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Reporting bias in completed epilepsy intervention trials: A cross-sectional analysis

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ABSTRACT

Objective: To explore the evidence of reporting bias among completed epilepsy intervention trials (EITs) and compliance of applicable EITs to Food and Drug Administration Amendments Act (FDAAA).
Methods: We included consecutive EITs registered as completed on ClinicalTrials.gov from 2008 to 2015. Descriptive data was collected including study type, study phase, funding source, primary completion date, and result reporting date. Time to result reporting was analyzed using Kaplan-Meier estimates for two time periods (2008–2011 and 2012–2015). PubMed, Web of Science, and Google scholar databases were manually searched for publication details.
Results: Overall, 95/126 EITs (75%) reported, while remaining 31/126 (25%) did not report their results. Time to reporting was significantly lower for trials completed during 2012–2015 (16.5 months; 95% CI: 13.60–19.40; p = .002; Cohen's d = 0.68) as compared to the trials completed during 2008–2011 (25.9 months; 95% CI: 21.56–30.22). 72/126 trials were conducted in at least one U.S. center. 56/72 (78%) of the trials met the FDAAA criteria, while only 19/56 (34%) reported within the mandated one-year time frame.
Conclusion: The lack of reporting of nearly one-quarter of completed epilepsy intervention trials suggests existence of reporting bias. As such, it should be considered an important criterion for determining risk of bias in epilepsy systematic reviews.

1. Introduction

Various biases have been reported during the conductance and reporting of clinical trials to date (Dickersin, 2008; Dwan et al., 2008; Turner et al., 2008). Reporting bias occurs when the dissemination of a study results are influenced by the direction of the results and clinical outcomes. Few key reporting biases are time-lag bias and outcome-reporting bias. Based on the nature and direction of study outcomes, time lag bias refers to the rapid or delayed dissemination of research findings and outcome-reporting bias arises when there is selective reporting of study results based on the clinical outcomes (Sterne et al., 2008). These biases significantly affect the availability and generalizability of scientific evidence, as evidence-based medicine is based on peer-reviewed publications and systematic reviews of clinical trials (Every-Palmer and Howick, 2014; Hopewell et al., 2009; Mechler et al., 2016; Melander et al., 2003).

Current literature suggests prospective registration of all clinical trials to a registry conforming with the required data elements to reduce the risk of reporting bias (Decullier et al., 2005; Dickersin and Min, 1993; Liebeskind et al., 2006; Stern and Simes, 1997). To promote prospective registration and availability of trial results to the public, the congress supported the creation of ClinicalTrials.gov (Zarin et al., 2016). With a goal to improve trial registrations and result reporting, the Food and Drug Administration Amendments Act (FDAAA) Section 801 in 2007, mandates all applicable clinical trials (ACTs) to register and report their results (FDAAA, 2007). ACTs are defined as non-phase 1 interventional drug, medical device or biological trials, that were active as of December 26, 2007 involving at least one site in the United States (U.S). They also include clinical trials involving investigation device exemption (IDE) or investigational new drug application (IND). These trials are mandated to report their results either on ClinicalTrials.gov or as a publication in a journal within one year of study completion. Previous studies have demonstrated non-compliance with the FDA expectations in medicine in general (Anderson et al., 2015; Lampert et al., 2016; Malhotra et al., 2017; Mechler et al., 2016), but the evidence in epilepsy trials for non-compliance and reporting bias is limited (Lampert et al., 2016).

Our primary goal was to assess the reporting bias in completed Epilepsy

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interventional trials (EITs) that were registered on ClinicalTrials.gov after the launch of FDAAA, Section 801. Our secondary goal was to assess concordance amongst primary outcomes initially planned during trial registration and final clinical outcomes reported after the trial completion.

2. Methods

2.1. Study design

This is a cross-sectional study. We used the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) criteria for reporting important details (Vandenbroucke et al., 2007).

2.2. Search criteria

An advanced search on Clinicaltrials.gov website was performed on September 14, 2016 using following keywords: 'epilepsy' and 'seizures'. Our inclusion criteria were: 1) trial active December 26; 2007; 2) studies completed between January 1; 2008 and January 1, 2015, and 3) therapeutic intervention trials in humans. We allowed participants of the trials to be of any age. Exclusion criteria were non-epilepsy interventions; trials with a primary completion date prior to January 1 2008 or after January 1 2015; non-phase 2; 3 or 4 and non-drug/device or biologics. All non-duplicated trials were screened by two of the authors (AR and KM) for inclusion. Any disagreements that arose during this process were resolved with mutual consensus or third party discussion. The resulting trials data was further categorized into centers involving at least one U.S and non − U.S sites prior to data extraction.

2.3. Definitions

Primary completion date refers to the date when the last subject in the particular trial was examined or had an intervention performed to collect the primary outcome measure, and the study was concluded as per the pre-specified protocol. Whenever the primary completion date was not available, the completion date was used for the data analysis. The study completion date is the date when the final participant was examined or had an intervention performed, all the outcomes (both primary and secondary), and the adverse events data were collected, and the study was concluded (ClinicalTrials.gov, 2017). The primary outcome measure is the outcome planned in the trial protocol or study design to evaluate the effect of an intervention. 'Applicable clinical trials' are those, which meet the registration and result reporting criteria per the FDAAA 2007. Funding source is the organization that supports or funds the trial and analyses of the data.

2.4. Data variables

The trial characteristics which were obtained from the clinicaltrials.gov website included the title, ClinicalTrials.gov unique identification (NCT – National clinical trial) number, primary completion or completion date, funding source, result reporting date, trial phase. The funding sources were NIH, industry (pharmaceutical or device companies) or other (academic institution and government agencies). It was considered either NIH or industry if one of them was the trial sponsor in addition to other institutions. Time to reporting was calculated as the duration lapsed over months between the primary completion date and reporting of results on ClinicalTrials.gov. When trial results were not reported or a URL link to a publication was not available on Clinicaltrials.gov, a search was performed using NCT number and title of the trial on PubMed, Web of Science and Google Scholar databases. We used the first publication date mentioned in the journals to calculate the time to reporting for trials that lacked the information for reporting date on Clinicaltrials.gov. All the results published in the journals were temporally correlated to the appropriate trial for accuracy. If the trial results were not published either in PubMed, Web of Science or Google scholar, it was considered to have no results.

All the trials involving drug, device or biological agent, meeting the FDAAA criteria for the registration were manually searched to determine the FDA approval status of their product. For this purpose we searched www.fda.gov website for approvals and clearances. Web searches were conducted wherever deemed necessary as well. Trials that met all the FDAAA criteria but were not mandated to report the results within 12 months were classified as non-applicable clinical trials or 'non-ACTs'. For all the trials with available results, the concordance between the primary outcomes intended prior to beginning of the trial and the outcomes reported after trial completion were obtained and analyzed. The primary outcome of the trial was considered 'positive' if it was reported to be statistically significant ($p < 0.05$ or 95% confidence interval (CI) excluding 1 for a ratio and 0 for the difference) and 'negative' if otherwise.

2.5. Statistical analysis

Standard descriptive statistics were used to examine all the categorical and continuous variables where applicable. ANOVA and *t*-tests were performed for analyzing p-values. Two sided p-values < 0.05 were considered statistically significant. Time to result reporting was analyzed using Kaplan-Meier estimates for 2008–2011 and 2012–2015 time periods to compare the trend of reporting or publishing of trial results since the introduction of FDAAA. Cohen's *d* was used wherever appropriate to estimate the effect size. IBM SPSS Statistics for Windows, Version 19 (IBM Corp., Armonk, N.Y., USA) was used for all the statistical analysis.

3. Results

The search identified 369 trials, of which 237 trials were unique. Of these, 126 trials met the inclusion and did not have exclusion criteria (Fig. 1).

3.1. Trial characteristics

A total of 22,811 subjects were enrolled in the included 126 trials. 79 trials (63%) were conducted during the early period (2008–2011), and remaining during the later period (2012–2015). Most of the studies were industry funded (83%), conducted a drug intervention (93%) and were phase 3 or 4 (68%). Out of 126 trials, 72 trials (57%) were conducted in at least one U.S center and the remaining 54 trials (43%) were conducted at non-US centers (Table 1).

3.2. Reporting of trials results after completion

Overall, 75% (95/126) of the trials reported their results, while the remaining 25% (31/126) did not report. A higher number of completed EITs in 2012–2015 periods reported their results in comparison to 2008- 2011 period (85% vs. 70%). Also, a greater number of EITs conducted in Non-U.S centers have reported their results compared to the trials involving at least one U.S center (80% vs. 72%). Based on the phase of the trial, phase III and IV trials were frequently reported as compared to phase I and II trials (84% vs. 59%). Interestingly, our study observed a significant difference in the reporting of trial results based on the FDAAA applicability, with the results of 86% (48/56) of the ACTs were available as compared to only 29% (4/14) of non-ACTs ($p < 0.001$).

3.3. Time to reporting results after trial completion

The time to reporting results was significantly shorter (16.5 months; 95% CI: 13.60–19.40; $p = .002$; Cohen's $d = 0.68$) for EITs completed during the 2012–2015 period compared to the 2008–2011 period where this period was 25.9 months (95% CI: 21.56–30.22) (Fig. 2). 19 of the 56 (34%) applicable trials were reported within the mandated