

**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)**

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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: <a href="https://www.isrctn.com/ISRCTN41225307">ISRCTN41225307</a>
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; <b>9</b> :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; <b>18</b> :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**

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**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.

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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.<sup>1,2</sup> 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.<sup>3-5</sup> Selective outcome reporting is widespread throughout the published biomedical literature, occurring in an estimated 30-40% of published clinical trials.<sup>3,6-9</sup>

Clinical trial registries were developed, in part, to solve the problem of selective outcome reporting.<sup>10-13</sup> 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,<sup>14</sup> 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.<sup>15</sup> Similar requirements have also been implemented by numerous other stakeholders and regulators, including the World Association of Medical Journal Editors,<sup>16</sup> the World Health Organization,<sup>17</sup> the European Union,<sup>18</sup> and the National Institutes of Health.<sup>19</sup>

Despite the widespread adoption of registration requirements, a substantial body of evidence shows that selective outcome reporting remains common,<sup>6</sup> and is routinely observed among trials published in both general medical and specialty journals,<sup>8,20,21</sup> and across a wide range of medical specialties and funding sources.<sup>7,9,21-37</sup> 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.<sup>38,39</sup> (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.<sup>40</sup> (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.<sup>41,42</sup> 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.<sup>44,45</sup> 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.<sup>46</sup> 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.<sup>46</sup> 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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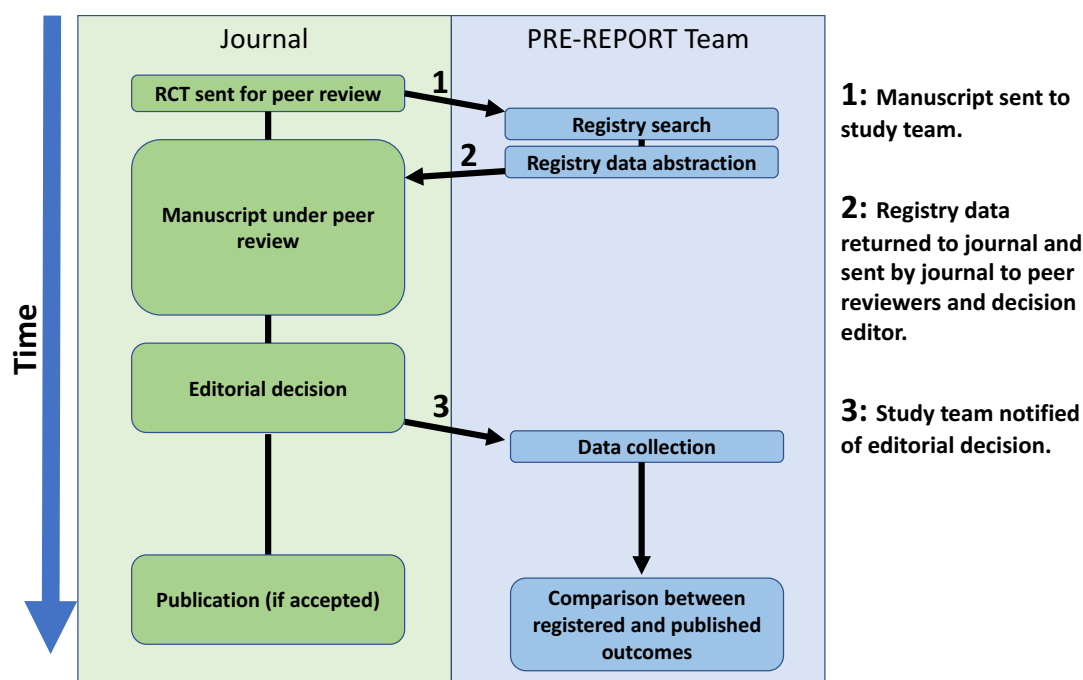
from participating trials accepted for publication have been published. At that point blinded outcome assessors will determine the consistency of the registered and published outcomes.

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.<sup>14</sup> 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<sup>25,47</sup> and others.<sup>8,9,21</sup>

**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 al<sup>3</sup> and refined by Mathieu et al (Table 2).<sup>8</sup> 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 ( $\kappa = 0.87$ ).<sup>25</sup> 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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<b>Table 2.</b> 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.<sup>48</sup> 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.<sup>49</sup> Based on our prior systematic review we assumed that 33% of published manuscripts would have inconsistent outcomes during the control phase,<sup>6</sup> 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.<sup>50</sup> 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.<sup>51</sup>

## 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 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.<sup>52,53</sup> 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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## PRE-REPORT Study Protocol

**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.

PRE-REPORT Study Protocol

**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**

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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.

## PRE-REPORT Study Protocol

### 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.<sup>1,2</sup> 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.<sup>3-5</sup> Selective outcome reporting is widespread throughout the published biomedical literature, occurring in an estimated 30-40% of published clinical trials.<sup>3,6-9</sup>

Clinical trial registries were developed, in part, to solve the problem of selective outcome reporting.<sup>10-13</sup> 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,<sup>14</sup> 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.<sup>15</sup> Similar requirements have also been implemented by numerous other stakeholders and regulators, including the World Association of Medical Journal Editors,<sup>16</sup> the World Health Organization,<sup>17</sup> the European Union,<sup>18</sup> and the National Institutes of Health.<sup>19</sup>

Despite the widespread adoption of registration requirements, a substantial body of evidence shows that selective outcome reporting remains common,<sup>6</sup> and is routinely observed among trials published in both general medical and specialty journals,<sup>8,20,21</sup> and across a wide range of medical specialties and funding sources.<sup>7,9,21-37</sup> 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.<sup>38,39</sup> (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.<sup>40</sup> (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.<sup>41,42</sup> 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



## PRE-REPORT Study Protocol

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.<sup>44,45</sup> 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.<sup>46</sup> 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.<sup>46</sup> 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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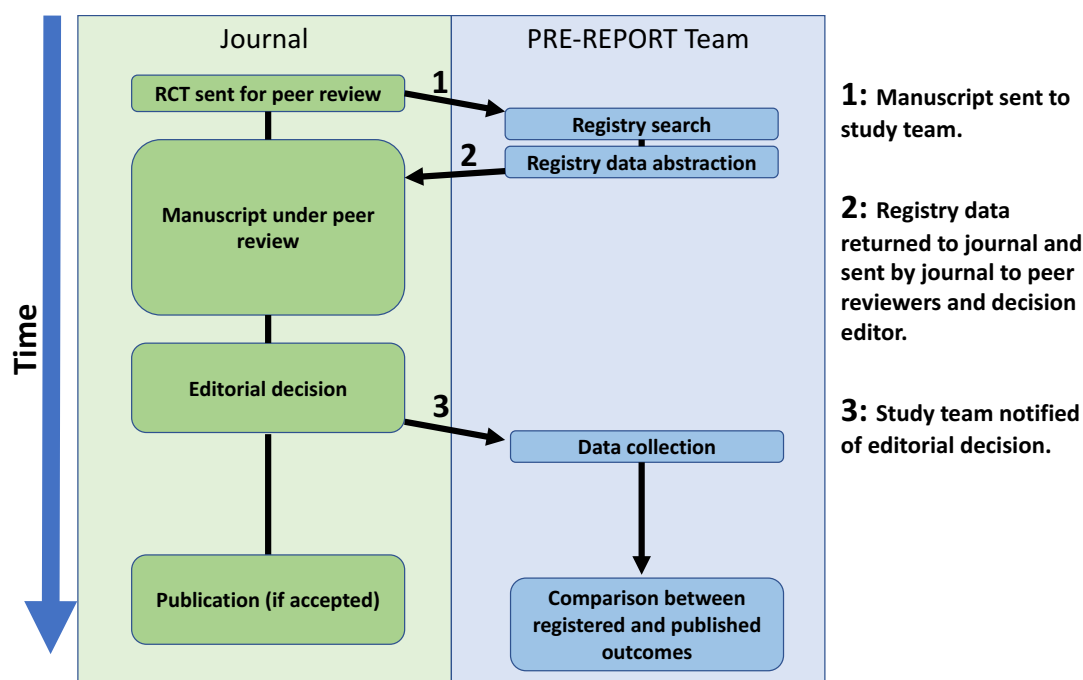
**Study Timeline:** During months one and two, all participating journals will be in the control group, and therefore no registry data will be provided to peer reviewers by the study team. Beginning in month 3, participating journals will be crossed over into the intervention group in random order at 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.<sup>14</sup> 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<sup>25,47</sup> and others.<sup>8,9,21</sup>

**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/ictcp/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 al<sup>3</sup> and refined by Mathieu et al (Table 2).<sup>8</sup> 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 ( $\kappa = 0.87$ ).<sup>25</sup> 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](https://www.isrctn.com/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.<sup>48</sup> We used Qaqish's conditional linear family approach to generate 2,000 simulated datasets with correlated binary

## PRE-REPORT Study Protocol

outcomes corresponding to the stepped-wedge design described above.<sup>49</sup> Based on our prior systematic review we assumed that 33% of published manuscripts would have inconsistent outcomes during the control phase,<sup>6</sup> 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.<sup>50</sup> 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  $j$ ,  $\beta_0$  is the model intercept term,  $\beta_1$  is the intervention effect,  $X_{ij}$  is an indicator variable for whether journal  $i$  belongs to the control or intervention condition in study month  $j$ ,  $\beta_2$  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  $\varepsilon_{ijk}$  represents the random error term.<sup>51</sup> In this model,  $\beta_0$ ,  $\beta_1$ , and  $\beta_2$  are the fixed effects, while  $b_{1,i}$ ,  $b_{2,ij}$ , and  $\varepsilon_{ijk}$  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.<sup>52</sup>

### 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.<sup>53,54</sup> 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.