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ORIGINAL ARTICLE

Compliance with prospective trial registration guidance remained low in high-impact journals and has implications for primary end point reporting

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Abstract

Objectives: To examine compliance with International Committee of Medical Journal Editors' (ICMJE) policy on prospective trial registration along with predictors of compliance.

Study Design and Setting: Cross-sectional analysis of all articles reporting trial results published in the six highest-impact general medicine journals in January−June 2014 that were registered in a public trial registry. The main outcome measure was compliance with ICMJE policy. The time frame for trial primary end point ascertainment was used to assess whether retrospective registration could have allowed changing of primary end points following an interim analysis.

Results: Forty of 144 (28%) articles did not comply with the ICMJE policy. Trials of non−FDA-regulated interventions were less compliant than trials of FDA-regulated interventions (i.e., medicines, medical devices) (42% vs. 21%; $P = 0.016$). Twenty-nine of these 40 (72%; 20% overall) were registered before any interim analysis of primary end points could have been conducted; 11 (28%; 8% overall) were registered after primary end point ascertainment, such that investigators could have had the opportunity to conduct an interim analysis before trial registration.

Conclusion: Twenty-eight percent of trials published in high-impact journals were retrospectively registered including nearly 10% that were registered after primary end point ascertainment could have had taken place. Prospective registration should be prompted and enforced to ensure transparency and accountability in clinical research.

Keywords: Clinical trials; ICMJE; Policy; Prospective registration; Nonregulated intervention trials; Compliance; Journal editors

1. Introduction

Clinical trial investigators should pursue transparency and accountability as cornerstones of their research activity [1−3]. Yet, we are far of achieving it. Thus, for example, many clinical investigators do not publish their research [4,5]. Furthermore, once published, it has been reported that anywhere from 4% to 50% of clinical trials have had at least one primary end point changed, omitted, or introduced [6]. Prospective registration of trials is expected to deter selective reporting of end points [7], which will in turn lead to less biased, more accurate representation of clinical trial findings in the medical literature to inform the decision making of patients and practicing physicians [8]. Prospective registration implies that the trial should

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What is new?

Key findings

- More than one-quarter of articles published in high-ranked general medicine journals did not comply with International Committee of Medicine Journal Editors (ICMJE) policy on trial prospective registration; 8% were registered after primary end point ascertainment, providing investigators the opportunity to conduct an interim analysis before trial registration.
- Trials of non−FDA-regulated interventions were significantly less likely to be compliant with ICMJE policy.

What this adds to what was known?

- Among retrospectively registered trials, special consideration should be given to the timing of registration and primary end point ascertainment.
- Trials of non−FDA-regulated interventions published in top-ranked journals are less likely to comply with the ICMJE policy on prospective trial registration.

What is the implication and what should change now?

- All journal editors should be aware of and enforce the ICJME policy on prospective trial registration; when publishing results of a retrospectively registered trial, journals should notify readers and clarify why an exception was made to the policy and whether the trial may have been subject to selective outcome reporting.

be registered at or before the first trial participant is enrolled. Few studies have assessed the effectiveness of prospective registration on selective outcome reporting, although one recent analysis showed that trials reported as registered were less likely to report positive findings than trials reported as nonregistered [9].

The International Committee of Medical Journal Editors (ICMJEs) require that any clinical trial initiated after July 1, 2005, irrespective of the assessed interventions, should be prospectively registered in a public registry as a prerequisite for manuscript submission [7]. According to the ICMJE registration policy (henceforth, ''ICMJE policy''), retrospective registration is when registration occurs after subject enrollment begins. Timely registration is key to prevent protocol modifications−such as changing, omitting, or introducing end points—that could be decided after preliminary examination of the clinical trial results and to disclose protocol modifications.

Although timely trial registration has been previously assessed [10−12], fulfillment of the requirement described previously varied depending on the definition of ''timely.'' Thus, among US trials registered on ClinicalTrials.gov, there was an increase in timely registration (within 21 days of trial start) from 45% in 2008 to 60% in 2011 [11]. Similarly, a steady increase in timely registration (defined as within 60 days of study start) for phase 2−4 trials registered on ClinicalTrials.gov was observed between 2006 and 2011, from 56% to 72%, respectively [12]. Finally, an increase in prospective registration of trials (i.e., before recruitment of the first participant) on ClinicalTrials.gov from 33% for the period 2004−2007 to 48% for the period 2007−2010 was observed [10]. Three analyses explicitly assessed timely registration of published trials. Among the five highest-impact general medicine journals, 83% of phase 2−4 trials published in 2010−2011 were registered within 60 days after the first participant enrollment [12]. Among five highest-impact factor emergency medicine journals, only 21% of trials were prospectively registered [13]. Finally, among randomized trials of pharmaceutical interventions submitted for publication in 2010−2012 in eight different journals, only 40% were registered before trial start [14].

Our study had two objectives. First, we determined compliance with the ICMJE policy for timely trial registration among the six highest-impact ICMJE member journals. Next, we characterized predictors of compliance, specifically focusing on trials that were not timely registered (i.e., retrospectively registered trials).

2. Methods

2.1. Source of articles

We performed a cross-sectional analysis of all trials published in the top ICMJE member general medicine journals—New England Journal of Medicine, Lancet, JAMA, The BMJ, Annals of Internal Medicine and PLOS Medicine—between January and June 2014. These journals were chosen because they were most likely to publish clinical trials among all 14 ICMJE member journals [15].

2.2. Definitions

The registration was considered timely if it occurred before or in the same date the first participant was recruited (i.e., date in which informed consent for the screening phase—if any—or the treatment phase was obtained from the first participant) [7]. Trials that began enrollment before July 1, 2005, are considered by the ICMJE as ''ongoing'' if investigators were collecting or analyzing data as of July 1, 2005. ''Ongoing'' trials should be registered before manuscript submission [7]. To account for month-based reporting of trial start date within articles, month was converted into the 15th of the month (e.g., June 2010 was converted into June 15, 2010). With these criteria, all articles were