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Clinical trials transparency and the Trial and Experimental Studies Transparency (TEST) act

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ABSTRACT

Clinical trial research is the cornerstone for successful advancement of medicine that provides hope for millions of people in the future. Full transparency in clinical trials may allow independent investigators to evaluate study designs, perform additional analysis of data, and potentially eliminate duplicate studies. Current regulatory system and publishers rely on investigators and pharmaceutical industries for complete and accurate reporting of results from completed clinical trials. Legislation seems to be the only way to enforce mandatory disclosure of results. The Trial and Experimental Studies Transparency (TEST) Act of 2012 was introduced to the legislators in the United States to promote greater transparency in research industry. Public safety and advancement of science are the driving forces for the proposed policy change. The TEST Act may benefit the society and researchers; however, there are major concerns with participants' privacy and intellectual property protection.

1. Introduction

Clinical research is not new; many investigators have been conducting clinical trials for decades in an attempt to bring new medications, devices, and procedures to clinical bedsides [1]. In addition, data obtained from clinical trials established the foundation for evidence-based practice and the development of many new guidelines [2]. Results from clinical trials are essential for the successful advancement of patient care, as new technologies bring new hope for millions of people. Everyone involved in clinical trials, including basic scientists, physicians, nurses, patients, pharmaceutical industries, and regulatory agencies, shares a common goal of bringing to clinical practice the latest innovations in an expedited manner [3]. Clinical research would not be possible if it were not for altruistic patients and research participants, who volunteer to take part in clinical trials in exchange for improving medical knowledge and providing hope for future generations [1].

Research participants trust their providers and clinical research investigators that information obtained through clinical trials will yield significant advancements in the medical industry. Indirectly, the research participants trust pharmaceutical industries and regulatory agencies that data from clinical trials will be fully disclosed and decisions for approval of new medicines or devices will be made accordingly. When research participants consent to be in a clinical trial, they anticipate learning the results and expect them to be publically available [4], Even though it is clearly stated in the Declaration of Helsinki (DOH) that the research participants are entitled to be informed about the study results, as well as new beneficial interventions, not all investigators and pharmaceutical industries distribute results to the research participants [5,6].

Clinical trials registry (ClinicalTrials.gov) is a public database of clinical trials conducted in the United States; it was developed in 2000 as a result of the U.S. Food and Drug

Abbreviations: DOH, Declaration of Helsinki; FDA, US Food and Drug Administration; HHS, US Department of Health and Human Services; INDs, Investigational New Drug Applications; IDEs, Investigational Device Exemptions; NDAs, New Drug Applications; TEST, Trial and Experimental Studies Transparency; FDAAA, FDA Amendment Act of 2007; ICMJE, International Committee of Medical Journal Editors; NIH, National Institutes of Health; TRIPS, Trade-Related Aspects of Intellectual Property Rights; WHO, World Health Organization; EMA, European Medicines Agency.

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Administration (FDA) Modernization Act of 1997 [7]. This was the first step the government took in increasing the transparency of clinical trials. The FDA is a federal agency within the U.S. Department of Health and Human Services (HHS) responsible for protecting the consumers and providing approvals for innovative therapies. The FDA's Center for Drug Evaluation and Research is responsible for review and approval of Investigational New Drug Applications (INDs) and Investigational Device Exemptions (IDEs) prior to conducting clinical trials and New Drug Applications (NDAs) for marketing products in the United States [8]. The FDA defines a clinical trial as any investigation involving human subjects to determine safety and efficacy of a drug or device for the purposes of advancing medical knowledge [9,10].

2. Health policy issue

Deciding which data and how much of it should be shared in a public domain is an important health policy issue currently being debated by the federal government and pharmaceutical industries. On August 2, 2012, a democratic House Representative, Ed Markey, introduced the Trial and Experimental Studies Transparency (TEST) Act of 2012, in an attempt "to close the loopholes" in clinical trials [11,12]. The TEST Act would amend title IV of the Public Health Service Act and further expand the clinical trials data bank to hold detailed information about clinical trials and participant-level data [13]. The 112th session of Congress closed and the bill was referred to the Committee on Energy and Commerce for review. On May 16, 2013, Ed Markey, with three supporters, reintroduced the TEST Act of 2013 and a congressional committee is currently reviewing it. The bill has only a 3% chance of getting past the committee and only 1% chance of being enacted most likely because there are not enough active supporters and because there are remaining concerns about provisions introduced in this act [14].

The purpose of the TEST Act is to ensure that information obtained through clinical trials is complete and fully disclosed to providers and patients [15]. Ed Markey proposes mandatory registration of Phase 1 clinical trials, reporting of postmarket surveillance results from class II and class III devices, full disclosure of approved consent documents, initial and modified versions of protocol, and data sets at the participant-level [16]. The TEST Act will require the pharmaceutical industries or investigators to register their trials in the database 21 days before the first subject is enrolled in the clinical trial. The Food and Drug Administration Amendment Act of 2007 (FDAAA) required that clinical trials had to be registered in the database; however, the compliance and enforcement were not in place, and it was unclear which department was responsible for monitoring the activities in the database. To ensure enforcement, in 2012, the HHS turned over the responsibility for enforcing the compliance to the FDA. Archer [11] reports that a year ago an audit conducted by Prayle and colleagues revealed that 80% of clinical trials were not registered in the database and the fines for noncompliance had never been issued. The TEST Act, if passed, would require the Director and the Commissioner of the FDA to provide a report to Congress on the compliance status with clinical trials registration and the processes for compliance enforcement (warning letters, fines, and withholding of federal funding) [14]. In addition, the TEST Act contains provisions for registration and result reporting for clinical trials conducted outside of the United States, specifically any trials supporting an NDA for marketing in the United States [17].

3. Significance of TEST Act

The TEST Act is important because it will lead to full transparency in clinical trials and eliminate hidden negative results that could potentially impact the safety of future research volunteers. Public health and safety are of the utmost importance when investigators are developing new therapies; the approval of the TEST Act could actually reduce duplicate exposure of research participants to harmful effects of investigational drugs, improve public trust in clinical trials participation, and further advance medical knowledge [18].

The International Committee of Medical Journal Editors (ICMJE) fully supports registration of clinical trials and full transparency of the results by requiring that submitted manuscripts contain confirmation of trial registration as a prerequisite for publication [19]. The editors of journals that are members of ICMJE have the right to refuse review and publication of a manuscript if the trial was not registered in ClinicalTrials.gov. However, a process for reporting unregistered trials does not exist, and investigators who do not comply with the registration requirement will likely submit their manuscripts to other journals that do not have such requirements.

It may be more difficult to prevent plagiarism in publications once results become readily available in public databases. All publishers should have a verbatim in their author's agreement asking for confirmation of data originality and proper citation or confirmation of release and reuse of disclosed data. If data are obtained from ClinicalTrials.gov, the authors should cite their sources properly. The purpose of full transparency of clinical trials results is to generate additional research, especially in a field of comparative effectiveness research.

In the past, clinicians often made their decisions to prescribe new medications based on marketing of the products by sales representatives from pharmaceutical industries; in current practice, however, pharmaceutical representatives are rarely allowed access to many medical centers due to concerns of inadequate disclosure of drug safety information and influence on providers to prescribe the medications being detailed [20]. While clinicians have access to the latest literature and full drug prescribing information; the proponents of full transparency in clinical trials found that the literature lacks full disclosure of data, leaving patients, healthcare providers, policymakers, and investigators with gaps in medical knowledge [21].

Research advocates and medical researchers have generally been excluded from sharing in important information when pharmaceutical industries submitted their data along with the application for marketing to the FDA. Furthermore, clinicians and consumers alike may not be aware that data elements collected during clinical trials may not be fully disclosed in the publications; there is strong evidence in the literature suggesting that only favorable or positive outcomes are included in published reports [5]. In fact, 22–47% of trials submitted for FDA review under the NDA were not published for at least five years or only positive outcomes were included in the reports [22]. Since pharmaceutical companies own their data, they decide what should be included in the analysis prior to publication. This type of