

Short Report

# Discontinuation and nonpublication of interventional clinical trials conducted in patients with mild cognitive impairment and Alzheimer's disease

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## Abstract

**Introduction:** Discontinuation and nonpublication of interventional clinical trials represents a waste of already scarce resources. We sought to identify the prevalence of discontinuation and nonpublication of interventional clinical trials conducted in patients afflicted by mild cognitive impairment and Alzheimer's disease.

**Methods:** We conducted a retrospective, cross-sectional study on mild cognitive impairment and Alzheimer's disease–based interventional clinical trials in [ClinicalTrials.gov](http://ClinicalTrials.gov) dating back to 1995. The analyzed data included trial phase, intervention type, enrollment, and funding sources. Fisher's exact and  $\chi^2$  tests were used to determine any potential associations between trial characteristics and completion.

**Results:** A total of 744 studies were identified, of which 502 (67%) were industry-sponsored ones. A total of 127 (17%) were discontinued prematurely. Of the 617 completed trials, 450 (73%) were not published, representing approximately 66,655 participants who incurred the risks of trial participation without subsequently contributing to the medical literature. Similarly, there were 18,246 patients from unpublished, discontinued trials. Of the 744 trials examined, 247 publications from 167 trials could be identified via PubMed/MEDLINE and EMBASE searches. Most notably, the odds of nonpublication among industry-sponsored trials were more than 75% higher than those in studies funded by academia (odds ratio = 1.78; 95% confidence interval, 1.14–2.78;  $P = .01$ ). Furthermore, industry-sponsored trials had a 50% greater odds of study discontinuation compared with trials funded by academia (odds ratio = 1.50; 95% confidence interval, 1.04–2.16;  $P = .03$ ).

**Discussion:** The nonpublication of many trials and preliminary results of trials that are discontinued early dilutes the quality and decreases the comprehensive nature of the medical literature. This occurs in both industry and academia. Publication of inconclusive or negative results ensures that all research activities, regardless of outcome, contribute to global medical knowledge.

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## Keywords:

Clinical trials; Discontinuation; Nonpublication; Mild cognitive impairment; Alzheimer's disease

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## 1. Introduction

Discontinuation of interventional clinical trials and nonpublication of completed trials represent a waste of already scarce resources. This waste relates to all types

of research occurring at multiple stages of the production of medical evidence, including the underreporting of trial methods and results [1,2]. There is evidence that trials with positive findings are published more often and more quickly than trials with negative findings [3]. Furthermore, citation bias has been shown to lead to an overrepresentation of positive results [4]. Academic researchers may not wish to invest the time and effort to publish studies that might yield negative outcomes. Academic competition and pressure have been shown to increase the risk of scientists' bias in not publishing negative studies [5]. Industry sponsors may be cautious to publish results which might reveal current or lack of progress of their research to competitors. Nevertheless, the nonpublication of trial findings undermines the available medical evidence by misrepresenting the apparent safety and efficacy of interventions and compromises clinical guidelines and evidence-based clinical practices [6–8]. This is of particular importance in the field of mild cognitive impairment (MCI) and Alzheimer's disease (AD) research, considering the many disappointing trials with high costs and lack of a successful drug after decades of research in addition to the urgent need of a therapy, given the aging world population, among others. The aim of this study was to identify the prevalence of discontinuation and nonpublication of interventional clinical trials conducted in MCI and AD patients.

## 2. Methods

We conducted a retrospective, cross-sectional search of MCI- and AD-based interventional clinical trials in [ClinicalTrials.gov](http://ClinicalTrials.gov) dating back to 1995. This search was limited to trials in humans and to studies listed as “completed,” “terminated,” “withdrawn,” or “suspended.” Data were collected from the registry, and associated publications were identified (final search was performed on January 15, 2018). We included interventional clinical trials that were not active, recruiting, or enrolling and for which recruitment status was known. Trials were considered published if they were linked with a national clinical trial identifier number. Details of analyzed trials provided data on the funding sources (industry or academia), intervention type, trial phase, and enrollment numbers (Table 1). Fisher's exact and  $\chi^2$  tests were used to determine any potential associations between trial characteristics and trial completion. Reasons for trial discontinuation were tabulated based on data provided in [ClinicalTrials.gov](http://ClinicalTrials.gov) entries.

We opted not to contact the trialists because we wanted to represent the amount of information and level of detail that is accessible to the average clinician searching the literature. Although we recognize that unpublished results can at times be obtained by reaching out to investigators, we felt that doing so would dilute the potential publication bias that we sought to evaluate.

Table 1  
Characteristics of completed and discontinued trials

Clinical trial characteristics	Completed trials	Discontinued trials	All trials	P
	(n = 617), n (%)	(n = 127), n (%)	(n = 744), n (%)	
Primary funding source				.01*
Academic institution	213 (35)	29 (23)	242 (33)	
Industry	404 (65)	98 (77)	502 (67)	
Intervention				.07†
Drug	476 (77)	110 (87)	586 (79)	
Other	54 (9)	8 (6)	62 (8)	
Behavioral	50 (8)	3 (2)	53 (7)	
Device/procedure	37 (6)	6 (5)	43 (6)	
Trial phase‡				.06*
Phase 1	125 (20)	23 (18)	148 (20)	
Phase 2	201 (33)	41 (32)	242 (33)	
Phase 3	119 (19)	38 (30)	157 (21)	
Phase 4	61 (10)	11 (9)	72 (10)	
Unknown	111 (18)	14 (11)	125 (17)	
Enrollment				<.0001†
<50	231 (37)	64 (50)	295 (40)	
50–100	118 (19)	16 (13)	134 (18)	
101–250	126 (20)	16 (13)	142 (19)	
>250	126 (20)	30 (24)	156 (21)	
Unknown	16 (3)	1 (1)	17 (2)	

\*Determined using  $\chi^2$  test.

†Determined using Fisher's exact test.

‡Trials described as phase 1/2 (n = 19) were categorized as phase 2, and trials described as phase 2/3 (n = 15) were categorized as phase 3.

## 3. Results

Seven hundred forty-four trials met our inclusion criteria, from which a total of 247 publications from 167 trials could be identified via PubMed/MEDLINE and EMBASE searches. The included trials employed strategies such as novel drugs (n = 586; 79%), other (such as cognitive training and exercise programs) (n = 62; 8%), behavioral interventions (n = 53; 7%), and devices/procedures (n = 43; 6%). Fifty-four percent of trials were performed in either phase 2 or 3 settings. Between 2007 and 2016, there were approximately two and half times as many trials as those in the previous decade. A total of 744 studies were identified, of which 502 (67%) were industry-sponsored ones. A total of 127 (17%) were discontinued prematurely whereby 111 were terminated. Of the 617 completed trials, 450 (73%) were not published, representing approximately 66,655 participants who incurred the risks of trial participation without subsequently contributing to the medical literature. Similarly, there were 18,246 patients from unpublished, discontinued trials. Only 19% (n = 86) of unpublished trials posted results on [ClinicalTrials.gov](http://ClinicalTrials.gov). Over 65% of the reasons for trial discontinuation were due to unspecified/unclear reasons or informative termination (changes in standard of care and safety or efficacy findings) (Table 2).

Table 2  
Reasons for trial discontinuation

Reason	n	%
None reported or unclear	51	40
Informative termination*	34	27
Patient accrual	17	13
Company/business decision	11	9
Principal investigator left	5	4
Conduct problems†	4	3
Regulatory issue‡	3	2
Funding issue	2	2

\*Changes in standard of care and safety or efficacy findings.

†Technical/logistical issues.

‡Issues with institutional review board or other regulatory body.

Most notably, the odds of nonpublication among industry-sponsored trials were more than 75% higher than those in trials funded by academia (National Institutes of Health, National Eye Institute, National Institutes of Health Clinical Center, US and foreign university-based teaching hospitals) (odds ratio = 1.78; 95% confidence interval, 1.14–2.78;  $P = .01$ ). Furthermore, industry-sponsored trials had a 50% greater odds of study discontinuation compared with trials funded by academia (odds ratio = 1.50; 95% confidence interval, 1.04–2.16;  $P = .03$ ).

#### 4. Discussion

Our study demonstrates that discontinuation and nonpublication of interventional trials involving MCI and AD patients are a common occurrence. More than 80% of completed trials were not published. Trial discontinuation and nonpublication represent not only a waste of already scarce research resources but raises ethical issues for participants of the trial. A total of 66,655 were enrolled in unpublished, completed trials, whereas 18,246 participants were enrolled in unpublished, discontinued trials. This represents a massive fund of information that was never integrated into medical science and clinical practice. Trials sponsored by academia are in general less likely to be discontinued owing potentially to the human resources available and a more comprehensive robust trial conduct strategy. The most challenging aspect of trial enrollment represents the recruitment of study patients and has been cited as the most prevalent factor in the discontinuation of clinical trials [7]. In our analysis, the most common reason for discontinuation of a trial was that there was none reported or unclear reasons were given (40% of discontinued trials). Other reasons included issues surrounding patient accrual, company/business decisions, and informative termination, among others. Issues surrounding the conduct of trials remain a perpetual problem for most clinical trials [6–10].

Our high nonpublication rate reflects the poor treatment outcomes with various treatment modalities over the decades as researchers are less likely to report on studies with negative outcomes. Not only does nonpublication of trials breach the ethical code of research, it also introduces

publication bias into the literature. Trial discontinuation and nonpublication of study results puts both the public's and patients' trust in clinical research in question in addition to potentially compromising the willingness of future patients to participate in trials [11].

When interpreting our findings, it is important to bear in mind a number of limitations. First, our study analyzed only those trials registered in [ClinicalTrials.gov](https://www.clinicaltrials.gov), thus leaving the possibility open for additional interventional studies that were not included in our analysis. Second, we were unable to verify the accuracy of the trial data on account of the fact that information in the registry is mainly provided by investigators and sponsors. Finally, we were limited by the data provided as some data were missing, such as trial phase and reasons for trial discontinuation.

There has been a remarkable upsurge of investment in MCI and AD research, particularly in the period between 2006 and 2016. New policies and initiatives have helped to usher in an era of improved methods for trial reporting and, in turn, provided the opportunity to perform more interventional trials. However, further action is needed to ensure that findings of all trials are shared to build a more comprehensive body of knowledge and potentially decrease redundancy. The nonpublication of many trials and preliminary results of trials that are discontinued early dilutes the quality and decreases the comprehensive nature of the medical literature. This occurs in both industry and academia although it is seemingly more common in industry-sponsored trials possibly on account of the fierce competition between companies to get drugs to as well as to keep on the market through favorable representation of their interventions [12–15]. However, unpublished studies raise questions and concerns regarding both the underreported risks and limitations in the efficacy of the interventions that industry might be promoting [15].

One such global initiative advocating for clinical research to adopt the principles of open research via a clinical trials registry is called AllTrials. The purpose is to have all past and present trials registered, and the full methods and results shared freely with all stakeholders [16]. Also, in efforts to improve the completeness of clinical trial reporting, such modalities such as the Consort-based WEB tool writing aid tool have been developed [17]. Publication of trials with inconclusive or negative results as well as those that are terminated early could minimize publication bias and ensures that all research activities, regardless of outcome, contribute to global medical knowledge. More knowledge about effective recruitment and enrollment strategies via increased awareness, access, and dispelling of myths surrounding clinical trial participation, use of different and possibly more promising interventions, and better selection of outcome measures might benefit the design and outcomes of future clinical trials. Hence, providing clinicians and researchers with more complete data would allow them to make even more informed decisions and thus provide ever better patient care while contributing to the ongoing quest for an effective therapy against AD.

## RESEARCH IN CONTEXT

1. Systematic review: The authors used [ClinicalTrials.gov](http://ClinicalTrials.gov) to determine the prevalence of discontinuation and nonpublication of interventional clinical trials conducted in patients afflicted by mild cognitive impairment and Alzheimer's disease. The publication status of these clinical trials was verified via searches in PubMed and EMBASE.
2. Interpretation: Our findings have demonstrated that discontinuation and nonpublication of interventional trials involving mild cognitive impairment and Alzheimer's disease patients are a common occurrence. Better strategies need to be employed to lessen and eventually eliminate the discontinuation as well as lack and underreporting of trial results.
3. Future directions: We propose that those conducting mild cognitive impairment and Alzheimer's disease research publish their results, irrespective of their outcomes, in a platform such as AllTrials so that all are made aware of the trials' findings. In an effort to improve the reporting of clinical trials, novel modalities such as the Consort-based WEB tool writing tool have been developed to assist researchers.

## References

- [1] Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. *Lancet* 2009;374:86–9.
- [2] Yordanov Y, Dechartres A, Porcher R, Boutron I, Altman DG, Ravaud P. Avoidable waste of research related to inadequate methods in clinical trials. *BMJ* 2015;350:h809.
- [3] Hopewell S, Loudon K, Clarke MJ, Oxman AD, Dickersin K. Publication bias in clinical trials due to statistical significance or direction of trial results. *Cochrane Database Syst Rev* 2009;MR000006.
- [4] Duyx B, Urlings MJE, Swaen GMH, Bouter LM, Zeegers MP. Scientific citations favor positive results: a systematic review and meta-analysis. *J Clin Epidemiol* 2017;88:92–101.
- [5] Fanelli D. Do pressures to publish increase scientists' bias? An empirical support from US States data. *PLoS One* 2010;5:e10271.
- [6] Pica N, Bourgeois F. Discontinuation and nonpublication of randomized clinical trials conducted in children. *Pediatrics* 2016; 138:e20160223.
- [7] DeAngelis CD, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. *JAMA* 2004;292:1363–4.
- [8] Zarin DA, Tse T. Medicine. Moving toward transparency of clinical trials. *Science* 2008;319:1340–2.
- [9] Chapman SJ, Shelton B, Mahmood H, Fitzgerald JE, Harrison EM, Bhangu A. Discontinuation and non-publication of surgical randomised controlled trials: observational study. *BMJ* 2014;349:g6870.
- [10] Kasenda B, von Elm E, You J, Blümle A, Tomonaga Y, Saccilotto R, et al. Prevalence, characteristics, and publication of discontinued randomized trials. *JAMA* 2014;311:1045–51.
- [11] Amstutz A, Schandelmaier S, Frei R, Surina J, Agarwal A, Olu KK, et al. Discontinuation and non-publication of randomised clinical trials supported by the main public funding body in Switzerland: a retrospective cohort study. *BMJ Open* 2017;7:e016216.
- [12] Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ* 2003;326:1167–70.
- [13] Psaty BM, Kronmal RA. Reporting mortality findings in trials of rofecoxib for Alzheimer disease or cognitive impairment: a case study based on documents from rofecoxib litigation. *JAMA* 2008;299:1813–7.
- [14] Bhandari M, Busse JW, Jackowski D, Montori VM, Schünemann H, Sprague S, et al. Association between industry funding and statistically significant pro-industry findings in medical and surgical randomized trials. *CMAJ* 2004;170:477–80.
- [15] Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. *JAMA* 2003; 289:454–65.
- [16] AllTrials. Available at: <http://www.alltrials.net/>. Accessed January 26, 2018.
- [17] Barnes C, Boutron I, Giraudeau B, Porcher R, Altman DG, Ravaud P. Impact of an online writing aid tool for writing a randomized trial report: the COBWEB (Consort-based WEB tool) randomized controlled trial. *BMC Med* 2015;13:221.