Journal of Clinical Epidemiology 104 (2018) 35−45

Journal of Clinical Epidemiology

ORIGINAL ARTICLE

Clinical trials on drug-drug interactions registered in ClinicalTrials.gov reported incongruent safety data in published articles: an observational study

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Accepted 31 July 2018; Published online 3 August 2018

Abstract

Objective: To assess safety data of trials on drug-drug interactions (DDIs) reported in ClinicalTrials.gov and published in journal articles, since DDIs are a growing concern.

Study Design and Setting: In an observational study of clinical trials retrieved by the search term ''drug-drug interaction(s),'' we collected the information on registration and on adverse events (AEs) from ClinicalTrials.gov and corresponding publications. Trials were included if they primarily investigated DDIs, had a National Clinical Trial identifier, and were closed and completed by October 16, 2015. Publication data were extracted until March 2017.

Results: Among 1,110 eligible trials, most were in phase 1 (76.8%), industry-funded (68.8%), and started before registration (56.9%). Results were not reported in the registry for 86.8% and not published for 68.1% trials. Published AE data were completely identical to the data submitted to ClinicalTrials.gov for only 15.6% trials. Among 64 trials with results reported both in ClinicalTrials.gov and publications, 34.4% published concordant number for other AEs.

Conclusion: Discrepancies that emerge from incomplete or changed reporting of AEs in publications emphasize the need to amend and enforce regulatory requirements for timely and complete submission of results, clearer AE reporting for trials focusing on DDIs, and regular assessment of the congruence of AE data submitted to ClinicalTrials.gov and scientific journals during the publication process.

Keywords: Clinical trials on drug-drug interaction as topic; Drug interaction; Databases; Reporting; Adverse events; Bias

1. Introduction

Drug-drug interactions (DDIs) may lead to decreased treatment efficacy or enhanced drug toxicity [1]. They present a growing concern because of more prevalent polypharmacy in the aging population [2], and rising numbers of drug chemical entities, which enhance therapeutic armamentarium but also the potential for DDIs [3].

Clinical studies focusing on DDIs during and after drug development are thus very important [4]. Although valuable insight into the preapproval DDI studies is provided in several regulatory guidelines [5−7], there is still a standing goal of harmonizing approaches to DDI studies to achieve better assessment of DDIs [8] and enhance the clinical usability of drugs [3,9]. The importance of monitoring for adverse events (AEs) in clinical studies investigating DDIs is especially important considering increased mortality, in-hospital stay [10,11], and several market withdrawals due to DDI-induced AEs [12−15]. The Food and Drug Administration Amendments Act (FDAAA) mandates the reporting of AEs to ClinicalTrials.gov for all interventional clinical trials except phase 1 involving drugs or devices under FDA jurisdiction [16] since September 2009 [17]. Nonetheless,

Ethics committee approval: Not required.

Availability of data: The data sets used and analyzed during the present study are available from the corresponding author on request.

Conflict of interest: The authors declare that they have no competing interests.

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https://doi.org/10.1016/j.jclinepi.2018.07.017
0895-4356/

What is new?

Key findings

- Trials on DDIs registered in ClinicalTrials.gov were mostly phase 1 trials and had low adherence to reporting of results and AEs, retrospective registration which occurred after the trial start date, and incongruent data on AEs reported in ClinicalTrials.gov and publications.

What this adds to what was known?

- Registration completeness has not been explored specifically for DDI trials, although DDIs are one of the major contributing factors to AEs, which have led to several market withdrawals.

What is the implication and what should change now?

- So far, DDI trials have been mostly exempt from registration legislation. More stringent publishing requirements and regulatory reforms for trials focusing on phase 1 trials are needed to reduce possible reporting ambiguity surrounding the overall safety of drug combinations.

there are still issues with the transparency of AEs reporting [18–20]. Publication bias or selective outcome reporting bias [21], including under-reporting of serious AEs (SAEs) or other unfavorable AEs, may impede the interpretation of the benefit-risk relationship [18]. Inconsistencies in the reporting of SAEs were found in matching articles on completed phase 3 or 4 RCTs with at least one SAE posted in ClinicalTrials.gov [19]. Similarly, a significantly lower completeness in the reporting of SAEs or other AEs (OAEs) was identified in published data, compared to what was posted in ClinicalTrials.gov [20].

We assessed the accuracy and completeness of AE reporting in ClinicalTrials.gov and subsequently published data for completed trials assessing DDIs.

2. Methods

2.1. Sample and inclusion criteria

For this observational study, a drug was defined as any substance, other than food and dietary supplements, regulated as a prescription or over-the-counter drug, including vaccines and biological products, and intended for use in the diagnosis, mitigation, treatment, or prevention of disease [22]. On October 16, 2015, we retrieved clinical trials focusing on DDIs from ClinicalTrials.gov using the search term "drug-drug interaction(s)," which 1) had a ClinicalTrials.gov registration number (NCT number, National Clinical Trial number), 2) were registered on or before October 16, 2015, and 3) were reported as closed and completed in the recruitment field by the same date. Closed studies were defined as "clinical studies that are no longer recruiting participants because they have enough participants already, because they are completed, or because they have been stopped for some reason" [23] and completed studies as "clinical studies that has ended normally, and participants are no longer being examined or treated." A clinical trial in ClinicalTrials.gov was considered a DDI trial if DDI was stated in the study title, or as the study objective or condition under the Descriptive Information heading in the ClinicalTrials.gov Tabular View, or as the outcome measure (OM) under Tracking Information section. The exclusion criteria were 1) trials with the recruitment status changed from completed during data extraction, 2) trials not actually investigating DDIs, in which identifying the words "drug(s)" or "interaction(s)" in the Descriptive Information heading did not correctly identify a DDI investigation, 3) trials investigating interactions between drug(s) and food, 4) trials investigating interactions between drug(s) and herbal remedies not registered as a drug, 5) trials investigating drug-dietary supplements or dietary supplement–dietary supplement interactions, and 6) trials investigating interactions between drug(s) and substances with pharmacological action but without registered therapeutic uses (e.g., ethanol, cocaine, 3,4-methylenedioxymethamphetamine [MDMA], nicotine related to cigarette smoking, and smoking marijuana). Vitamins, minerals, omega-3 fatty acids, their fixed-dose combinations, and probiotics were considered as dietary supplements and not drugs. Because there are significant inconsistencies in the regulatory categories of herbal products by different World Health Organization (WHO) Member States regarding food, functional food, dietary supplements, and traditional herbal medicine, as well as disparate quality control and evaluation of safety and efficacy [24], we considered a herbal remedy as a drug only in cases when investigators registered it as a drug under the Intervention field in ClinicalTrials.gov.

2.2. Publication search

Corresponding publications were identified in February and March 2017 by screening the Publications subheading under the Descriptive Information heading of the ClinicalTrials.gov Tabular View; we disregarded commentaries on articles of interest and publications reporting on study protocols or providing related background information. We searched PubMed/MEDLINE and Scopus using: 1) [si] tag and/or NCT number [25] to identify all publications with a recorded NCT number in their abstracts; 2) each name recorded in the Administrative Information heading of the Tabular View in the registry combined with the brief and official study title to identify any additional publication. We considered a publication to correspond to the registered trial if five of the following six criteria matched: study design, drug interventions, primary outcomes, condition, enrollment, and study location.