilitating within-cluster comparisons between outcomes in the preintervention and postintervention phases.^{21 22}

This study also has several limitations, which should be considered when interpreting our findings. First, while the included journals were diverse in many important respects, it is our impression that the editors of each journal primarily or in part chose to participate because they had a particular interest in improving both the quality of trial reporting and current peer review processes. While it is likely that most journal editors share these characteristics, the intervention may perform differently among other journals. Second, the stepped wedge design allows for partial control of secular trends affecting peer review processes over the duration of the trial, but we are unable to entirely exclude the possibility that such trends influenced the study results. Third, the determination of whether registered outcomes were clearly defined and comparisons between registered and published outcomes both necessarily rely on subjective judgement. We addressed this concern by having two outcome assessors independently perform each comparison using standardised data forms and by blinding these assessors to the intervention status of the included trials. Both assessors were physicians with expertise in the use of registry data and with previous experience performing similar comparisons between registered and published outcomes. Fourth, the intervention was delivered to reviewers at some of the participating journals by email after they had already agreed to review; we were not able to confirm that these emails were received and considered when the reviews were written. As a result, we are unable to determine which step(s) within the peer review process allowed outcome discrepancies to persist despite our intervention. Future studies should consider incorporating the use of qualitative methods to better understand how reviewers and editors might use similar interventions most effectively.

In conclusion, this stepped wedge trial found that the tested method of distributing an information sheet containing registry data to peer reviewers was ineffective at increasing the proportion of published clinical trial manuscripts reporting primary outcomes that matched prospectively registered primary outcomes. Alternative methods of implementing the intervention may have increased its effectiveness, though this requires further study. The continued high prevalence of unregistered or retrospectively registered trials and of discrepancies between registered and published trial outcomes necessitate the identification of effective interventions for these problems.

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Peer Reviewed Evaluation of Registered End-Points of Randomized Trials
(PRE-REPORT study)

Supplementary Appendix: Study Protocol and Statistical Plan

Contents of the supplementary appendix:

- 1. Summary of changes to study protocol and statistical plan**
- 2. Original study protocol and statistical plan (July 10, 2018)**
- 3. Final study protocol and statistical plan (Nov 6, 2021)**

Peer Reviewed Evaluation of Registered End-Points of Randomized Trials
(PRE-REPORT study)

Protocol/Statistical Plan Revision Sequence

Jul 10, 2018	Original protocol and statistical plan (version 1) completed
Sep 25, 2018	Amendment to protocol and statistical plan (version 2)
	List of participating journals updated to include Clinical Orthopaedics and Related Research, Thorax, Heart, and British Journal of Ophthalmology
	Primary outcome clarified to include an explicit definition of prospective registration and to describe criteria for assessing the clarity of registered outcomes.
Oct 26, 2018	Study registered with ISRCTN: ISRCTN41225307
Nov 1, 2018	Study screening initiated
Dec 19, 2018	Study protocol and statistical plan submitted for publication (BMJ Open)
Jun 1, 2019	Study protocol and statistical plan published online: Jones CW, Adams A, Weaver MA, <i>et al.</i> Peer reviewed evaluation of registered end-points of randomised trials (the PRE-REPORT study): protocol for a stepped-wedge, cluster-randomised trial. <i>BMJ Open</i> 2019; 9 :e028694. doi: 10.1136/bmjopen-2018-028694
Oct 31, 2019	Study screening concluded
Nov 6, 2021	Amendment to protocol and statistical plan (version 3)
	Added registry identifier to protocol.
	Updated statistical approach to reflect use of a linear mixed model.
	Added reference #51: Hemming K, Taljaard M, Forbes A. Analysis of cluster randomized stepped wedge trials with repeated cross-sectional samples. <i>Trials</i> 2017; 18 :101.

PRE-REPORT Study Protocol

Peer Review Evaluation of Registered End-Points of Randomized Trials

The PRE-REPORT Study

Study Protocol and Statistical Plan

Version 1

July 10, 2018

Principal Investigator: Christopher W Jones

Cooper Medical School of Rowan University

Camden, NJ USA

PRE-REPORT Study Protocol

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PRE-REPORT Study Protocol

1. Abstract

Clinical trials are a critically important means of advancing medical knowledge and improving clinical outcomes. However, the reliability of information generated by clinical trials depends in part on consistency between pre-planned and reported primary study outcomes. Selective outcome reporting occurs when investigators publish manuscripts describing trial outcomes which are inconsistent with the outcomes they planned to assess as the start of the trial. Often this practice results in the selective publication of statistically significant study outcomes which favor the intervention being studied, while outcomes which show that an intervention may not be effective are suppressed. This form of research misconduct is unfortunately quite common, affecting approximately one-third of all published clinical trial manuscripts.

The World Health Organization, International Committee of Medical Journal Editors, National Institutes of Health, and many other stakeholders currently require that investigators for most human-subjects trials upload a summary of the planned trial methods to a publicly available clinical trial registry such as ClinicalTrials.gov before beginning enrollment. Trial registries therefore have the potential to help identify and stop selective outcome reporting during the peer review process by allowing peer reviewers to compare pre-specified, registered outcomes with the outcomes presented in manuscripts submitted for publication. However, the persistent high rate of selective outcome reporting among published trials demonstrates that current peer review and editorial practices do not effectively prevent this form of research misconduct.

This year-long study will test whether providing peer reviewers with a summary of registered, pre-specified primary trial outcomes will decrease the incidence of inconsistencies between prospectively registered and published primary outcomes among clinical trials published in participating journals. The tested intervention will consist of a brief email describing the timing of registration and definitions of any prospectively registered primary outcomes, which peer reviewers will receive after they agree to review a clinical trial manuscript under consideration at one of the participating journals. Using a stepped-wedge, cluster randomized trial design, we will transition journals between the control group (no email to reviewers) and intervention group (email to reviewers) at one month intervals. Blinded outcome assessors will compare registered and published primary outcomes for all included trials, and we will compare rates of selective outcome reporting between the control and intervention groups. Results from this trial will improve our understanding of how to identify and prevent selective outcome reporting using a simple, scalable intervention.

PRE-REPORT Study Protocol

2. Specific Aims

Clinical trials are a critical means of advancing medical knowledge, and trial results form a cornerstone of most clinical guidelines and practice. The identification of a well-defined, pre-specified primary outcome is an essential trial component. Equally important is consistency between this pre-specified trial outcome and the outcome reported in the published manuscript. Inconsistent pre-specified and reported outcomes (i.e. “selective outcome reporting”) threaten the validity of reported trial results by increasing the likelihood that chance or selective reporting, rather than true treatment effects, account for the conclusions in published reports. This often results in the selective publication of statistically significant outcomes favoring the intervention being studied, while outcomes showing that an intervention may not be effective are suppressed. As a result, selective outcome reporting can directly influence both clinical policy creation and physician decision-making in ways that adversely influence patient care.

Despite legislative action in both the United States (US) and European Union (EU) aimed at limiting selective outcome reporting, this remains a common form of research misconduct, occurring in approximately one-third of published clinical trials.

Clinical trial registries provide a publicly available record of pre-specified trial outcomes, allowing planned outcomes to be compared against outcomes reported in published manuscripts. Despite mandates requiring trial registration which have been in place for over a decade, discrepancies between pre-planned and reported outcomes remain common, indicating a failure of journal editors and reviewers to incorporate registry information into the peer review process.

This project is intended to improve the quality of clinical trial reporting by reducing selective outcome reporting. We propose a multi-journal sequential crossover study (stepped-wedge cluster-randomized trial) of an efficient, easy to implement intervention that will streamline the use of registry information during the peer review process. The intervention will provide editors and peer reviewers with information on (1) the timing of trial registration relative to the trial’s initiation, (2) registered primary outcome measure(s) at the time enrollment began, and (3) the timing and nature of any changes to the registered primary outcome measure(s) during the course of the trial. Project goals will be achieved through completion of the following specific aims:

Aim 1: To test whether providing peer reviewers with information from clinical trial registries about trial outcomes will decrease the incidence of inconsistencies between prospectively registered and published primary outcomes.

Hypothesis 1: Providing peer reviewers with information on prospectively registered clinical trial outcomes will reduce the incidence of selective outcome reporting in published manuscripts.

Aim 2: To test whether providing peer reviewers with information about registered trial outcomes will decrease the proportion of trials with inconsistencies between registered and published outcomes that fail to disclose the change in outcome within the published manuscript.

Hypothesis 2: Among published trials with inconsistencies between registered and published primary outcomes, providing peer reviewers with clinical trial registry information will increase the proportion of published manuscripts which disclose and explain the outcome change.

Results from the proposed trial will advance knowledge of how to identify and prevent selective outcome reporting during peer review. The long-term effect of this and subsequent dissemination and implementation efforts have the potential to dramatically diminish selective outcome reporting in the clinical trial literature, thereby reducing a critical source of research misconduct during trial publication and improving the quality of reported clinical trial results.

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3. Background and Significance

Randomized trials can reliably establish causality between interventions and patient outcomes, and therefore form a critically important foundation upon which much of the evidence-based medicine movement has been built. However, the reliability of clinical trial data depends on the consistent reporting of pre-specified trial outcomes.^{1,2} Often, changes between the pre-specified and reported outcome reflect selective outcome reporting in which investigators or study sponsors report statistically significant treatment effects which may result from multiple hypothesis testing and chance rather than actual efficacy of the studied intervention.³⁻⁵ Selective outcome reporting is widespread throughout the published biomedical literature, occurring in an estimated 30-40% of published clinical trials.^{3,6-9}

Clinical trial registries were developed, in part, to solve the problem of selective outcome reporting.¹⁰⁻¹³ Registries are publicly available databases that make trial information available to both the scientific community and the general public. This information includes descriptions of trial eligibility criteria and treatment arms, along with definitions of pre-specified primary and secondary outcomes. Since 2005, the International Committee of Medical Journal Editors (ICMJE) has mandated the prospective registration of clinical trials as a condition of publication in member journals,¹⁴ and in 2007 the Food and Drug Administration Amendments Act made prospective registration with ClinicalTrials.gov a requirement under federal law for many US clinical trials.¹⁵ Similar requirements have also been implemented by numerous other stakeholders and regulators, including the World Association of Medical Journal Editors,¹⁶ the World Health Organization,¹⁷ the European Union,¹⁸ and the National Institutes of Health.¹⁹

Despite the widespread adoption of registration requirements, a substantial body of evidence shows that selective outcome reporting remains common,⁶ and is routinely observed among trials published in both general medical and specialty journals,^{8,20,21} and across a wide range of medical specialties and funding sources.^{7,9,21-37} Because trial registry data are publicly available, selective outcome reporting can be detected during peer review. However, the ongoing frequency of this form of research misconduct indicates that current peer review practices have proven largely inadequate to identify and facilitate correction of selective outcome reporting.

Several barriers impair the ability of standard peer review processes to detect and correct selective outcome reporting. (1) Some reviewers and journal editors are not fully aware of existing registry resources, or of best practices regarding trial registration and outcome reporting.^{38,39} (2) Submitted manuscripts often fail to include the unique identifiers assigned to each trial at the time of registration, thereby necessitating an extensive search of multiple trial registries to identify a matching registry entry.⁴⁰ (3) Many registries allow investigators to edit existing registry data at any time, meaning that the registered trial outcomes can be changed after trial completion to match the outcomes reported in a submitted manuscript. Such changes occur in more than 30% of registered trials.^{41,42} ClinicalTrials.gov and WHO-approved trial registries track these changes, but accessing the audit trail which captures changes to prospectively registered outcomes is more time-consuming than simply viewing the updated registry webpage. (4) Some reviewers may be hesitant to review registry sites because these sites typically list the study sponsor and participating enrollment sites and identify the principal study investigator. Thus, direct registry review is not compatible with blinded peer review.

To address each of these barriers, we have developed a simple, scalable, journal-level intervention in which information from the clinical trial registry is provided to decision editors

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and peer reviewers for all randomized trials. The intervention will involve a comprehensive third-party registry search, abstraction of information from the registry, and provision of this information to peer reviewers and editors. We propose a randomized, stepped wedge trial to test the effect of this intervention on selective outcome reporting. The goal of this study will be to determine whether implementation of the intervention improves clinical trial reporting by increasing the consistency between prospectively registered and reported trial outcomes.

4. Methods

Study Design Overview: We will perform a stepped-wedge, cluster-randomized trial to test the impact of providing peer reviewers with easily accessible registry information on the consistency between registered and published trial outcomes. Individual clusters will comprise all clinical trial manuscripts sent for peer review during the pre- or post-intervention phase for each journal. A cluster design, rather than manuscript-level randomization, is necessary to minimize contamination of the intervention: Journals typically utilize a limited roster of decision editors and peer reviewers, and once an individual has participated in the intervention condition he or she may be more likely to seek out registry data when evaluating subsequent manuscripts.

Stepped-Wedge Randomization: At the beginning of a stepped-wedge trial, all participating clusters are in the control phase. Clusters are then crossed over to the experimental intervention in random order, and at the end of the trial all clusters receive the experimental intervention.^{44,45} An important advantage of this study design is the ability to compare pre- and post-intervention outcomes within individual clusters, thereby controlling for potentially confounding characteristics unique to those clusters.⁴⁶ For example, participating journals differ with respect to their existing peer review processes, as well as the volume, quality, and type of individual manuscripts undergoing review. The stepped wedge design also allows for controlling the study analyses for the confounding effect of time.⁴⁶ This is important given that registration, reporting, and peer review practices may change over the duration of the study.

Table 1. Sample study timeline. Shaded cells represent clusters in the intervention group.

Journal	Month											
	1	2	3	4	5	6	7	8	9	10	11	12
<i>Gastroenterology</i>												
<i>Acad Emerg Med</i>												
<i>Neurology</i>												
<i>Arch Phys Med Rehabil</i>												
<i>J Am Coll Surg</i>												
<i>Int J Cancer</i>												
<i>Ann Emerg Med</i>												
<i>Am J Transplant</i>												

Study Timeline: During months one and two, all participating journals will be in the control group, and therefore no registry data will be provided to peer reviewers by the study team. Beginning in month 3, participating journals will be crossed over into the intervention group in random order at one-month intervals. During the final two months of enrollment all participating journals will be in the intervention group. Data collection will continue until all manuscripts

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from participating trials accepted for publication have been published. At that point blinded outcome assessors will determine the consistency of the registered and published outcomes.

Manuscript Eligibility Criteria: Manuscripts reporting the results of a clinical trial will be eligible for inclusion if they are sent for peer review during the one year study period by any of the participating journals. In order to be included manuscripts must include human subjects or groups of humans (e.g. cluster randomized trials), and must report results from an interventional study which prospectively assigns participants to one or more arms consisting of health-related interventions in order to evaluate an effect on health outcomes.¹⁴ We will exclude manuscripts if they describe a planned trial without reporting trial results, or if they clearly state that the manuscript is not intended to report on the trial's primary outcome (ie. manuscript describes only secondary or subgroup analyses). We will also exclude resubmitted manuscripts which have already completed the first round of peer review at the time our study begins. Manuscripts sent for peer review from multiple participating journals during the study will be analyzed in the first journal's cluster, and will not be included a second time if resubmitted to a different participating journal.

Randomization: Using a random number generator, we will randomly order participating journals and assign them to crossover dates at monthly intervals between the beginning of study month 3 and the end of month 10 (Table 1). The editor-in-chief and relevant journal staff members will be notified through email of their crossover date at the beginning of the study, with reminders sent two weeks before the crossover date and on the crossover date.

Control Phase: The stepped-wedge crossover design will involve exposing each participating journal (cluster) to the control group initially. During the control phase, the PRE-REPORT study team will review potentially eligible trial manuscripts sent for peer review, and will determine manuscript eligibility based on the criteria above. The specific mechanism by which the study team will access potentially eligible manuscripts will be determined on a case-by-case basis at each of the participating journals. During this phase no registry data will be returned to the journal staff, editor, or reviewers.

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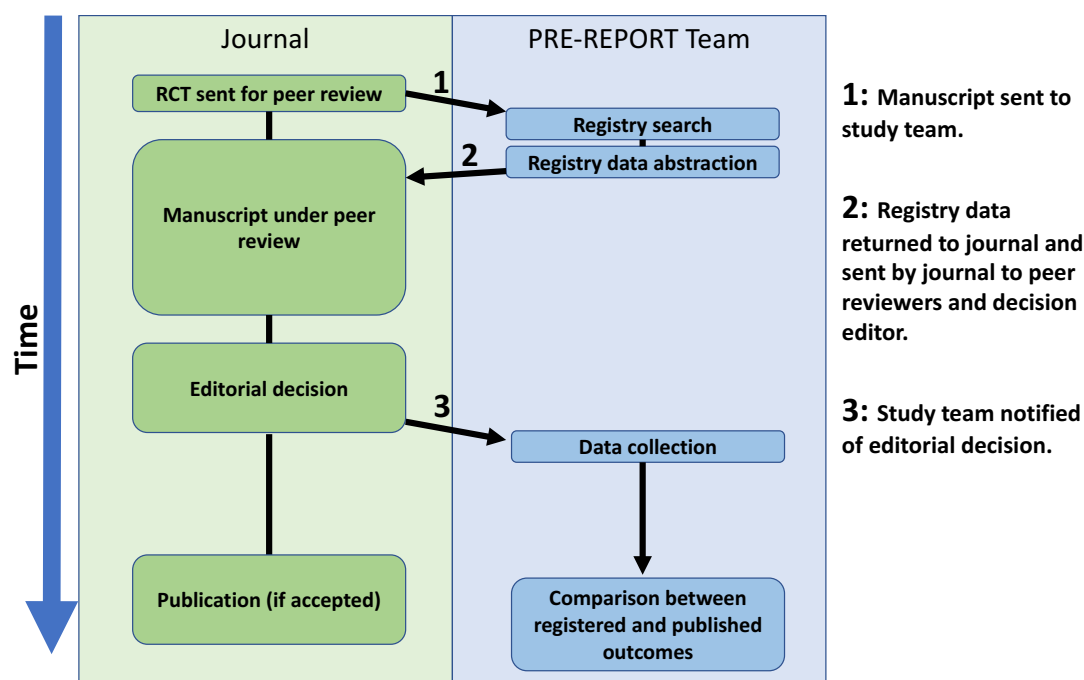


Figure 1. Information flow between participating journals and PRE-REPORT team.

Intervention Phase: At the randomly designated crossover date for each journal, the journal will be crossed over into the intervention phase. During the intervention phase, when alerted that a potentially eligible trial has been sent for review, the PRE-REPORT study coordinator or principal investigator will assess its eligibility (Figure 1). If eligible, the coordinator or investigator will perform a registry search. After confirming a match between the submitted manuscript and a corresponding registry entry, the PRE-REPORT staff member will abstract information from the registry into the registry data form, including the following information: whether the trial was registered, the date of registration, the registered primary outcome(s) at the time study enrollment began, the currently registered primary study outcome(s), and the dates of any outcome changes. Most registries allow investigators to alter the registered outcomes even after the initial registration information is submitted, though audit trails which record these changes make it possible to identify and report outcome changes over time. Our study team will then distribute the completed data form to the peer reviewers selected to review the manuscript in question (Appendix). The specific mechanism by which this information will be distributed to the appropriate reviewers will be determined on a case-by-case basis with each participating journal. If the search fails to identify a registration entry for the study, the absence of registry data will be reported to the peer reviewers. Our study team will return the completed data form to the journal staff within 24 hours of receiving the manuscript in most cases and within 72 hours in all cases to ensure that the registry data can be incorporated into editorial decision making.

Mechanism of Effect: Reviewers/editors in the intervention group will receive the registry data sheet, allowing them to easily compare primary outcomes between the registry and manuscript and to ask authors to correct or explain any inconsistencies before manuscript publication.

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Registry Data Abstraction: For each eligible manuscript, the PRE-REPORT program coordinator (Ms. Adams) or principal investigator (Dr. Jones) will review the published manuscript for a trial registration number or other evidence of trial registration. If no registration information is provided within the manuscript, he or she will then search ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform search portal, and any national or regional registries corresponding to the principal investigators' countries of origin (eg, Australian New Zealand Clinical Trials Registry) by keyword and title to identify a matching registry entry. Potential matches between registry entries and manuscripts will be assessed by the principal investigator by comparing the study title, interventions, planned sample sizes, enrolment dates and trial locations between the registry and manuscript. Manuscripts will be classified as unregistered when they do not include a registry identification number and when the registry search does not identify a matching registry entry. This registry search strategy has been previously used by our research group^{25,47} and others.^{8,9,21}

Data Collection: Participating journals will supply the PRE-REPORT study team with a copy of the initial manuscript submitted for peer review, which will be used to perform the registry search, as detailed above. We will collect data from the relevant registry entry for each trial, including the registry used, registration date, and study start date. Journals will notify the PRE-REPORT team when an initial editorial decision (accept, revise, reject) has been reached on an included trial. When the initial decision involves a request for revisions, journals will also notify our study team when a final editorial decision has been made. For accepted manuscripts, after publication of the finalized version of the manuscript has occurred we will abstract additional data from the final manuscript using a standardized data collection template. Data abstracted at this stage will include information about the sample size, description of the statistical plan, and the published primary and secondary outcome definitions. Any outcome(s) described by study authors within the abstract or manuscript as primary study outcomes will be considered primary outcomes. If no outcome is explicitly identified as the primary outcome but a sample size calculation was performed, the outcome used in this calculation will be considered the primary outcome. If no outcome was explicitly identified as the primary outcome, and no sample size calculation was performed, the published primary outcome will be considered undefined.

Primary Outcome: Our primary study outcome will be consistency for each included published clinical trial between the prospectively registered primary trial outcome(s) and the published primary outcome(s). We will characterize outcome inconsistencies according to the classification of outcome discrepancies developed by Chan et al³ and refined by Mathieu et al (Table 2).⁸ Outcomes will be considered to be consistent if every primary outcome described in the registry is reported as a primary outcome in the manuscript, and every primary outcome reported in the manuscript is described as a primary outcome in the registry. Two investigators will independently assess all registered and published outcomes for consistency. Both investigators will be blinded to whether the manuscript was in the control or intervention phase and to the content of the manuscript draft sent for initial peer review. Inter-rater reliability will be assessed using a kappa value; our group has previously performed similar analyses with excellent inter-rater agreement ($\kappa = 0.87$).²⁵ Any discrepancies will be resolved by consensus after having both authors review the full text of the manuscript and registry; persistent disagreements will be adjudicated by a third investigator. Trials not prospectively registered will be considered to have inconsistent outcomes, as these publications will introduce new outcomes by definition.

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Table 2. Classification of discrepancies between registered and published primary outcomes.
1. Registered primary outcome reported as secondary outcome in published manuscript
2. Registered primary outcome not reported in published manuscript
3. Published manuscript includes new primary outcome
4. Published primary outcome described as secondary in registry
5. Timing of assessment of primary outcome variable differs between registry and manuscript

Secondary Outcomes: Among trials with primary outcome inconsistencies present, we will assess whether the published manuscript included a disclosure of this change and an explanation of the reason for the change. Also, by comparing primary outcomes in the initial submitted manuscript to the primary outcome in the published version of the manuscript, we will be able to directly measure the impact of peer reviewer/editor feedback related to outcome consistency. We will also measure and report changes in acceptance rates for clinical trials over the course of our study period. Additionally, we will classify any observed primary outcome inconsistencies according to whether or not they impact the statistical significance of the published outcome. Exploratory outcomes will include the impact of the intervention on the delay between initial submission and publication, discrepancies between secondary registered and published outcomes, and the rate of inconsistencies between the registry and manuscript for factors other than study outcomes (sample size, eligibility criteria, study results).

Trial Registration: The trial protocol and outcomes will be registered at ClinicalTrials.gov before the study begins, and outcome data will be uploaded to ClinicalTrials.gov after study completion.

5. Analytic Plan

Sample Size and Power: We used simulations to calculate power for comparing our primary outcome (outcome inconsistency) between intervention and control phases.⁴⁸ We used Qaqish’s conditional linear family approach to generate 2,000 simulated datasets with correlated binary outcomes corresponding to the stepped-wedge design described above.⁴⁹ Based on our prior systematic review we assumed that 33% of published manuscripts would have inconsistent outcomes during the control phase,⁶ and based on 2017 data we assumed that the participating journals would accept for publication, on average, 2 trial manuscripts per month. We further assumed that responses from manuscripts from the same journal in the same phase would have an intra-cluster correlation of no more than 0.50 (ICC1), and that responses from manuscripts from the same journal but from different phases would have an intra-cluster correlation of at least 0.05 (ICC2). Generally, higher levels of ICC1 lead to decreased power whereas higher levels of ICC2 lead to increased power.⁵⁰ Under these assumptions, 8 participating journals will provide at least 80% power to detect an 80% reduction in outcome inconsistency using a one-sided test at the 0.05 significance level. We have elected to use a one-sided test because it is extremely unlikely that the intervention could lead to an increased rate of outcome switching.

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Data Analysis: For all analyses, we will use all available relevant manuscript data from each participating journal. Manuscripts will be counted in the month in which notification from the journal is first received by the PRE-REPORT study team. For our primary outcome of outcome inconsistency, we will use mixed effect logistic regression models to compare observations between intervention and control phases. Mixed models allow for different numbers of manuscripts per journal, and also account for correlated responses between manuscripts published within the same journal. The model will include fixed effects for study phase (control or intervention) and study month, and will include journal-specific random effects that allow for different levels of correlation depending on whether manuscripts are reviewed in the same month or in different months. A one-sided test at the 5% level will be conducted to compare the intervention and control phases. In addition, an odds ratio will be estimated along with a 90% confidence interval (to be consistent with the one-sided 5% level). For Aim 2, the sample size will be conditioned on studies that have been published with inconsistencies, and so will be greatly reduced relative to Aim 1. If the sample size allows, we will fit a similar model for Aim 2. Otherwise, we will present descriptive statistics to compare study phases.

6. Participating Journals

Journal Selection: Coordinated information transfer between the PRE-REPORT study team and participating journals is required to ensure the trial's success. Participating journals must also not already have in place a robust method of ensuring that a comprehensive registry analysis is performed for every trial manuscript undergoing peer review. Finally, participating journals must regularly publish clinical trials, which we define as publishing a mean of at least 10 trials per year over the past three years. Journals solicited for participation in the proposed study were initially identified through personal networks of the PRE-REPORT study team and through review of participants in the 2017 Peer Review Congress. Additional participating journals will be identified by approaching the editors of high-impact journals across a wide range of general medical and surgical journals and medical specialties.

Current Participants: The editors-in-chief of the following journals have agreed to participate:

Academic Emergency Medicine
American Journal of Transplantation
Annals of Emergency Medicine
Archives of Physical Medicine & Rehabilitation
Gastroenterology
International Journal of Cancer
Journal of the American College of Surgeons
Neurology

7. Data Management and Confidentiality

Responsible Conduct of Research Plan: All study investigators, consultants, and research staff take the Responsible Conduct of Research (RCR) seriously, and are actively engaged in both formal and informal training programs. Formal training includes completion of human subjects

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research training programs required by their local IRBs to remain active participants in research activities within their respective institutions. Within the past year, Dr. Jones has completed the NIH Protecting Human Research Participants, CITI Human Subjects Basic Course, and CITI Good Clinical Practice training courses. He mentors numerous residents and medical students in RCR by leading monthly journal club sessions for medical students, resident physicians, and faculty members within the Cooper University Hospital Department of Emergency Medicine. All investigators and consultants have previously published manuscripts addressing responsible publication practices.

Confidentiality: Our study team will strictly guard the confidentiality of all unpublished manuscripts we receive for review. Only two study members (Jones, Adams) will have access to unpublished manuscripts, and these manuscripts will be stored on a secure, password protected database housed at Cooper University Hospital. Even though no patient information will be collected as part of the study, data storage measures will meet or exceed all existing NIH and local institution requirements for the storage of identifiable health information. These manuscripts will be permanently deleted from the study database following completion of the study analyses. All data from clinical trial registries and published manuscripts are publicly available.

Journals utilizing blinded peer review will not be asked to disclose the identities of their reviewers or editors to our study team; participating journals will have the option of establishing an administrative contact within the journal's editorial office through whom all contact between the study team and the journal will occur. If the editor-in-chief of a participating journal explicitly requests that the PRE-REPORT study team assumes responsibility for directly contacting relevant editors or reviewers in order to reduce the administrative burden that participation will place on journal staff, we will work with the journal in question to establish an individualized work flow which will maintain the strict confidentiality of the peer review process. The principal investigator will enter into and comply with a confidentiality agreement between the study team and participating journals which request that such an agreement be in place.

REDCap will be used for data entry and storage. REDCap is a web-based, secure clinical research database with features to constrain the form and values of inputted data in order to reduce data entry errors.⁵¹

8. Human Subjects Protection

Per the United States Federal Code of Regulations, Human Subjects Research must meet the following conditions:

46.102(d) Research means a **systematic** investigation, designed to develop **generalizable** knowledge.

46.102(f) Human subject means a living individual about whom an investigator conducting research obtains data through **interaction** with the individual OR obtains **identifiable** Protected Health Information (PHI).

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This study does not involve the collection of human subject data, and does not involve the collection of identifiable protected health information. Therefore this study does not involve human subjects research. The study protocol will be submitted to the Cooper University Hospital Institutional Review Board (IRB) to confirm this determination that it does not involve human subjects research and is therefore exempt from the need for IRB review.

9. Personnel

Our study brings together a group of investigators and consultants who are national experts in the domains relevant to this trial. The principal investigator is Christopher Jones, MD, Assistant Professor of Emergency Medicine at Cooper Medical School of Rowan University in Camden, NJ. Co-investigators are:

Timothy Platts-Mills, MD, MSc, Assistant Professor of Emergency Medicine, University of North Carolina Chapel Hill, Chapel Hill NC;

David Schrager, MD, MPH, Professor of Emergency Medicine, University of California, Los Angeles School of Medicine, Los Angeles CA;

Benjamin Misemer, MD, Flint Hurley Medical Center, Flint MI;

Mark Weaver, PhD, Research Assistant Professor, Department of Biostatistics, University of North Carolina Chapel Hill, Chapel Hill NC.

Program Coordinator: Amanda Adams, MS, Research Librarian, Cooper Medical School of Rowan University.

Pertinent areas of expertise are clinical trial registration (Jones, Platts-Mills), journal editorial practices (Platts-Mills), peer review (Platts-Mills, Jones, Weaver), outcome reporting (Jones, Platts-Mills), and cluster-randomized trial design and analysis (Weaver). Drs. Jones, Platts-Mills, and Weaver have collaborated for over 6 years in a highly productive partnership involving multiple studies across a broad range of topics, including trial registration and selective outcome reporting. This includes a study published in the *BMJ* in 2013 which used trial registry data to show evidence of publication bias among large randomized controlled trials, and which influenced the World Health Organization's decision to call for improved trial reporting.^{52,53} Additionally, Dr. Platts-Mills has worked closely on issues related to peer review through his role as a member of the *Annals of Emergency Medicine* Editorial Board. Dr. Schrager is a deputy editor at *Annals of Emergency Medicine*, and an editor at *JAMA*. He has a longstanding track record of studying the dissemination of clinical trial results. Dr. Misemer has collaborated with Dr. Jones and Dr. Platts-Mills on prior work involving selective outcome reporting. Amanda Adams, the program coordinator, is a research librarian experienced in the use of Clinicaltrials.gov. She has also collaborated with our research group in the past on a study assessing the accuracy of registry information.

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11. Appendix

Sample Data Sheet for distribution to peer reviewers:

You recently agreed to review the following study: **Intravenous Fluid Therapy for the Treatment of Emergency Department Patients with Migraine Headache** for *Annals of Emergency Medicine*.

You may find the following information to be helpful as you perform your review. The trial was registered with ClinicalTrials.gov (NCT02933060) on October 14, 2016, prior to the start of enrollment.

At the time enrollment began the primary outcome measure was listed as:

Pain score at 60 minutes [Time Frame: 60 minutes] The primary outcome will be the difference in verbal pain rating (0-10) between the start of the study intervention and one hour later, at completion of the intervention. The minimum clinically significant difference between treatment groups on the 0-10 verbal scale is 1.3.

There were no changes to the registered primary outcome after enrollment began.

As a reminder, the 2010 CONSORT guidelines for reporting randomized trials recommend that all trials should be registered prior to the start of enrollment, that all primary and secondary outcome measures should be pre-specified and clearly defined, and that any outcome changes should be explained and justified.

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Peer Review Evaluation of Registered End-Points of Randomized Trials

The PRE-REPORT Study

Study Protocol and Statistical Plan

Version 3

November 6, 2021

Principal Investigator: Christopher W Jones

Cooper Medical School of Rowan University

Camden, NJ USA

PRE-REPORT Study Protocol

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1. Abstract

Clinical trials are a critically important means of advancing medical knowledge and improving clinical outcomes. However, the reliability of information generated by clinical trials depends in part on consistency between pre-planned and reported primary study outcomes. Selective outcome reporting occurs when investigators publish manuscripts describing trial outcomes which are inconsistent with the outcomes they planned to assess as the start of the trial. Often this practice results in the selective publication of statistically significant study outcomes which favor the intervention being studied, while outcomes which show that an intervention may not be effective are suppressed. This form of research misconduct is unfortunately quite common, affecting approximately one-third of all published clinical trial manuscripts.

The World Health Organization, International Committee of Medical Journal Editors, National Institutes of Health, and many other stakeholders currently require that investigators for most human-subjects trials upload a summary of the planned trial methods to a publicly available clinical trial registry such as ClinicalTrials.gov before beginning enrollment. Trial registries therefore have the potential to help identify and stop selective outcome reporting during the peer review process by allowing peer reviewers to compare pre-specified, registered outcomes with the outcomes presented in manuscripts submitted for publication. However, the persistent high rate of selective outcome reporting among published trials demonstrates that current peer review and editorial practices do not effectively prevent this form of research misconduct.

This year-long study will test whether providing peer reviewers with a summary of registered, pre-specified primary trial outcomes will decrease the incidence of inconsistencies between prospectively registered and published primary outcomes among clinical trials published in participating journals. The tested intervention will consist of a brief email describing the timing of registration and definitions of any prospectively registered primary outcomes, which peer reviewers will receive after they agree to review a clinical trial manuscript under consideration at one of the participating journals. Using a stepped-wedge, cluster randomized trial design, we will transition journals between the control group (no email to reviewers) and intervention group (email to reviewers) at one month intervals. Blinded outcome assessors will compare registered and published primary outcomes for all included trials, and we will compare rates of selective outcome reporting between the control and intervention groups. Results from this trial will improve our understanding of how to identify and prevent selective outcome reporting using a simple, scalable intervention.

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2. Specific Aims

Clinical trials are a critical means of advancing medical knowledge, and trial results form a cornerstone of most clinical guidelines and practice. The identification of a well-defined, pre-specified primary outcome is an essential trial component. Equally important is consistency between this pre-specified trial outcome and the outcome reported in the published manuscript. Inconsistent pre-specified and reported outcomes (i.e. “selective outcome reporting”) threaten the validity of reported trial results by increasing the likelihood that chance or selective reporting, rather than true treatment effects, account for the conclusions in published reports. This often results in the selective publication of statistically significant outcomes favoring the intervention being studied, while outcomes showing that an intervention may not be effective are suppressed. As a result, selective outcome reporting can directly influence both clinical policy creation and physician decision-making in ways that adversely influence patient care.

Despite legislative action in both the United States (US) and European Union (EU) aimed at limiting selective outcome reporting, this remains a common form of research misconduct, occurring in approximately one-third of published clinical trials.

Clinical trial registries provide a publicly available record of pre-specified trial outcomes, allowing planned outcomes to be compared against outcomes reported in published manuscripts. Despite mandates requiring trial registration which have been in place for over a decade, discrepancies between pre-planned and reported outcomes remain common, indicating a failure of journal editors and reviewers to incorporate registry information into the peer review process.

This project is intended to improve the quality of clinical trial reporting by reducing selective outcome reporting. We propose a multi-journal sequential crossover study (stepped-wedge cluster-randomized trial) of an efficient, easy to implement intervention that will streamline the use of registry information during the peer review process. The intervention will provide editors and peer reviewers with information on (1) the timing of trial registration relative to the trial’s initiation, (2) registered primary outcome measure(s) at the time enrollment began, and (3) the timing and nature of any changes to the registered primary outcome measure(s) during the course of the trial. Project goals will be achieved through completion of the following specific aims:

Aim 1: To test whether providing peer reviewers with information from clinical trial registries about trial outcomes will decrease the incidence of inconsistencies between prospectively registered and published primary outcomes.

Hypothesis 1: Providing peer reviewers with information on prospectively registered clinical trial outcomes will reduce the incidence of selective outcome reporting in published manuscripts.

Aim 2: To test whether providing peer reviewers with information about registered trial outcomes will decrease the proportion of trials with inconsistencies between registered and published outcomes that fail to disclose the change in outcome within the published manuscript.

Hypothesis 2: Among published trials with inconsistencies between registered and published primary outcomes, providing peer reviewers with clinical trial registry information will increase the proportion of published manuscripts which disclose and explain the outcome change.

Results from the proposed trial will advance knowledge of how to identify and prevent selective outcome reporting during peer review. The long-term effect of this and subsequent dissemination and implementation efforts have the potential to dramatically diminish selective outcome reporting in the clinical trial literature, thereby reducing a critical source of research misconduct during trial publication and improving the quality of reported clinical trial results.

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3. Background and Significance

Randomized trials can reliably establish causality between interventions and patient outcomes, and therefore form a critically important foundation upon which much of the evidence-based medicine movement has been built. However, the reliability of clinical trial data depends on the consistent reporting of pre-specified trial outcomes.^{1,2} Often, changes between the pre-specified and reported outcome reflect selective outcome reporting in which investigators or study sponsors report statistically significant treatment effects which may result from multiple hypothesis testing and chance rather than actual efficacy of the studied intervention.³⁻⁵ Selective outcome reporting is widespread throughout the published biomedical literature, occurring in an estimated 30-40% of published clinical trials.^{3,6-9}

Clinical trial registries were developed, in part, to solve the problem of selective outcome reporting.¹⁰⁻¹³ Registries are publicly available databases that make trial information available to both the scientific community and the general public. This information includes descriptions of trial eligibility criteria and treatment arms, along with definitions of pre-specified primary and secondary outcomes. Since 2005, the International Committee of Medical Journal Editors (ICMJE) has mandated the prospective registration of clinical trials as a condition of publication in member journals,¹⁴ and in 2007 the Food and Drug Administration Amendments Act made prospective registration with ClinicalTrials.gov a requirement under federal law for many US clinical trials.¹⁵ Similar requirements have also been implemented by numerous other stakeholders and regulators, including the World Association of Medical Journal Editors,¹⁶ the World Health Organization,¹⁷ the European Union,¹⁸ and the National Institutes of Health.¹⁹

Despite the widespread adoption of registration requirements, a substantial body of evidence shows that selective outcome reporting remains common,⁶ and is routinely observed among trials published in both general medical and specialty journals,^{8,20,21} and across a wide range of medical specialties and funding sources.^{7,9,21-37} Because trial registry data are publicly available, selective outcome reporting can be detected during peer review. However, the ongoing frequency of this form of research misconduct indicates that current peer review practices have proven largely inadequate to identify and facilitate correction of selective outcome reporting.

Several barriers impair the ability of standard peer review processes to detect and correct selective outcome reporting. (1) Some reviewers and journal editors are not fully aware of existing registry resources, or of best practices regarding trial registration and outcome reporting.^{38,39} (2) Submitted manuscripts often fail to include the unique identifiers assigned to each trial at the time of registration, thereby necessitating an extensive search of multiple trial registries to identify a matching registry entry.⁴⁰ (3) Many registries allow investigators to edit existing registry data at any time, meaning that the registered trial outcomes can be changed after trial completion to match the outcomes reported in a submitted manuscript. Such changes occur in more than 30% of registered trials.^{41,42} ClinicalTrials.gov and WHO-approved trial registries track these changes, but accessing the audit trail which captures changes to prospectively registered outcomes is more time-consuming than simply viewing the updated registry webpage. (4) Some reviewers may be hesitant to review registry sites because these sites typically list the study sponsor and participating enrollment sites and identify the principal study investigator. Thus, direct registry review is not compatible with blinded peer review.

To address each of these barriers, we have developed a simple, scalable, journal-level intervention in which information from the clinical trial registry is provided to decision editors

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and peer reviewers for all randomized trials. The intervention will involve a comprehensive third-party registry search, abstraction of information from the registry, and provision of this information to peer reviewers and editors. We propose a randomized, stepped wedge trial to test the effect of this intervention on selective outcome reporting. The goal of this study will be to determine whether implementation of the intervention improves clinical trial reporting by increasing the consistency between prospectively registered and reported trial outcomes.

4. Methods

Study Design Overview: This stepped-wedge, cluster-randomized trial will test the impact of providing peer reviewers with easily accessible registry information on the consistency between registered and published trial outcomes. Individual clusters will comprise all clinical trial manuscripts sent for peer review during the pre- or post-intervention phase for each journal. A cluster design, rather than manuscript-level randomization, is necessary to minimize contamination of the intervention: Journals typically utilize a limited roster of decision editors and peer reviewers, and once an individual has participated in the intervention condition he or she may be more likely to seek out registry data when evaluating subsequent manuscripts.

Stepped-Wedge Randomization: At the beginning of a stepped-wedge trial, all participating clusters are in the control phase. Clusters are then crossed over to the experimental intervention in random order, and at the end of the trial all clusters receive the experimental intervention.^{44,45} An important advantage of this study design is the ability to compare pre- and post-intervention outcomes within individual clusters, thereby controlling for potentially confounding characteristics unique to those clusters.⁴⁶ For example, participating journals differ with respect to their existing peer review processes, as well as the volume, quality, and type of individual manuscripts undergoing review. The stepped wedge design also allows for controlling the study analyses for the confounding effect of time.⁴⁶ This is important given that registration, reporting, and peer review practices may change over the duration of the study.

Table 1. Sample study timeline. Shaded cells represent clusters in the intervention group.

Journal	Month											
	1	2	3	4	5	6	7	8	9	10	11	12
<i>Gastroenterology</i>												
<i>Acad Emerg Med</i>												
<i>Neurology</i>												
<i>Arch Phys Med Rehabil</i>												
<i>J Am Coll Surg</i>												
<i>Int J Cancer</i>												
<i>Ann Emerg Med</i>												
<i>Am J Transplantation</i>												
<i>Brit J Ophthalmology</i>												
<i>Clin Ortho and Rel Res</i>												
<i>Heart</i>												
<i>Surgery</i>												
<i>Thorax</i>												

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Study Timeline: During months one and two, all participating journals will be in the control group, and therefore no registry data will be provided to peer reviewers by the study team. Beginning in month 3, participating journals will be crossed over into the intervention group in random order at one-month intervals. During the final two months of enrollment all participating journals will be in the intervention group. Data collection will continue until all manuscripts from participating trials accepted for publication have been published. At that point blinded outcome assessors will determine the consistency of the registered and published outcomes.

Manuscript Eligibility Criteria: Manuscripts reporting the results of a clinical trial will be eligible for inclusion if they are sent for peer review during the one year study period by any of the participating journals. In order to be included manuscripts must include human subjects or groups of humans (e.g. cluster randomized trials), and must report results from an interventional study which prospectively assigns participants to one or more arms consisting of health-related interventions in order to evaluate an effect on health outcomes.¹⁴ We will exclude manuscripts if they describe a planned trial without reporting trial results, or if they clearly state that the manuscript is not intended to report on the trial's primary outcome (ie. manuscript describes only secondary or subgroup analyses). We will also exclude resubmitted manuscripts which have already completed the first round of peer review at the time our study begins. Manuscripts sent for peer review from multiple participating journals during the study will be analyzed in the first journal's cluster, and will not be included a second time if resubmitted to a different participating journal.

Randomization: Using a random number generator, we will randomly order participating journals and assign them to crossover dates at monthly intervals between the beginning of study month 3 and the end of month 10 (Table 1). The editor-in-chief and relevant journal staff members will be notified through email of their crossover date at the beginning of the study, with reminders sent two weeks before the crossover date and on the crossover date.

Control Phase: The stepped-wedge crossover design will involve exposing each participating journal (cluster) to the control group initially. During the control phase, the PRE-REPORT study team will review potentially eligible trial manuscripts sent for peer review, and will determine manuscript eligibility based on the criteria above. The specific mechanism by which the study team will access potentially eligible manuscripts will be determined on a case-by-case basis at each of the participating journals. During this phase no registry data will be returned to the journal staff, editor, or reviewers.

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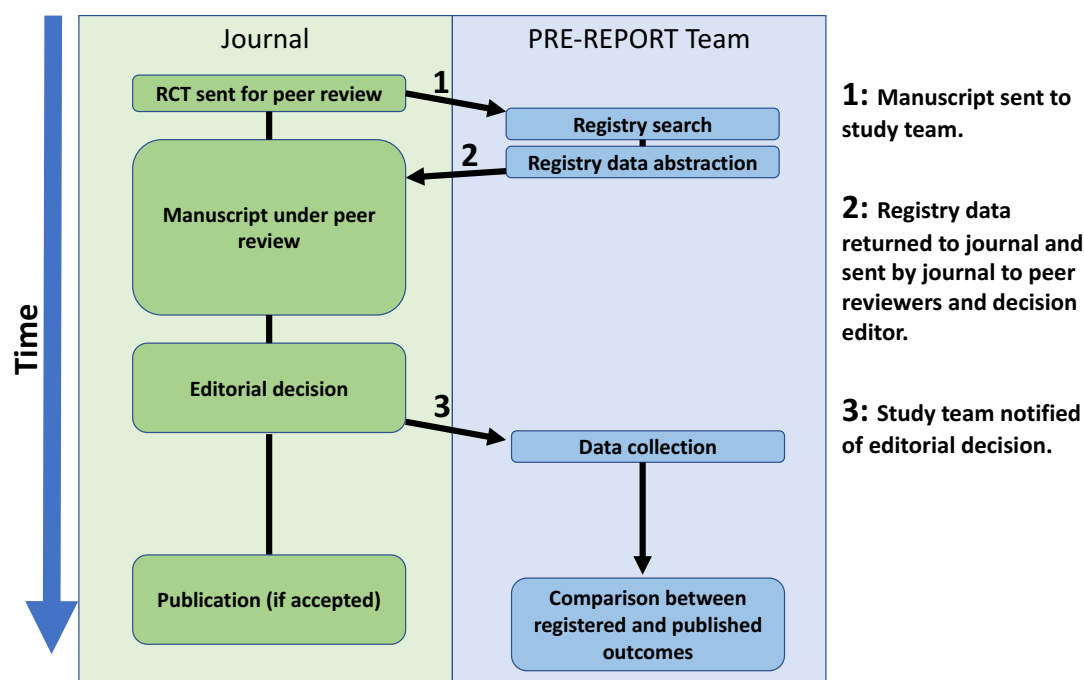


Figure 1. Information flow between participating journals and PRE-REPORT team.

Intervention Phase: At the randomly designated crossover date for each journal, the journal will be crossed over into the intervention phase. During the intervention phase, when alerted that a potentially eligible trial has been sent for review, the PRE-REPORT study coordinator or principal investigator will assess its eligibility (Figure 1). If eligible, the coordinator or investigator will perform a registry search. After confirming a match between the submitted manuscript and a corresponding registry entry, the PRE-REPORT staff member will abstract information from the registry into the registry data form, including the following information: whether the trial was registered, the date of registration, the registered primary outcome(s) at the time study enrollment began, the currently registered primary study outcome(s), and the dates of any outcome changes. Most registries allow investigators to alter the registered outcomes even after the initial registration information is submitted, though audit trails which record these changes make it possible to identify and report outcome changes over time. Our study team will then distribute the completed data form to the peer reviewers selected to review the manuscript in question (Appendix). The specific mechanism by which this information will be distributed to the appropriate reviewers will be determined on a case-by-case basis with each participating journal. If the search fails to identify a registration entry for the study, the absence of registry data will be reported to the peer reviewers. Our study team will return the completed data form to the journal staff within 24 hours of receiving the manuscript in most cases and within 72 hours in all cases to ensure that the registry data can be incorporated into editorial decision making.

Mechanism of Effect: Reviewers/editors in the intervention group will receive the registry data sheet, allowing them to easily compare primary outcomes between the registry and manuscript and to ask authors to correct or explain any inconsistencies before manuscript publication.

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Registry Data Abstraction: For each eligible manuscript, the PRE-REPORT program coordinator (Ms. Adams) or principal investigator (Dr. Jones) will review the published manuscript for a trial registration number or other evidence of trial registration. If no registration information is provided within the manuscript, he or she will then search ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform search portal, and any national or regional registries corresponding to the principal investigators' countries of origin (eg, Australian New Zealand Clinical Trials Registry) by keyword and title to identify a matching registry entry. Potential matches between registry entries and manuscripts will be assessed by the principal investigator by comparing the study title, interventions, planned sample sizes, enrolment dates and trial locations between the registry and manuscript. Manuscripts will be classified as unregistered when they do not include a registry identification number and when the registry search does not identify a matching registry entry. This registry search strategy has been previously used by our research group^{25,47} and others.^{8,9,21}

Data Collection: Participating journals will supply the PRE-REPORT study team with a copy of the initial manuscript submitted for peer review, which will be used to perform the registry search, as detailed above. We will collect data from the relevant registry entry for each trial, including the registry used, registration date, and study start date. Journals will notify the PRE-REPORT team when an initial editorial decision (accept, revise, reject) has been reached on an included trial. When the initial decision involves a request for revisions, journals will also notify our study team when a final editorial decision has been made. For accepted manuscripts, after publication of the finalized version of the manuscript has occurred we will abstract additional data from the final manuscript using a standardized data collection template. Data abstracted at this stage will include information about the sample size, description of the statistical plan, and the published primary and secondary outcome definitions. Any outcome(s) described by study authors within the abstract or manuscript as primary study outcomes will be considered primary outcomes. If no outcome is explicitly identified as the primary outcome but a sample size calculation was performed, the outcome used in this calculation will be considered the primary outcome. If no outcome was explicitly identified as the primary outcome, and no sample size calculation was performed, the published primary outcome will be considered undefined.

Primary Outcome: Our primary outcome is the presence of a clearly defined, prospectively registered primary trial outcome that is consistent with the primary outcome in the published manuscript, as determined by two independent outcome assessors. We define prospective registration as registration of a primary outcome with ClinicalTrials.gov or any of the Primary Registries in the WHO Registry Network (<http://www.who.int/ictip/network/primary/en/>) prior to enrollment of the trial's first participant (or prior to Sept 13, 2005 for trials beginning before July 1, 2005). A clearly defined outcome provides sufficient information to reasonably allow its identification on review of the study results and to allow an independent investigator to design a study measuring the same parameter. In general, this requires that registration include both a specifically defined variable and a specifically defined period for assessment. A specifically defined period is not required if the nature of the study limits the outcome assessment to an obvious time frame.

We will characterize outcome inconsistencies according to the classification of outcome discrepancies developed by Chan et al³ and refined by Mathieu et al (Table 2).⁸ Outcomes will

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be considered to be consistent if every primary outcome described in the registry is reported as a primary outcome in the manuscript, and every primary outcome reported in the manuscript is described as a primary outcome in the registry. Two investigators will independently assess all registered and published outcomes for consistency. Both investigators will be blinded to whether the manuscript was in the control or intervention phase and to the content of the manuscript draft sent for initial peer review. Inter-rater reliability will be assessed using a kappa value; our group has previously performed similar analyses with excellent inter-rater agreement ($\kappa = 0.87$).²⁵ Any discrepancies will be resolved by consensus after having both authors review the full text of the manuscript and registry; persistent disagreements will be adjudicated by a third investigator. Trials not prospectively registered will be considered to have inconsistent outcomes, as these publications will introduce new outcomes by definition.

Table 2. Classification of discrepancies between registered and published primary outcomes.
1. Registered primary outcome reported as secondary outcome in published manuscript
2. Registered primary outcome not reported in published manuscript
3. Published manuscript includes new primary outcome
4. Published primary outcome described as secondary in registry
5. Timing of assessment of primary outcome variable differs between registry and manuscript

Secondary Outcomes: Among trials with primary outcome inconsistencies present, we will assess whether the published manuscript included a disclosure of this change and an explanation of the reason for the change. Also, by comparing primary outcomes in the initial submitted manuscript to the primary outcome in the published version of the manuscript, we will be able to directly measure the impact of peer reviewer/editor feedback related to outcome consistency. We will also measure and report changes in acceptance rates for clinical trials over the course of our study period. Additionally, we will classify any observed primary outcome inconsistencies according to whether or not they impact the statistical significance of the published outcome. Exploratory outcomes will include the impact of the intervention on the delay between initial submission and publication, discrepancies between secondary registered and published outcomes, and the rate of inconsistencies between the registry and manuscript for factors other than study outcomes (sample size, eligibility criteria, study results). Among trials with registered primary outcomes that were registered prospectively but not clearly, we will determine whether the registered outcomes are consistent with the published outcomes.

Trial Registration: The trial protocol and outcomes were registered before initiating the study at ISRCTN: [ISRCTN41225307](#). Outcome data will be uploaded to the registry site after study completion.

5. Analytic Plan

Sample Size and Power: We used simulations to calculate power for comparing our primary outcome (outcome inconsistency) between intervention and control phases.⁴⁸ We used Qaqish’s conditional linear family approach to generate 2,000 simulated datasets with correlated binary

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outcomes corresponding to the stepped-wedge design described above.⁴⁹ Based on our prior systematic review we assumed that 33% of published manuscripts would have inconsistent outcomes during the control phase,⁶ and based on 2017 data we assumed that the participating journals would accept for publication, on average, 2 trial manuscripts per month. We further assumed that responses from manuscripts from the same journal in the same phase would have an intra-cluster correlation of no more than 0.50 (ICC1), and that responses from manuscripts from the same journal but from different phases would have an intra-cluster correlation of at least 0.05 (ICC2). Generally, higher levels of ICC1 lead to decreased power whereas higher levels of ICC2 lead to increased power.⁵⁰ Under these assumptions, 8 participating journals will provide at least 80% power to detect an 80% reduction in outcome inconsistency using a one-sided test at the 0.05 significance level. We have elected to use a one-sided test because it is extremely unlikely that the intervention could lead to an increased rate of outcome switching.

Data Analysis: For all analyses, we will use all available relevant manuscript data from each participating journal. Manuscripts will be counted in the month in which notification from the journal is first received by the PRE-REPORT study team. For our primary outcome of outcome inconsistency, we will use a linear mixed model to compare observations between intervention and control phases. Mixed models allow for different numbers of manuscripts per journal, and also account for correlated responses between manuscripts published within the same journal. The model will include fixed effects for study phase (control or intervention) and study month, and will include journal-specific random effects that allow for different levels of correlation depending on whether manuscripts are reviewed in the same month or in different months. The linear mixed model will take the form:

$$Y_{ijk} = \beta_0 + \beta_1 X_{ij} + \beta_2 t_{ij} + b_{1,i} + b_{2,ij} + \varepsilon_{ijk},$$

where Y_{ijk} is the outcome for the k th manuscript for the i th journal in study month j , β_0 is the model intercept term, β_1 is the intervention effect, X_{ij} is an indicator variable for whether journal i belongs to the control or intervention condition in study month j , β_2 represent the time trend, t_{ij} represents study month, $b_{1,i}$ is the random effect for manuscripts from the i th journal, $b_{2,ij}$ is the random effect for manuscripts in the j th month from the i th journal, and ε_{ijk} represents the random error term.⁵¹ In this model, β_0 , β_1 , and β_2 are the fixed effects, while $b_{1,i}$, $b_{2,ij}$, and ε_{ijk} are the random effects which are assumed to be mutually independent, normally distributed with mean zero and separate variance components. It is the random effects which account for the correlation between outcomes noted in the sample size justification.

The model will be used to conduct a one-sided test at the 5% level to compare the intervention and control phases. In addition, a difference in proportions with the primary outcome will be estimated along with a 90% confidence interval (to be consistent with the one-sided 5% level).

For Aim 2, the sample size will be conditioned on studies that have been published with inconsistencies, and so will be greatly reduced relative to Aim 1. If the sample size allows, we will fit a similar model for Aim 2. Otherwise, we will present descriptive statistics to compare study phases.

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6. Participating Journals

Journal Selection: Coordinated information transfer between the PRE-REPORT study team and participating journals is required to ensure the trial's success. Participating journals must also not already have in place a robust method of ensuring that a comprehensive registry analysis is performed for every trial manuscript undergoing peer review. Finally, participating journals must regularly publish clinical trials, which we define as publishing a mean of at least 10 trials per year over the past three years. Journals solicited for participation in the proposed study were initially identified through personal networks of the PRE-REPORT study team and through review of participants in the 2017 Peer Review Congress. Additional participating journals subsequently identified by approaching the editors of high-impact journals across a wide range of general medical and surgical journals and medical specialties.

Current Participants: The editors-in-chief of the following journals have agreed to participate:

Academic Emergency Medicine
American Journal of Transplantation
Annals of Emergency Medicine
Archives of Physical Medicine & Rehabilitation
Gastroenterology
International Journal of Cancer
Journal of the American College of Surgeons
Neurology
British Journal of Ophthalmology
Thorax
Heart
Surgery
Clinical Orthopedics and Related Research

7. Data Management and Confidentiality

Responsible Conduct of Research Plan: All study investigators, consultants, and research staff take the Responsible Conduct of Research (RCR) seriously, and are actively engaged in both formal and informal training programs. Formal training includes completion of human subjects research training programs required by their local IRBs to remain active participants in research activities within their respective institutions. Within the past year, Dr. Jones has completed the NIH Protecting Human Research Participants, CITI Human Subjects Basic Course, and CITI Good Clinical Practice training courses. He mentors numerous residents and medical students in RCR by leading monthly journal club sessions for medical students, resident physicians, and faculty members within the Cooper University Hospital Department of Emergency Medicine. All investigators and consultants have previously published manuscripts addressing responsible publication practices.

Confidentiality: Our study team will strictly guard the confidentiality of all unpublished manuscripts we receive for review. Only two study members (Jones, Adams) will have access to unpublished manuscripts, and these manuscripts will be stored on a secure, password protected

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database housed at Cooper University Hospital. Even though no patient information will be collected as part of the study, data storage measures will meet or exceed all existing NIH and local institution requirements for the storage of identifiable health information. These manuscripts will be permanently deleted from the study database following completion of the study analyses. All data from clinical trial registries and published manuscripts are publicly available.

Journals utilizing blinded peer review will not be asked to disclose the identities of their reviewers or editors to our study team; participating journals will have the option of establishing an administrative contact within the journal's editorial office through whom all contact between the study team and the journal will occur. If the editor-in-chief of a participating journal explicitly requests that the PRE-REPORT study team assumes responsibility for directly contacting relevant editors or reviewers in order to reduce the administrative burden that participation will place on journal staff, we will work with the journal in question to establish an individualized work flow which will maintain the strict confidentiality of the peer review process. The principal investigator will enter into and comply with a confidentiality agreement between the study team and participating journals which request that such an agreement be in place.

REDCap will be used for data entry and storage. REDCap is a web-based, secure clinical research database with features to constrain the form and values of inputted data in order to reduce data entry errors.⁵²

8. Human Subjects Protection

Per the United States Federal Code of Regulations, Human Subjects Research must meet the following conditions:

46.102(d) Research means a **systematic** investigation, designed to develop **generalizable** knowledge.

46.102(f) Human subject means a living individual about whom an investigator conducting research obtains data through **interaction** with the individual OR obtains **identifiable** Protected Health Information (PHI).

This study does not involve the collection of human subject data, and does not involve the collection of identifiable protected health information. Therefore this study does not involve human subjects research. The study protocol was submitted to the Cooper University Hospital Institutional Review Board (IRB) and was determined to be exempt from the need for IRB review because it does not involve human subjects research as defined by the U.S. Department of Health and Human Services Office for Human Research Protections.

9. Personnel

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Our study brings together a group of investigators and consultants who are national experts in the domains relevant to this trial. The principal investigator is Christopher Jones, MD, Assistant Professor of Emergency Medicine at Cooper Medical School of Rowan University in Camden, NJ. Co-investigators are:

Timothy Platts-Mills, MD, MSc, Assistant Professor of Emergency Medicine, University of North Carolina Chapel Hill, Chapel Hill NC;

David Schriger, MD, MPH, Professor of Emergency Medicine, University of California, Los Angeles School of Medicine, Los Angeles CA;

Benjamin Misemer, MD, Flint Hurley Medical Center, Flint MI;

Mark Weaver, PhD, Research Assistant Professor, Department of Biostatistics, University of North Carolina Chapel Hill, Chapel Hill NC.

Program Coordinator: Amanda Adams, MS, Research Librarian, Cooper Medical School of Rowan University.

Pertinent areas of expertise are clinical trial registration (Jones, Platts-Mills), journal editorial practices (Platts-Mills), peer review (Platts-Mills, Jones, Weaver), outcome reporting (Jones, Platts-Mills), and cluster-randomized trial design and analysis (Weaver). Drs. Jones, Platts-Mills, and Weaver have collaborated for over 6 years in a highly productive partnership involving multiple studies across a broad range of topics, including trial registration and selective outcome reporting. This includes a study published in the *BMJ* in 2013 which used trial registry data to show evidence of publication bias among large randomized controlled trials, and which influenced the World Health Organization's decision to call for improved trial reporting.^{53,54} Additionally, Dr. Platts-Mills has worked closely on issues related to peer review through his role as a member of the *Annals of Emergency Medicine* Editorial Board. Dr. Schriger is a deputy editor at *Annals of Emergency Medicine*, and an editor at *JAMA*. He has a longstanding track record of studying the dissemination of clinical trial results. Dr. Misemer has collaborated with Dr. Jones and Dr. Platts-Mills on prior work involving selective outcome reporting. Amanda Adams, the program coordinator, is a research librarian experienced in the use of Clinicaltrials.gov. She has also collaborated with our research group in the past on a study assessing the accuracy of registry information.

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11. Appendix

Sample Data Sheet for distribution to peer reviewers:

You recently agreed to review the following study: **Intravenous Fluid Therapy for the Treatment of Emergency Department Patients with Migraine Headache** for *Annals of Emergency Medicine*.

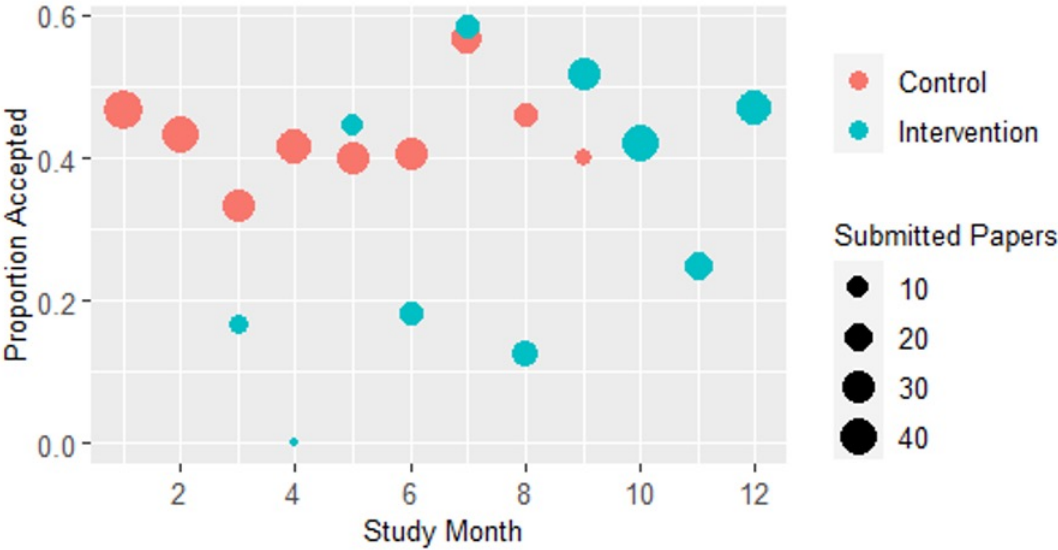
You may find the following information to be helpful as you perform your review. The trial was registered with ClinicalTrials.gov (NCT02933060) on October 14, 2016, prior to the start of enrollment.

At the time enrollment began the primary outcome measure was listed as:

Pain score at 60 minutes [Time Frame: 60 minutes] The primary outcome will be the difference in verbal pain rating (0-10) between the start of the study intervention and one hour later, at completion of the intervention. The minimum clinically significant difference between treatment groups on the 0-10 verbal scale is 1.3.

There were no changes to the registered primary outcome after enrollment began.

As a reminder, the 2010 CONSORT guidelines for reporting randomized trials recommend that all trials should be registered prior to the start of enrollment, that all primary and secondary outcome measures should be pre-specified and clearly defined, and that any outcome changes should be explained and justified.



Supplementary Methods. Template of registry data form for peer reviewers

You recently agreed to review the following study: [Manuscript Title] for [Journal Name] (manuscript # XXXXXXXX).

You may find the following information helpful as you perform your review. The trial was registered with [Registry Name] (Registration Number) on [Registration Date], [before/after] the start of enrollment.

At the time enrollment began the primary outcome measure was: [Registered Primary Outcome Measure(s)]

As a reminder, the World Health Organization (WHO) defines a clinical trial as any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes; you are receiving this information because the study under review meets this definition.

The WHO and International Committee of Medical Journal Editors mandate that all clinical trials be registered prior to the start of enrollment, and that all primary and secondary outcome measures be clearly defined before participant enrollment begins

Supplementary Table 1. Characteristics of participating journals

Journal	Specialty	2019 Impact Factor ^a	Impact Factor Rank within Journal Category	Editorial Office Location	Clinical Trials Published in 2018 ^b
Academic Emergency Medicine	Emergency Medicine	3.064	6/31	United States	19
American Journal of Transplantation	Transplantation; Surgery	7.338	2/24; 6/210	United States	39
Annals of Emergency Medicine	Emergency Medicine	5.799	1/31	United States	22
Archives of Physical Medicine and Rehabilitation	Rehabilitation; Sport Sciences	3.098	9/68; 17/85	United States	65
British Journal of Ophthalmology	Ophthalmology	3.611	9/60	United Kingdom	30
Clinical Orthopaedics and Related Research	Orthopedics; Surgery	4.329	5/82; 19/210	United States	17
Gastroenterology	Gastroenterology and Hepatology	17.373	4/88	United States	44
Heart	Cardiac and Cardiovascular Systems	5.213	26/138	United Kingdom	23
International Journal of Cancer	Oncology	5.145	59/244	Germany	28
Journal of the American College of Surgeons	Surgery	4.590	13/210	United States	11
Neurology	Clinical Neurology	8.770	10/204	United States	59
Surgery	Surgery	3.356	41/210	United States	16
Thorax	Respiratory System	10.844	5/64	United Kingdom	31

^a 2019 Journal Impact Factor, Journal Citation Reports (Clarivate Analytics, 2021)

^b Based on PubMed search for: "2018/01/01-2019/01/01" [Publication Date] AND "clinical trial" [Publication Type] AND Journal Title [Journal].

Supplementary Table 2. Characterization of outcome changes among published trials with inconsistent registered and published outcomes

Type of Outcome Inconsistency ^a	Control Group Trials (n=21)	Intervention Group Trials (n=15)
Registered primary outcome reported as secondary outcome in published manuscript; n (%)	13 (62%)	7 (47%)
Registered primary outcome not reported in published manuscript; n (%)	8 (38%)	7 (47%)
Published manuscript includes new primary outcome ^b ; n (%)	16 (76%)	9 (60%)
Published primary outcome described as secondary in registry; n (%)	7 (33%)	6 (40%)
Timing of assessment of primary outcome variable differs between registry and manuscript; n (%)	15 (71%)	8 (53%)

^a More than one type of outcome inconsistency per trial was possible^b Does not include unregistered and retrospectively registered trials

Supplementary Figure 1. Proportion of manuscripts accepted for publication, by intervention phase and study month.