Reporting Compliance of Stroke Trials: Cross-Sectional Analysis

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Background: The FDA mandates timely reporting of all clinical trials conducted in the United States. However, often the results are not reported in a timely manner, resulting in wastage of finite resources. We assessed the reporting of results of completed stroke trials and compared the reporting trends between U.S. and non-U.S. stroke trials. *Methods:* We assessed consecutive clinical stroke trials registered as completed in ClinicalTrials.gov between January 1, 2008 and January 1, 2015. Descriptive data collected included study phase, study type, participant age, number of enrolled patients, study locations, start and primary completion dates, result availability, time to reporting (months), sponsorship, funding sources, and publication status. We also performed manual search for stroke trials in Pubmed, Web of Science, and Google scholar. *Results:* Out of a total 140 completed trials, 39 trials (35,359 patients) involved at least 1 U.S. center and 101 trials (58,542 patients) were conducted in non-U.S. centers. Of the trials involving at least a single U.S. center, 31 of 39 (79%) reported their results, whereas only 6 of 31 (19%) reported their results within 1 year. Of the trials conducted at non-U.S. centers, 72 of 101 (71%) reported their results, whereas results for 24 of 72 (33%) trials were available within a year of completion. The time to reporting of results was significantly lower for all the included clinical trials in the 2012-2014 period ($P < .001$, Cohen's $d = .726$) as compared to the 2008-2011 period. *Conclusion:* Only one-fifth of completed stroke trials involving at least a single U.S. center report their results within 1 year. Additionally, every fifth completed trial involving stroke patients at U.S. centers remain unreported. **Key Words:** Clinicaltrials.gov—stroke—clinical trials—NIH—database.

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Introduction

Stroke is one of the leading cause of morbidity with a high recurrence rate that accounts for elevated global burden of stroke.[1,2] Although the mortality rate has reduced recently, the morbidity rate and the associated healthcare cost in the poststroke care remains a major concern. With the advent of novel diagnostic neuroimaging techniques, the stroke community has experienced success in multitude aspects of stroke care.[3] This success can be attributed, at least in part, to the cognizance of recent advancements in the research sector throughout the world.

Clinical trials act as a benchmark to represent biomedical research involving human participants, evaluate existing health-related interventions, assess safety of new treatment options, and generate clinical evidence to accept

or refute proposed clinical interventions. The National Institutes of Health (NIH) monitors the successful completion and reporting of the clinical trial results.[4,5] Being the largest public funder in the United States, the NIH invests more than 3 billion dollars annually to conduct clinical trials, monitor trial protocol, and assess result reporting. Research volunteers participate under an impression that ethical and scientific standards pertaining to a clinical trial would be strongly executed, and the trials would deliver impactful results that could be used in timely fashion. Delayed reporting of results and lack of publication violates ethical and regulatory obligations of the trial investigators.[6,7] Although clinical trials have been of paramount importance in the expansion of existing medical knowledge, transparency and efficiency continue to hinder critical success of clinical trials.

Swift acceptance of positive trials to peer-reviewed journals leads to publication bias.[8] Following the creation of ClinicalTrials.gov as a platform for transparent reporting of clinical trials, Section 801 of the Food and Drug Administration Amendments Act (FDAAA) of 2007 mandated the sponsors of clinical trials to register and report their study results within 1 year of completion of data collection for their prespecified primary outcome, provided no valid reasons for delays are evident.[9] The policy encompassed non-phase 1 interventional trials for drugs, devices, or biological interventions involving at least 1 U.S. based research center, initiated either after September 27, 2007 or before that date, but were still active as of December 26, 2007. However, multiple investigations concluded that less than 15% of these clinical trials are reported within 1 year of trial completion.[10]

Various studies have demonstrated poor compliance with the FDAAA legislation in the past.[11-14] Non-phase 1 clinical trials usually promote new innovations, steer clinical guidelines for reported level of evidence, and carry high impact on therapeutic decisions. Clinical trial reporting has been a subject of active scrutiny for the past decade; however, no prior studies have been performed to assess the publication rates in trials involving stroke patients. Hence, our aim was to assess the rate of result reporting in stroke trials throughout the world. We primarily assessed the publication status of all the stroke trials registered in ClinicalTrials.gov between 2008 and 2014. Our secondary objective was to assess the time from completion of the trial until the reporting of results and to analyze the trend after a decade of FDAAA legislation.

Methods

Data Source

We performed our search using ClinicalTrials.gov, the largest publicly available online database registry for clinical trials. It is maintained by the NIH that promotes sponsors and clinical trial investigators to register their research trials and report results in a timely fashion.[15] Various strategies for quality assurance and methods to register trials in ClinicalTrials.gov have been reported previously.[16,17]

Search Methodology and Eligibility Criteria

We performed our web-based analysis based on STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) criteria. A web-based search was conducted on September 9, 2016, to identify all the completed cerebrovascular disease clinical trials registered on ClinicalTrials.gov using following keywords: "stroke," "cerebral infarction," "brain attack," and "cerebrovascular diseases." We included all the trials registered as completed in ClinicalTrials.gov and used primary completion date or completion date, whichever was available. We further obtained the time to reporting of study data from the primary completion date until the results were reported on ClinicalTrials.gov or published in a peer-reviewed journal.

Eligibility of all the clinical trials were independently assessed by 2 authors (KM and AR) and disagreements, if any, were resolved with mutual consensus. Our inclusion criteria were (1) clinical trials involving patients diagnosed with either ischemic or hemorrhagic stroke; (2) adult patients (18 years and above); (3) trials in phase 2, phase 2/3, phase 3, phase 3/4, or phase 4; (4) trials initiated between January 1, 2008 and January 1, 2015; and (5) trials reported in English language. We also stratified clinical trials based on conductance involving either a single U.S. center or non-U.S. centers. The search strategy is explained as a flowchart in Figure 1.

Data Extraction

We downloaded all the available data fields in a comma-separated value format for all the stroke trials registered as completed in ClinicalTrials.gov by January 1, 2015. Further, selective data was exported and extracted into Excel sheet for further analysis.

Definitions

Completed trials were defined as trials that have finished recruitment for diagnostic and therapeutic interventions. Trials were deemed as completed if the study results were available in ClinicalTrials.gov between January 1, 2008 and January 1, 2015. We considered a trial as reported if at least one of their primary outcome results were available, either on ClinicalTrials.gov or published online in peer-reviewed journals. ClinicalTrials.gov defines primary completion date as the date when the final participant of the trial was examined or received an intervention for data collection. If primary completion date was not available, completion date was retrieved and used instead. Time to publication was calculated as number