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Adherence to Prospective Registration Policy and Implications for Clinical Trial
Endpoint Integrity

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by

Anand D. Gopal

2018

Abstract

ADHERENCE TO PROSPECTIVE REGISTRATION POLICY AND IMPLICATIONS FOR CLINICAL TRIAL ENDPOINT INTEGRITY

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Abstract: Since implementation of the International Committee of Medical Journal Editors' (ICMJE) prospective registration policy in 2005, trial registration has increased significantly. Registering clinical trials is critical in promoting transparency and integrity in medical research, however trials must be registered in an appropriate manner to deter unaccounted protocol modifications or selection of alternate endpoints that may enhance favorability of reported results. This thesis provides relevant background on clinical trial registration and appropriate reporting in addition to evaluating adherence with the ICMJE's prospective trial registration policy and the implications of inappropriate adherence for the integrity of reported results. In a cross-sectional, retrospective analysis of recent trials published in the highest-impact journals associated with US professional medical societies, we identified the frequency of registrations occurring late in addition to those late enough to potentially permit protocol modifications based on premature examination of collected data. We further examined whether trials that are unregistered or registered late enough to permit interim analyses were more likely to report favorable results. We used descriptive statistics to characterize the proportions of trials that were: registered; registered retrospectively; registered retrospectively potentially after initial ascertainment of primary endpoints; and reporting favorable results, overall and stratified by journal and trial characteristics. Among 486 trials published between January 1, 2010 and December 31, 2015, 47 (10%) were unregistered. Among 439 registered trials, 340 (77%) were registered prospectively and 99 (23%) retrospectively. Sixty-seven (68%) of these 99 retrospectively registered trials, or 15% of all 439 registered trials, were registered late enough to have potentially permitted premature examination of primary endpoint

data ascertained among participants enrolled at inception. Unregistered trials were more likely to report favorable results than registered trials (89% vs. 64%; $p=0.004$), irrespective of registration timing. Adherence to the ICMJE's prospective registration policy remains sub-standard, even in the highest impact journals associated with US professional medical societies. These journals frequently published unregistered trials and trials registered late enough to have potentially experienced unaccounted protocol modifications after observation of primary endpoints.

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TABLE OF CONTENTS

I.	Introduction	1
	a. Rationale for Clinical Trial Transparency.....	1
	b. Evolution of Trial Registration and the ICMJE Policy.....	3
	c. Current Trial Registration Landscape.....	4
	d. Statement of Purpose.....	6
II.	Methods	7
	a. Journal Selection.....	7
	b. Clinical Trial Sample Selection.....	7
	c. Data Collection.....	8
	d. Main Outcome Measures.....	10
	e. Statistical Analysis.....	12
III.	Results	13
	a. Search Results.....	13
	b. Characteristics of Eligible Trials.....	15
	c. Registration.....	16
	d. Timeliness of Registration.....	22
	e. Primary Endpoint Concordance.....	24
	f. Favorability of Trial Results.....	25

IV. Discussion	26
a. Implications of Findings.....	29
b. Limitations	30
c. Conclusions.....	32
V. References	34

INTRODUCTION

Universal registration of clinical trials is critical for promoting transparency and integrity in medical research, helping to ensure a complete and unbiased record of all clinical trials.[1-3] Clinical trial registration is defined as the “systematic public disclosure of key descriptive information about a clinical trial.”[4] Registration alone, however, is insufficient, as trials must be registered in a timely fashion to deter selective reporting, which may include addition or removal of endpoint measures, preferential publication of statistically significant findings, and modification of which endpoint measures were pre-specified as primary.[5] Accordingly, registering trials prospectively, or before enrollment of participants, helps foster integrity and confidence in the clinical research enterprise by limiting the opportunity for interim analyses to distort the validity of reported results.

Rationale for Clinical Trial Transparency

Clinical trials represent the primary mechanism through which novel laboratory discoveries are initially applied to human subjects and through which therapies and interventions garner evidence in favor of or against standard use. The knowledge derived from clinical trials forms the foundation for the evidence used to drive medical decision-making, as trial data are frequently fed into systematic reviews and meta-analyses. The aggregate findings from these larger analyses generate a more robust, unbiased evidence base than can be discerned from individual studies alone, though depend critically on the completeness and accuracy of the individual studies from which they draw. Because of their pivotal contributions to broader analyses, clinical trials must be disclosed and their results

made readily accessible. Otherwise, clinical decisions may be biased by the selective availability of clinical trial information, placing patients at risk by subjecting them to care based on partial evidence. In the absence of systematic public disclosure, data from clinical trials are limited to those disseminated through peer-reviewed publications or presented at scientific meetings, a limitation known as publication bias.[1, 6, 7] As studies reporting significant findings are more frequently published than those reporting null findings, publication bias risks a body of evidence that overestimates benefits and exposes patients to suboptimal interventions supported by skewed or inconsistent data.[2] Registering clinical trials precludes publication bias by helping to facilitate the incorporation of unpublished knowledge into the medical evidence base.

Because of their significance in driving medical decision-making, clinical trials must be consistently held to the highest standards of integrity and scientific rigor.[8] Besides fulfilling an ethical mandate to trial volunteers, who knowingly assume risk to advance science, registering clinical trials provides a mechanism to safeguard the integrity of studies and deter scientific fraud and misconduct.[9] The systematic disclosure of summary information about a trial enables scientists and the public to critically assess the integrity of a trial's design as it was intended and provides accountability in the reporting of analyses and endpoints. More practically, registration offers a means for the scientific community and the public to learn about ongoing and completed trials as well as to assess the allocation of and prevent the unnecessary duplication of research efforts. These benefits can be realized only

if trials are not only uniformly registered, but also registered in a timely fashion and with sufficient detail.[10]

Evolution of Trial Registration and the ICMJE Policy

Recognizing the potential for greater transparency to mitigate the influence of publication and selective reporting biases and in response to high-profile controversies involving lack of transparency and suppression of evidence within the pharmaceutical industry,[9] various governing bodies and organizations have in the last couple decades developed legal and editorial measures to promote the prospective registration of clinical trials. Among the first to do so was the International Committee of Medical Journal Editors (ICMJE), an editorial body comprising leading biomedical journals whose guidelines and policies set the standards for ethics and conduct in the publication of biomedical research. In September 2004, the ICMJE adopted a policy to encourage timely clinical trial registration, mandating that all trials beginning July 2005 register prospectively, at or before the time of first patient enrollment, as a condition for publication in its member journals.[11] Since implementation of the ICMJE policy, efforts to augment clinical trial transparency have born fruit through a series of policies and regulations requiring the registration and reporting of clinical trial information. In 2006, the World Health Organization (WHO) released a statement endorsing the registration of all clinical trials in addition to declaring a minimum set of requisite information that should be specified upon trial registration. While the Food and Drug Administration Modernization of Act (FDAMA) of 1997 established the first federal legal mandate for trial registration in the United States, requiring the

registration of a subset of trials studying the interventions for patients with serious or life threatening diseases, the Food and Drug Administration Amendments Act (FDAAA) of 2007 expanded federal registration requirements to include all non-Phase I trials of FDA-regulated interventions, namely drugs, devices, and biologics. The law also defined monetary penalties for failure to comply in addition to outlining requirements for trial results reporting. More recently, the National Institutes of Health (NIH) has issued a policy requiring registration and results reporting for all NIH-funded clinical trials with the penalty of suspension of NIH-funding for investigators found to be in violation of these requirements.[4] Nevertheless, among existing efforts to promote clinical trial registration, the ICMJE policy remains the most inclusive in scope, applying to all clinical trials regardless of study type, intervention, or funding source. In this regard, the ICMJE policy represents the broadest-reaching device in the push toward universal trial registration, though, without legal or fiduciary jurisdiction, it relies critically on journals refusing to publish inadequately registered trials as its primary mechanism of enforcement.

Current Trial Registration Landscape

Since implementation of the ICMJE policy, trial registration at ClinicalTrials.gov, the largest international clinical trial registry, and other trial registries has increased substantially.[12] In the five-month period surrounding implementation of ICMJE's trial registration policy alone, the number of registrations on ClinicalTrials.gov grew by 73 percent.[12] However, despite nearly

a decade since the policy went into effect, a small but significant number of trials remain unregistered, including those that are published.[13-19]

Moreover, despite increasing rates of registration, timely registration of trials is still lacking.[13, 14, 17-22] A recent analysis published in 2017 demonstrated that nearly one-third of interventional trials registered on ClinicalTrials.gov between 2012 and 2014 were registered more than three months after their start dates and nearly a fifth were registered more than a year after,[23] suggesting that large numbers of clinical studies are registered late and hence may be vulnerable to unaccounted protocol modifications. While ICMJE policy mandates prospective registration as a prerequisite for publication, retrospectively registered trials continue to enter the published literature. Previous research suggests that even in the highest-impact general medical journals, 28% of published trials were registered retrospectively.[21] In some cases, registration occurred late enough to raise concerns about whether the specified primary outcome measure had been modified after trial inception,[21] as retrospective registration may provide opportunity for unaccounted protocol modifications or selection of alternate endpoints to enhance the favorability of reported results. Although more than 2,900 journals support general ICMJE manuscript publication guidelines,[24] a 2014 survey found that journal editors do not consistently adhere to ICMJE's prospective trial registration policy.[25, 26]

While previous studies of journal adherence to the ICMJE prospective trial registration policy have thus far either focused on the highest-impact general medical journals or sampled within field-specific journals, [13, 14, 17-21] little is

known about registration of trials published among high-impact specialty society journals. Specialty society journals, administered by professional organizations (e.g. the American Society of Clinical Oncology), tend to represent the views of their constituent specialists. They publish trials that are of great interest to their respective communities, which influence mainstream clinical practice.[27] Although specialty journals typically have lower impact factors than the highest-impact general medical journals, they are often a preferred source of clinical information and guidelines for specialists.[28]

Statement of Purpose

The purpose of this study was to assess adherence to the ICMJE's prospective clinical trial registration policy among a large sample of clinical trials recently published in the ten highest-impact specialty journals affiliated with US professional medical specialty societies. Specifically, this study evaluated rates of prospective trial registration; identified instances of registration occurring late enough to potentially permit premature examination of collected data; and determined characteristics associated with timely registration. Further, this study compared registered and published primary endpoints among prospectively and retrospectively registered trials and identified predictors of endpoint concordance.

Finally, this study examined whether trials that were unregistered or registered late enough to potentially permit interim analyses were more likely to report favorable study results. Because failing to register trials or registering trials retrospectively creates opportunity for investigators to selectively report primary endpoints with the intent of increasing the trial's attractiveness for publication, this

study hypothesized that, among published trials, unregistered trials and those registered late enough to potentially permit premature primary endpoint observation will report favorable primary endpoints at a higher rate than trials registered prospectively in accordance with ICMJE policy.

METHODS

Journal Selection

We identified US specialty society medical journals using a list of US-based medical professional organizations associated with any of the specialties registered with the American Board of Medical Specialties. [29] We searched for additional journals using SCImago Journal & Country Rank listings, adding to our list any journals associated with a US-based medical specialty organization [30]. We selected the ten journals with the highest impact factors after excluding general practice journals and journals that do not publish clinical trials.[31] For each journal in our sample, we verified endorsement of trial registration as indicated by a statement on the journal's website or listing of the journal on the ICMJE's catalogue of journals that follow its recommendations as a condition for inclusion.[24]

Clinical Trial Sample Selection

We reviewed original research articles, including brief reports and communications but not research letters or correspondences, to identify the 50 most recent primary publications of clinical trials in each journal, beginning with articles published in print journal issues in December 2015 and continuing in reverse chronology as far back as January 2010. We used the table of contents of

each print journal issue to identify articles for possible inclusion. One author (A.D.G) reviewed articles for eligibility in consultation with a senior author (J.S.R.). Clinical trials were systematically identified by screening the article's abstract and, if necessary, the methods section, for statements meeting the WHO's definition of a clinical trial, also used by ICMJE, namely any study that "prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the cause-and-effect relationship between a health-related intervention and a health outcome." [32]

We limited our sample to publications reporting a trial's primary analysis, which is most pertinent to the information contained within its registration, and excluded trials reporting secondary analyses of previously published results, secondary outcomes only, or interim analyses of primary endpoints. We further excluded publications describing Phase I trials, as these studies typically do not assess effectiveness and have minimal impact, if any, on clinical practice. We additionally excluded trials beginning prior to July 2005, since trials preceding the ICMJE policy were unlikely to be prospectively registered.

Data Collection

From trial publications, we extracted information on journal, intervention, allocation, manuscript submission date, enrollment start date, primary outcome(s) with associated results, and registration number(s) corresponding to the trial(s) reported. To account for the possibility of duplicate registrations, we searched the WHO International Clinical Trials Registry Platform (ICTRP), which aggregates registrations across registries endorsed by WHO, and in turn endorsed by ICMJE,

using the reported registration numbers and additionally reviewed registrations for alternate identifiers to determine the earliest registration for each trial. For publications not reporting registration information, we searched the WHO ICTRP platform using search terms pertaining to intervention, first author, senior author, and sponsor to identify unpublished registrations, cross-referencing potential matches against sample size and enrollment criteria. We contacted corresponding authors of unmatched trials for registration information before concluding that the published trial was unregistered.

Using the earliest registration for each trial, we collected registration date, primary outcome submission date, primary completion date, start date, primary outcome(s) at initial registration, enrollment, phase, location, and funding source. We supplemented information on the latter four elements from trial publications when missing from the registry. Among trials we determined to have been first registered on ClinicalTrials.gov, we additionally collected date of original primary outcome submission, which the registry uniquely lists separately from the trial registration date. We categorized intervention, funding source, location, enrollment, and allocation as outlined in **Table 1** for use in pre-specified stratified analyses. We considered interventions involving drugs, devices, or biological as regulated by the Food and Drug Administration (FDA).

Data abstractions were performed in tandem by A.D.G and J.A.A. Consistency and accuracy were verified through a 10% random sample validation of each investigator's collections. A third author (J.D.W) repeated all searches for trials that were determined to be unregistered, supplementing with additional searches of the

National Institutes of Health (NIH) funding database using grant funding identifiers when listed in publications.[33] All disagreements were resolved by consensus with input from the senior investigator (J.S.R).

Main Outcome Measures

We first determined whether each trial was registered by ensuring that a corresponding registration record could be located. For registered trials, we next ascertained timeliness of registration by determining whether the trial was registered within 30 days of its enrollment start date. Although ICMJE policy mandates registration at or before the time of first patient enrollment, we allowed a 30-day grace period between registration and enrollment initiation in order to account for potential flexibility on the part of journal editors with regard to registration timeliness. Month-based representations of dates were recorded as the last day of the corresponding month (i.e. September 2012 was transcribed as September 30, 2012) to conservatively classify registrations as “retrospective”. We elected to use enrollment start dates reported in registries as opposed to those reported in publications in our determinations of registration timeliness, as we believed that enrollment start date may not be consistently reported in publications, while, in registries, it is a mandatory registration element and, hence, less easily excluded or otherwise misrepresented.

Among trials registered retrospectively, we established whether registration might have occurred after ascertainment of the primary outcome, and hence potentially permitted unaccounted protocol modifications after interim analyses, by comparing the trial’s registration date against the date on which the primary

outcome would have been collected for the trial's first enrolled participant(s). For example, a trial with a primary endpoint assessing serum creatinine levels at 6 weeks that registered in November 2012 but that began enrolling patients in February 2012 would have been retrospectively registered after observation of the primary outcome among participants enrolled at the trial's initiation. In instances where multiple time frames were designated as primary, we based our calculations on the shortest primary endpoint time frame specified in the registry. If no time frame was listed in association with the registered primary outcome, we used the time frame described in the trial's publication. We noted cases where the nature of the primary outcome (e.g. median survival) did not permit this determination.

We next compared primary outcomes at initial registration against those specified in publications, excluding any primary endpoints pertaining specifically to safety or tolerability. We classified registered-published primary outcome pairs as discordant if they differed in any of the following: number of primary outcomes, definition(s) of primary outcomes, or specified time frame(s) for outcome(s) ascertainment. If no discrepancies were noted in these three domains, pairs were classified as concordant. We noted cases where registered endpoints were too poorly specified (e.g. vague study of "efficacy of intervention") to permit comparison. Trials without a designated primary outcome specified in the publication were excluded from endpoint comparison analyses.

Finally, we categorized each trial on the basis of its primary outcome results whenever formal hypothesis testing had been conducted or inferences could be made regarding the statistical significance of reported results (i.e. inferential

studies). We determined whether the trial's findings indicated, based on the reported primary endpoint(s), that a study intervention was statistically significantly better (i.e. positive), statistically significantly worse (i.e. negative), or not statistically significantly different (i.e. not significant) than a designated comparison (placebo group, active group, or predefined threshold) and classified the overall trial accordingly. For trials that assessed a non-inferiority hypothesis, we considered establishment of non-inferiority to represent a "positive" result and failure to establish non-inferiority a "not significant" result. In instances where more than one primary endpoint was reported, we categorized trials with at least one significant primary endpoint as "positive" or "negative" on the basis of the statistically significant endpoint; trials with mixed results (some positive and some negative primary endpoints) were classified by prioritizing the results of clinical outcomes over surrogate markers. Trials with mixed all clinical or all surrogate primary endpoint results were arbitrated based on the relative importance of the significant endpoints in question. For trials that did not specifically designate a primary outcome, any outcomes reported in the trial's abstract were considered primary and the overall study was categorized using the scheme described previously. Trials that presented analyses in a solely descriptive manner or that lacked a designated comparison against which to judge the statistical significance of reported results were noted as "non-inferential" and excluded from analyses of association. Trials categorized as "positive" were judged to report overall favorable results, whereas those categorized as "negative" or "not significant" were judged to report overall unfavorable results.

Statistical Analysis

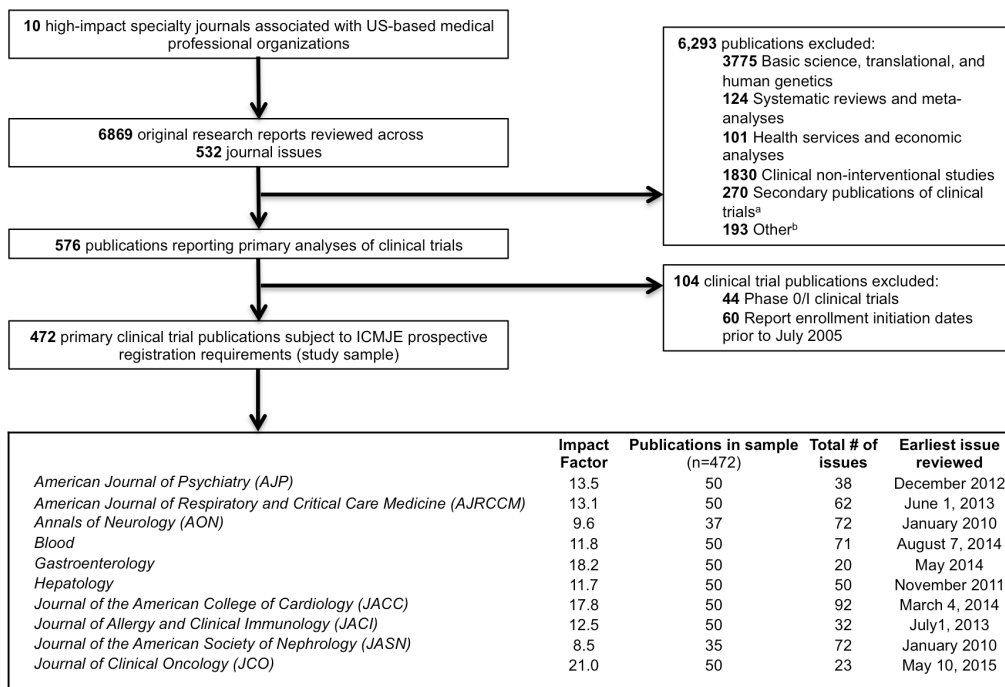
We used descriptive statistics to characterize the proportion of trials registered, the proportion registered retrospectively, as well as the proportion registered after initial primary outcome ascertainment, overall, and stratified by specialty journal and trial characteristics. We additionally determined the proportion of trials with concordant registered and published primary outcome measures and the proportion reporting favorable results, overall, and stratified by journal, registration timeliness, intervention, funding source, location, allocation, and enrollment. We used Chi-squared testing to assess differences in registration and registration timeliness by journal and by each of the aforementioned trial characteristics. We also used Chi-squared testing to assess differences in primary endpoint concordance and study results by journal, trial characteristics, and timeliness of registration. In cases involving small sample sizes, we used Fisher's exact tests in place of Chi-squared testing. All tests were performed using a 2-sided type I error level of 0.006 to account for multiple comparisons. Statistical analyses were performed using JMP Pro Version 11.2.0 (SAS Institute, Inc.).

RESULTS

Search Results

We reviewed 6,869 original research reports published in the period between January 1, 2010 and December 31, 2015 to identify the 50 most recent primary trial publications in each of ten high-impact specialty journals (**Figure 1**).

Figure 1. Construction of study sample comprising the 50 most recent clinical trial publications appearing in each of ten high-impact specialty journals between January 1, 2010 and December 31, 2015.



Notes: ^a Includes *post hoc* analyses, exploratory analyses, analyses of secondary outcomes, long-term follow-up, interim analyses, pooled analyses, extension trials, and studies utilizing data derived from clinical trials

^b Includes case reports, case series, modeling studies, twin studies

Abbreviations: *AJP* = *American Journal of Psychiatry*; *AJRCCM* = *American Journal of Respiratory and Critical Care Medicine*; *AON* = *Annals of Neurology*; *Gast.* = *Gastroenterology*; *Hep.* = *Hepatology*; *JACI* = *Journal of Allergy and Clinical Immunology*; *JCO* = *Journal of Clinical Oncology*; *JACC* = *Journal of the American College of Cardiology*; *JASN* = *Journal of the American Society of Nephrology*

Two journals (*Annals of Neurology*, n=37; *Journal of the American Society of Nephrology*, n=35) published fewer than 50 eligible primary trial publications in this period. After excluding publications describing phase I trials (n=44) and trials initiating enrollment prior to July 2005 (n=60), there were 472 publications

reporting the primary results of 486 clinical trials (14 articles described multiple trials).

Characteristics of Eligible Trials

Among our final sample of 486 trials, 76% (n=372) were randomized studies (**Table 1**). Eighty-one percent (n=392) assessed interventions involving drugs, devices, or vaccines/biologicals. Forty-four percent received industry funding (n=216), and just over half recruited patients at one or more sites located in the US (n=250; 51%). Phase II designations were most frequent (n=190; 39%). Median enrollment across all trials was 127 participants (interquartile range [IQR], 49-300). Eighty-nine percent (n=433) of trials were published since 2013. The median impact factor among journals in our sample was 12.24 (range, 8.5-21.0).

Table 1. Characteristics of clinical trials published in ten high-impact specialty journals between January 1, 2010 and December 31, 2015 (N=486).

	n	(%)
Intervention^a		
Drug	287	59.1
Device	46	9.5
Vaccine or biological	86	17.7
Other	102	21.0
Phase^b		
Phase II	190	39.1
Phase III	110	22.6
Phase IV	46	9.5
Not listed	153	31.5
Randomization		
Yes	372	76.5
No	114	23.5
Funding^{c, d}		
Industry	216	44.4
Non-industry	270	55.6
Enrollment		
≥ 100	280	57.6
< 100	206	42.4
Location(s)		
US only	166	34.2
US and international	84	17.3

International only	236	48.6
Trial registry^e		
ClinicalTrials.gov	383	87.2
EU-CTR	76	17.3
ISRCTN	24	5.5
Other registries ^f	47	10.7

Notes: ^a Clinical trials may have involved more than one intervention type

^b Thirteen trials were designated as Phase II/Phase III

^c Funding information was not reported in the publications of 5 trials, all of which were unregistered; these trials were designated as not reporting industry funding.

^d Industry funding includes partial or full support.

^e 439 trials were registered. Percentages are expressed based on a denominator of 439. 81 trials were registered in multiple registries, hence percentages may not sum to 100.

^f "Other registries" includes: Australia New Zealand Clinical Trials Register (ANZCTR), Chinese Clinical Trial Registry (ChiCTR), Clinical Trial Registry of India (CTRI), German Clinical Trials Register (DRKS), Japan Pharmaceutical Information Center Clinical Trials Information (JAPIC-CTI), Netherlands Trial Register (NTR), University Hospital Medical Information Network (UMIN) (a Japanese registry).

Abbreviations: EU-CTR = European Union Clinical Trials Register; ISRCTN = International Standard Randomised Controlled Trial Network

Registration

Forty-seven (10%) of the 486 trials were not registered. Two trials (0.4%) reported registration numbers for which a matching registration could not be located. Of 439 registered trials, 33 (8%) did not report a trial registration number in their publication, requiring further searching to identify corresponding registrations records. All registered trials (n=439, 100%) were registered in registries endorsed by ICMJE, though duplicate registrations across more than one registry were not uncommon (n=81; 18%). Eight-seven percent of registered trials (n=383) were registered on ClinicalTrials.gov, which accounted for 79% of initial trial registrations (n=346).

Specialty journals differed in their rates of trial registration (**Table 2**) (p<0.001). *Annals of Neurology* published the greatest proportion of unregistered trials (43%; 16 of 37), accounting for 34% of trials without registration; in

comparison, all trials published in the *Journal of Clinical Oncology* and *Blood*, both of which primarily publish oncology trials, were registered. Registration was more frequent among trials involving drugs, devices, or vaccines/biologicals (361 of 392; 92%) compared to those involving other intervention types (78 of 94; 83%), though this did not reach statistical significance ($p=0.007$). Randomization, larger trial size, enrollment sites in the US, and industry funding were each additionally associated with higher rates of registration (**Table 3**).

Table 2. Registration, timeliness of registration, and primary endpoint concordance among clinical trials published in ten high-impact US medical specialty society journals, stratified by journal.

	Total (column %)	Registration		Timeliness of Registration ^a				Primary Endpoint Concordance ^e		Primary Endpoint Results	
		Unregistere d (%) ^b	P Value	Retrospectiv e (%) ^c	P Value	Retrospective after initial primary endpoint ascertainment (%) ^{c, d}	P Value	Concordan t (%) ^c	P Value	Favorable (%) ^f	P Value
Total	486 (100)	47 (9.7)	<0.00 1	99 (22.6)	0.21	67 (15.3)	0.004	249 (56.7)	.049	282 (66.4)	0.11
<i>AJP</i>	52 (10.7)	6 (11.5)		15 (32.6)		14 (30.4)		17 (37.0)	45 (86.5)		
<i>AJRCCM</i>	51 (10.5)	4 (7.8)		7 (14.9)		7 (14.9)		28 (59.6)	29 (60.4)		
<i>AON</i>	37 (7.6)	16 (43.2)		5 (23.8)		3 (14.3)		8 (38.1)	24 (72.7)		
<i>Blood</i>	52 (10.7)	0 (0.0)		9 (17.3)		4 (7.7)		26 (50.0)	23 (60.5)		
<i>Gast.</i>	53 (10.9)	1 (1.9)		7 (13.4)		7 (13.5)		30 (57.7)	30 (68.2)		
<i>Hep.</i>	50 (10.3)	7 (14.0)		9 (20.9)		4 (9.3)		27 (62.8)	21 (60.0)		
<i>JACI</i>	51 (10.5)	7 (13.7)		12 (27.3)		5 (11.4)		25 (56.8)	27 (64.3)		
<i>JCO</i>	51 (10.5)	0 (0.0)		10 (19.6)		4 (7.8)		35 (68.6)	28 (57.1)		
<i>JACC</i>	50 (10.3)	4 (8.0)		16 (34.8)		15 (32.6)		34 (73.9)	30 (66.7)		
<i>JASN</i>	39 (8.0)	2 (5.1)		9 (24.3)		4 (10.8)		19 (51.4)	25 (64.1)		

Notes:

^a Among 439 registered trials, we could not determine timeliness of registration for 2 (1 published in *Gastroenterology* and the other in *JCO*), as enrollment start date was missing from registrations. We excluded these 2 trials from analyses of association pertaining to overall timeliness of registration and timeliness of registration relative to initial primary outcome ascertainment.

^b Percentages are expressed as fraction of total trials in each row.

^c Percentages are expressed as fraction of registered trials in each row.

^d Due to the nature of the primary outcome (i.e. median survival), we could not determine if retrospective registration occurred after initial primary outcome ascertainment in 8 cases: 1 in *Blood*; 1 in *Hepatology*; 2 in *JACI*; and 4 in *JCO*. These trials were excluded from analyses of association pertaining to timeliness of registration relative to initial primary outcome ascertainment.

^e Twenty-six of 439 registered trials did not have a primary outcome designated in their publication and were therefore excluded from analyses of association pertaining to primary endpoint concordance.

^f Percentages are expressed as fraction of trials in each journal for which primary endpoint favorability could be judged (row totals not shown).

Abbreviations: *AJP* = *American Journal of Psychiatry*; *AJRCCM* = *American Journal of Respiratory and Critical Care Medicine*; *AON* = *Annals of Neurology*; *Gast.* = *Gastroenterology*; *Hep.* = *Hepatology*; *JACI* = *Journal of Allergy and Clinical Immunology*; *JCO* = *Journal of Clinical Oncology*; *JACC* = *Journal of the American College of Cardiology*; *JASN* = *Journal of the American Society of Nephrology*

Table 3. Registration, timeliness of registration, primary endpoint concordance, and study results across clinical trials published in ten high-impact US medical specialty society journals, stratified by trial characteristics.

	Total (column %)	Registration		Timeliness of Registration ^{c, d}				Primary Endpoint Concordance ^{g, h}		Primary Endpoint Results ⁱ	
		Unregistered (%) ^b	P Value	Retrospective (%) ^e	P Value	Retrospective after initial primary endpoint ascertainment (%) ^{e, f}	P Value	Concordant (%) ^e	P Value	Favorable (%) ⁱ	P Value
Total	486 (100)	47 (9.7)		99 (22.6)		67 (15.3)		249 (56.7)		282 (66.4)	
Drug/Device / Biological									0.009		0.16
Yes	392 (80.7)	31 (7.9)	0.007 3	65 (18.0)	< 0.001	42 (11.6)	< 0.001	216 (59.8)		218 (64.7)	
No	94 (19.3)	16 (17.0)		34 (43.6)		25 (32.1)		33 (42.3)		64 (72.7)	
Funding^a											
Industry	216 (44.4)	11 (5.1)	0.002 3	25 (12.2)	< 0.001	18 (8.8)	< 0.001	131 (63.9)	0.014	117 (65.7)	0.82
Non-industry	270 (55.6)	36 (13.3)		74 (31.6)		49 (20.9)		118 (50.4)		165 (66.8)	
Location											
≥ 1 US site	250 (51.4)	15 (6.0)	0.004 8	35 (14.9)	< 0.001	23 (9.8)	< 0.001	133 (56.6)	0.44	148 (65.8)	0.79
Non-US	236 (48.6)	32 (13.5)		64 (31.4)		44 (21.6)		116 (56.9)		134 (67.0)	
Randomized											
Yes	372 (76.5)	23 (6.2)	< 0.001	79 (22.6)	0.91	56 (16.0)	0.39	195 (55.9)	0.10	231 (64.0)	0.01
No	114 (23.5)	24 (21.1)		20 (22.2)		11 (12.2)		54 (60)		51 (79.7)	
Enrollment											
≥ 100	280 (57.6)	9 (3.2)	< 0.001	58 (21.4)	0.49	43 (15.9)	0.69	162 (59.8)	0.47	161 (62.7)	0.046

< 100	206 (42.4)	38 (18.5)		41 (24.4)		24 (14.3)		87 (51.8)		121 (72.0)	
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Notes:

^a Trials receiving either full or partial industry support were designated as having received industry funding.

^b Percentages are expressed as the fraction of total trials in each row.

^c Trials registered > 30 days after enrollment start were considered to have been registered retrospectively. Note that ICMJE policy mandates registration prior to enrollment start.

^d Among 439 registered trials, we could not determine timeliness of registration for 2 (1 published in *Gastroenterology* and the other in *Journal of Clinical Oncology*), as enrollment start date was missing from registrations. We excluded these 2 trials from analyses of association pertaining to overall timeliness of registration and timelines of registration relative to initial primary outcome ascertainment.

^e Percentages are expressed as the fraction of registered trials (total - unregistered) in each row.

^f Due to the nature of the primary outcome (i.e. median survival), we could not determine if retrospective registration occurred after initial primary outcome ascertainment in 8 cases: 1 in *Blood*; 1 in *Hepatology*; 2 in *Journal of Allergy and Clinical Immunology*; and 4 in *Journal of Clinical Oncology*. These trials were excluded from analyses of association pertaining to timeliness of registration relative to initial primary outcome ascertainment.

^g Registered and published primary endpoints were considered concordant if they did not differ in any of the following 3 domains: number of outcomes, outcome definition(s), or outcome time frame(s).

^h Twenty-six of 439 registered trials did not have a primary outcome designated in their publication and were therefore excluded from analyses of association pertaining to primary endpoint concordance.

ⁱ Primary endpoint favorability could not be judged for 61 trials. These trials were excluded from analyses of association pertaining to primary endpoint favorability.

^j Percentages are expressed as the fraction of trials in each row for which primary endpoint favorability could be judged (row totals not shown)

Timeliness of Registration

Among the 439 registered trials, 99 (23%) were registered retrospectively (i.e. at least 30 days after beginning patient enrollment) based on the enrollment start date reported in the registry. The median delay in registration was 8 months (IQR, 5-19; range, 1-88). Sixty-seven (68%) of the 99 retrospectively registered trials, or 15% of all 439 registered trials, were registered late enough to have potentially permitted premature examination of trial results after collection of the primary outcome among participants enrolled at inception (**Table 4**). Of 302 trials with a registered primary completion date, 7 (2%) were registered after reported completion of data collection for the trial's primary outcomes. Two (2%) of 88 retrospectively registered trials that listed a manuscript submission date were found to have registered after submission of the manuscript to the publishing journal. Only one (1%) of 99 retrospectively registered trials acknowledged late registration in its publication, attributing the delay to principal investigator oversight and offering access to the original study protocol upon request.[34]

Table 4. Illustrative examples of prospective trial registration, retrospective trial registration occurring without possibility for informed interim analyses, and retrospective registration occurring with possibility for interim analyses.

Reference	Registration No.	Registration Date	Enrollment Start	Registration Delay	Registered Primary Endpoint (Time Frame)	Registration Timing
<u>J Am Soc Nephrol.</u> 2010 Jun;21(6):1052-61.	NCT00426153	1/22/2007	1/31/2007	N/A	Percentage change in liver volume (12 months)	Prospective
<u>J Allergy Clin Immunol.</u> 2015 Mar;135(3):670-5.e3.	NTR2205	2/8/2010	1/1/2010	1 month	Induced sputum neutrophil and eosinophil percentage counts (9 weeks)	Retrospective
<u>J Allergy Clin Immunol.</u> 2015 Apr;135(4):922-29.e6.	NCT02024659	12/27/2013	9/30/2010	39 months	Nasal polyp size (2 weeks)	Retrospective (after initial primary endpoint ascertainment)

Journals did not differ significantly in their rates of overall timely registration ($p=0.21$), but did differ in their rates of registration before initial primary outcome ascertainment ($p=0.004$) (**Table 2**). Trials involving industry funding, enrollment sites in the US, and assessing drugs, devices, or vaccines/biological each had higher rates of prospective registration as compared to those without industry funding, enrolling at only non-US sites, and assessing non-regulated interventions (**Table 3**).

Primary Endpoint Concordance

Among the 439 registered trials, 15 (3.4%) failed to register a primary outcome at initial registration, though 14 of these 15 published a primary endpoint. Twenty-six trials, nearly all of which ($n=25$; 96%) registered a primary endpoint at initial registration, did not explicitly name a primary endpoint in their publications. Of 413 registered trials designating at least one primary outcome in their publications, sixty percent ($n=249$) published primary endpoints fully concordant with those specified at initial registration. Twenty-six percent ($n=109$) published primary endpoints discrepant from those initially registered. Seventy-eight (72%) of these 109 discrepancies were based on either the number or definition of primary endpoints, whereas 31 (28%) were based on the specified time frame of primary outcome ascertainment. The remaining 13% (55 of 413) registered initial primary endpoints that were too poorly specified to permit comparison with published endpoints. Among the 346 trials registered first on ClinicalTrials.gov, 19 (5%) trials listed original primary outcome measures that were submitted at least

30 days subsequent to the reported registration date. Seven (37%) of these 19 involved trials whose registration was already retrospective.

Among the 249 trials reporting discrepant published and registered primary endpoints, 80% (n=198) were registered prospectively; 20% (51 of 249) were retrospectively registered. Neither overall timely registration (p=0.31) nor registration prior to initial primary outcome ascertainment (p=0.29) was associated with concordance between registered and published primary endpoints. Even so, just 1 of 7 trials determined to have been registered after their primary completion date published outcomes concordant with those initially registered, despite the significant delay in registration.

Favorability of Trial Results

Among the 486 trials in our sample, 425 (87%) reported primary endpoint results from which inferences about the statistical significance of reported outcomes could be drawn; 61 trials (13%) were non-inferential, including descriptive or single-arm studies without a specified comparator, and could not be judged accordingly. Sixty-six percent (n=282) of the 425 inferential trials reported favorable primary outcome results. Of 143 (34%) trials reporting unfavorable primary outcome results, most (n=135; 94%) reported findings that were not significant, while 8 (6%) reported negative results. Unregistered trials were more likely to report favorable results (31 of 35; 89%) than were registered trials (251 of 390; 64%) (p=0.004), irrespective of registration timing. Favorable results reporting appeared to be more frequent among trials potentially vulnerable to unaccounted primary endpoint modifications (73 of 96; 76%), which included those

that were unregistered and those registered after initial primary outcome ascertainment, compared to those registered prior to initial primary outcome ascertainment (206 of 321; 64%), but our findings did not reach statistical significance ($p=0.03$).

DISCUSSION

Our study of clinical trials recently published in ten high-impact specialty society journals, all requiring trial registration, found that 10% of published trials were unregistered. Moreover, among registered trials, nearly one quarter were registered retrospectively. Of these, more than two-thirds, or 15% of all registered trials, were registered late enough after participant enrollment to afford opportunity for unaccounted protocol modifications based on potential premature analyses of observed primary endpoint data. Irrespective of registration timing, post-registration modifications to primary endpoints were frequent, as 26% of trials published primary outcomes that differed from those specified at initial registration. Finally, unregistered trials reported favorable results at a higher rate than trials that had registered. The publication of unregistered trials and trials registered after initial primary outcome ascertainment raises concerns about selective reporting and the integrity of reported endpoints, as these trials are vulnerable to potential changes obscured from public record.

Despite policies to improve registration rates,[32, 35, 36] publication of unregistered trials persists. Our study demonstrates that even the highest impact journals associated with US professional medical societies publish unregistered

trials, albeit some more frequently than others. Consistent with earlier studies,[13-19] our findings suggest that, more than a decade since implementation of policies designed to promote universal registration, continued efforts are needed to ensure that all trials are registered, even among those that are published. Registration was more frequent among trials assessing FDA-regulated interventions as compared to trials evaluating non-regulated interventions, such as behavioral and procedural interventions, as prior research has suggested.[16] We additionally noted higher registration rates among larger trials and those receiving industry support. As each of the specialty society journals we assessed requires trial registration, our results indicate that some journals do not consistently adhere to their own registration policies. Prior work indicates that journals may in fact relax their own registration requirements for various reasons, including reluctance to penalize otherwise sound research, apprehension about losing manuscripts to rival journals, and misconceptions about the applicability of registration policies.[26] Regardless of the rationale, publication of unregistered trials risks dissemination of trials lacking accountability and potentially influenced by selective reporting. Our study and prior work examining cardiovascular clinical trials demonstrate that unregistered trials more frequently report favorable findings,[37] though a recent study examining a large sample of unselected trials found only a marginal association.[38] Nevertheless, stricter adherence to registration policies may help prevent the publication of trials that are selectively reporting results, biasing the medical literature.

While registering trials can help mitigate selective reporting, registration must occur prospectively, in accordance with ICMJE policy, to effectually detect and deter biased reporting. Despite the importance of timely registration, nearly one in four trials in our sample was published despite having been registered retrospectively. Furthermore, the majority of late registrations were delayed to such a degree after enrollment of the trials' first participants that it could have permitted investigators the opportunity to amend primary endpoints after conducting interim analyses. For trials registered after ascertainment of endpoints, it is nearly impossible to ascertain the degree to which published reports diverge from original protocol given the potential for modifications occurring covertly pre-registration. While the frequency of post-registration endpoint modifications does not appear to depend on the timeliness of trial registration, we cannot comment on the frequency and effects of pre-registration protocol modifications beyond identifying situations in which they could have potentially occurred.

This study's findings are consistent with prior research that timely registration is more frequent among certain trial types, including those involving FDA-regulated interventions and those receiving industry support.[14, 21] Compared with existing studies,[14, 21, 23] however, retrospective registration was overall less frequent in our sample. Notwithstanding the possibility that specialty society journals are in better overall adherence, there are several methodological explanations for this observation, including utilization of each trial's earliest registration record, which is not always reported in publications, application of a 30-day grace period between enrollment initiation and registration, and our

conservative treatment of month-based reporting of enrollment start dates to ensure that true prospective registrations were not misclassified. Only one prior study has assessed timeliness of registration as it relates to its potential effect on reported outcomes, specifically within the context of the six highest impact general medical journals.[21] While late registration was less frequent among specialty society journals as compared to the general medical journals assessed in the prior study (23% v. 28%), this study observed a higher proportion of late registrations that potentially permitted an opportunity for endpoint modification informed by potential interim analyses (15% vs. 8%).

Implications of Findings

Because journals control the dissemination of research, they are well positioned to help ensure the integrity of published material, which includes adequate and timely registration of published trials.[39] Specialty society journals, in particular, bear a significant responsibility to this end, as they publish trials that are of great interest and potential influence to their targeted clinical readerships. As part of the peer-review process, journals generally require the disclosure of trial registration information, though discrepancies between registered and reported material do not appear to influence the decision to accept or reject manuscripts,[40] suggesting that editors may not scrutinize or may choose to disregard discrepancies. If oversight is in fact the driver, greater attention paid to trial registration during editorial review may reduce the rate at which potentially biased trials are published, including those that are unregistered or retrospectively registered.

However, while ICMJE policy advocates barring retrospectively registered trials from publication, it acknowledges that editors may judge for themselves the circumstances surrounding late registration and its potential bearing on reported endpoints.[32] Accordingly, our findings may instead stem from editors deliberately choosing to publish non-compliant trials, which they may do for reasons suggested previously.[26] A survey of editors from journals endorsing ICMJE guidelines found that two-thirds would consider publication of retrospectively registered trials, though just 13% indicated that consideration would be situation-dependent.[25] For journal editors weighing the decision to publish such trials, ascertaining whether registration was sufficiently delayed to have potentially biased the reported results may help guide decisions regarding appropriate exceptions. The significance of study findings should be carefully evaluated in the decision to accept or reject given the potential for bias that exists among unregistered or retrospectively registered trials. If journals elect to move forward with publishing these trials, steps should be taken to ensure that original trial protocols, approved by and obtained directly from institutional review boards, are made publicly available. Additionally, as ICMJE policy suggests, publication of non-compliant trials should be accompanied by published statements explaining why registration did not occur or was delayed and, further, why journal editors nonetheless judged the trial fit for publication.[32] Just one retrospectively registered trial in our sample addressed its delayed registration, offering to make available its original protocol upon request. While routine posting of original protocols for all trials, regardless of registration compliance, may mitigate concerns regarding biased reporting, such

practices are infrequent.[41] Among journals in our sample, only the *Journal of Clinical Oncology* requires submission and publication of trial protocols, albeit only for phase II and III trials.[42]

Limitations

This study has several limitations. First, the ICMJE definition of a clinical trial is subject to interpretation, particularly in terms of what constitutes a “health-related intervention” and a “health outcome”. ICMJE adopted an expanded clinical trial definition in 2007 clarifying the scope of these terms.[43] Nevertheless, confusion regarding the applicability of registration requirements for interventional clinical studies may exist among investigators and journals editors. While ICMJE believes that investigators should err towards prospectively registering all interventional studies of human subjects in cases of uncertainty,[43] subjectivity in classifying studies as “clinical trials” may have influenced our observed frequency of unregistered trials, particularly in cases where the applicability of the ICMJE definition may not be patent. Second, this analysis does not represent a perfect audit of ICMJE registration policy, given its concession of a 30-day grace period and exclusion of Phase I studies. Nevertheless, this study aimed to capture the spirit of the policy rather than the strict letter of the law to account for potential flexibility on the part of journals in the case of minimally delayed registrations. Third, our sample by design comprised a group of clinical trials recently published in select high-impact specialty society journals; accordingly, our findings may not be representative of overall trial registration patterns or of all specialty society journals. Nevertheless, this study selected the highest-impact specialty journals, the

most prestigious in their respective fields, which are expected to adhere to the highest standards of trial registration practices. Fourth, our cross-sectional analysis did not examine potential improvements in trial registration within journals over time nor account for the fact that journals may have adopted the ICMJE's registration policy at different time points since its implementation. Even so, the earliest trials in our sample were published in January 2010, nearly half a decade since the policy went into effect, with 89% of sampled trials being published in a three-year span since 2013. Finally, our study only assessed frequency of modifications to primary endpoints, though selective reporting may manifest through post-registration protocol modifications to other elements of trial design, including secondary endpoints and sample size, which were not examined. Moreover, this study is only able to comment on the possibility of retrospective registration to invite unaccounted interim analyses or pre-registration protocol modifications and not on whether such analyses or modifications actually occurred. Such information could only be ascertained through examination of original trial protocols, which are often unavailable and lack complete information.[41] Additionally, how informative interim analyses are, in some cases, depends on the trial's experience of participant accrual, details of which are also generally not readily accessible.

Conclusions

Our large study of clinical trials published in ten high impact specialty society journals demonstrates that registration of trials continues to fall short of the ICMJE's standards necessary to ensure a complete and unbiased evidence base. Ten percent

of published trials were unregistered. Moreover, nearly a quarter of registered trials were registered late, the majority of these late enough to afford investigators the chance to implement modifications potentially informed by collected data. Unregistered trials reported favorable study findings at a higher rate than registered trials, raising concerns that lack of accountability may exert undue influence on reported results. While journals should generally avoid publishing improperly registered trials, exceptions should be acknowledged, justified, and furthermore accompanied by an evaluation and public posting of the study's original protocol. Greater adherence to the ICMJE's prospective trial registration policy may help reduce the publication of studies failing to meet proper standards and improve the integrity of published trial results.

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