Journal of Clinical Epidemiology 77 (2016) 78–83

Journal of Clinical Epidemiology

Timing of pivotal clinical trial results reporting for newly approved medications varied by reporting source

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Accepted 1 April 2016; Published online 22 April 2016

Abstract

Objective: The study aimed to characterize the public availability of pivotal clinical trial results for newly approved drugs.

Study Design and Setting: We examined the availability of pivotal clinical trial results for new molecular entities (NMEs) approved by the US Food and Drug administration (FDA) from 2009 to 2013. For each NME, we quantified the time from approval date until results were available on the FDA web site, in the ClinicalTrials.gov basic results database, and in a medical journal.

Results: Two hundred fifty-five pivotal trials supporting 88 NMEs met our criteria. The median time until pivotal trial results were available on the FDA web site, ClinicalTrials.gov, and in a publication was 42 days, 27 days, and −28 days, respectively. In the first 30 days after approval, 52% of pivotal trials were summarized in ClinicalTrials.gov, 20% were posted to the FDA web site, and 46% were published in a journal. Across all sources, 79% of pivotal trials had results available within 30 days of approval. From 2009 to 2013, the average time until public availability has improved for federal sources.

Conclusions: Pivotal trials of newly approved drugs appeared first in publications. Results from most pivotal trials were publicly available in some source within 30 days of approval.

Keywords: Unpublished evidence; Clinical trial reporting; US Food and Drug administration; Clinical trial registries

1. Introduction

Timely and accurate access to clinical trial data is paramount for making informed medical decisions. This is especially true for new medications, where trial data are often limited following initial approval by the US Food and Drug Administration (FDA). Clinical evidence for new medications is often inadequate for decision making due to the limited number of trials and design deficiencies such as short duration, use of surrogate outcomes, and lack of active control comparisons [1,2]. As a basis for approval, The Federal Food, Drug, and Cosmetic Act of 1962 requires ‘‘evidence consisting of adequate and well-controlled investigations’’ [3]. The FDA has generally interpreted this statute to mean at least two clinical trials. However, the results of these trials may not be fully available for clinicians or policy makers who intend to use or manage the use of these medications once available [4]. A recent analysis by Smithy et al. indicated pivotal trials supporting the approval of new drugs between 2005 and 2011 were published 86% of the time, and the median time until publication was 7 months [5]. Of the published pivotal trials, less than half were published before or during the month of approval. Although most pivotal trial results eventually became available, prompt access to trial summaries after approval is critical for both clinicians as well as policy makers who need to make drug coverage decisions.

In response to concerns about dissemination biases, there has been growing interest in improving clinical trial transparency and reporting. In the absence of trial results published in a medical journal, other sources of trial data play a vital role for filling the evidence gap for new medications. Scientific reviews by regulatory bodies such as the FDA can be an important source of both published and unpublished data. The most salient features of important clinical trials are reported in Medical and Statistical Officer Reviews, which can be accessed through the Drugs@FDA

Funding: D.M.H. has grant funding from the US Centers for Disease Control (U01 CE002500 02) and Agency for Healthcare Research and Quality (R18 HS024227 01).

Conflict of interest: None.

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http://dx.doi.org/10.1016/j.jclinepi.2016.04.007

What is new?

- In the first 30 days after approval, pivotal trial results were most likely to appear in ClinicalTrials.gov (52%), followed by publication (46%) and on the Food and Drug administration (FDA) web site (20%).
- 79% of pivotal trials of new drugs were publically available in published form, on the FDA web site, or in the ClinicalTrials.gov basic results database within 30 days of approval.
- From 2009 to 2013, the availability of pivotal trial results for new drugs has improved in ClinicalTrials.gov and on the FDA web site.

What this adds to what was known?

- This study extends our understanding of pivotal clinical trial reporting for newly approved medications in non-publication sources of trial data.

What is the implication and what should change now?

- While ClinicalTrials.gov results reporting has improved for pivotal drug trials, it remains suboptimal. Efforts should be directed at enhancing reporting compliance for these key clinical trial data.

database [6]. However, these reviews are often not standardized and can be difficult to navigate, which limits their transparency and ultimate utility [7].

One of the most significant developments in the enhancement of clinical trial reporting was the passage of the FDA Amendments Act (FDAAA) of 2007. In addition to broadening trial registration requirements in ClinicalTrials.gov, FDAAA mandated the reporting the results of certain clinical trials in a publically accessible basic results database [8,9]. According to Section 801 of FDAAA (FDAAA 801), basic summary results (subject demographics, baseline characteristics, primary and secondary outcomes, and adverse events) must be submitted for applicable clinical trials. In particular, applicable trials include phase 2 through 4 trials of drugs, devices, or biologics regulated by the FDA. Under most circumstances, basic results must be submitted within 1 year of trial completion or within 30 days of product approval or clearance (for trials not yet approved or cleared by the FDA at trial completion), although extensions for up to two additional years are possible [10]. Investigators who fail to comply with the reporting requirements of FDAAA 801 are subject to significant monetary penalties. Despite this, initial investigations have suggested that reporting is deficient. Studies have shown that approximately one-quarter of applicable trials have met the reporting deadline 1 year after completion [11–13]. Although industry-funded trials appear to be more compliant with the reporting requirement than trials with other funding sources (e.g., NIH), it is unclear if reporting differs for trials in direct support of FDA New Drug Applications (NDAs).

The emergence of different sources of clinical trial data is a significant advancement towards sorely needed transparency in the clinical trial enterprise [9]. For newly approved drugs, the need for rapid synthesis of supportive trials is important for decision makers, most notably those who develop drug use policy or guidance. To help inform this process, the goal of this study was to characterize the timeliness of clinical trial results reporting in the published literature, ClinicalTrials.gov, and on the FDA web site for recently approved medications.

2. Methods

2.1. Trial selection

We assessed the reporting of trials supporting newly approved drugs between 2009 and 2013. Our definition of a new drug was a new molecular entity (NME), which the FDA considers as an active chemical moiety that has not been previously approved in any formulation. Candidate NMEs were first identified from Web-accessible annual reports summarizing approvals for the years 2009 through 2013 [14]. Because of differences in the FDA approval process, we excluded products if they were approved with an orphan drug designation or if they were diagnostic imaging products. For each NME, we extracted data about supporting trials from three sources: FDA review documents, ClinicalTrials.gov, and journal publications. Drug approval dates and supporting trial information were obtained through queries of the Drugs@FDA database (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm) [6]. Trials were included if they were regarded as "pivotal" in the FDA Medical and Statistical Review documents. Similar to Downing et al., if no trials were explicitly identified as pivotal, the primary phase three trials within the FDA efficacy and safety deliberations were included [2]. In addition, the "date created" listed on the Drug Approval Package web site was considered to be the date on which FDA Medical and Statistical Reviews were made publically available.

We then attempted to link the pivotal clinical trials identified through Drugs@FDA to results summaries posted on ClinicalTrials.gov and in the published medical literature. Using the ClinicalTrials.gov basic search function with the NME generic name, we identified matching pivotal trials based on the number of trial arms, comparative interventions, and the number of subjects enrolled. Because reporting discrepancies are known to exist, a pivotal trial was considered a match if all criteria were consistent and the number enrolled only differed by 5% [15]. Once a match was determined, the date that