Editorial

Keep the pressure on for more transparency of clinical trials on endometriosis

In the past decade, about half a dozen books have been published that are very critical of the pharmaceutical industry, some of them scathingly so. They include Merrill Goozner’s The $800 Million Pill, Jerry Avorn’s Powerful Medicines, John Aramson’s Overdosed America, Jerome Kassirer’s On the Take, Marcia Angell’s The Truth About the Drug Companies, and, very recently, Ben Goldacre’s Bad Pharma. From various angles, these books provide an unflattering—sometimes disturbing—but consistent portrait of drug companies’ behaviors.

The seeming deluge of these books on a similar topic cannot be dismissed offhand as a pharma-bashing fad, because these books appear to be well researched and based on credible sources. A few of them are written by former editors of some prestigious medical journals who witnessed firsthand some high-profile cases of clinical trials sponsored by the industry, such as the Vioxx saga. One troubling behavior is the selective publication and the suppression of “negative” information arising from clinical trials funded by drug companies.

Against this foreground is the enactment of several legislations in the United States (U.S.) mandating more openness in clinical trials and the birth of a handful of clinical trial registries. Notably, Section 113 of the Food and Drug Administration Modernization Act (FDAMA 113) was enacted by the U.S. Congress in 1997. Section 113 ultimately led to the creation of ClinicalTrials.gov as an Internet-based public depository for information on studies of drugs (including biological compounds) that are conducted under the FDA’s investigational new drug regulations.¹ In 2007, the U.S. Congress enacted the FDA Amendments Act of 2007 (FDAAA), or Public Law 110-85. On the same day, the FDA Revitalization Act was signed into law, with the aim of improving the FDA’s ability to ensure the safety of the nation’s drugs and medical devices. Section 801 of the FDAAA mandates the expansion of ClinicalTrials.gov and provides for the first federally funded trial results database. These legislations and trial registries are intended to encourage and promote openness in clinical trials.

As elaborated in these books, the selective reporting and the suppression of “negative” data are quite ubiquitous and pervasive across the entire industry. Not surprisingly, endometriosis trials are no exception. In a survey conducted 4 years ago, it was found that 57 endometriosis-related clinical trials were registered at ClinicalTrials.gov.² Among the 15 completed Phase II or Phase III trials that evaluated the efficacy of various promising compounds, only three (20%) had published their results, but the remaining 12 (80%) did not. In other words, most endometriosis trials were shrouded in secrecy.

Four years have since passed. A recent analysis of trials registered at ClinicalTrials.gov found that the situation has changed very little.³ Specifically, it reports that among 35 completed trials on endometriosis, only 11 (31.4%) published their results, which is below the 66.3% reported in a recent survey of nonendometriosis trials.² More disturbingly, trials sponsored by industry were about four times less likely than those sponsored by nonindustry to publish the results, even though they were typically larger in size and completed quicker—likely because of more resources. Industry-sponsored trials that did get published were those that led to the regulatory approval for marketing. Conspicuously, no “negative” trials sponsored by industry have ever been published. Such an abject failure to publish and selective reporting pose a serious threat to professional access to all trial results and to the validity of evidence-based medicine. It also goes against the mounting pressure around the globe for greater transparency of clinical trials.

One can argue that the ultimate goal of disease-focused research such as endometriosis research is better clinical care of patients through providing better diagnosis, treatment, or even innovative ways of prevention. Toward this goal, one important intermediate linking basic research and clinical practice is randomized clinical trials that evaluate the safety and efficacy of compounds deemed to be promising in preclinical research. Results from successful clinical trials may also be submitted to regulatory agencies to obtain approval for marketing.

Clinical trials are known to contribute to our knowledge base in evidenced-based medicine. Yet, this hinges critically on the timely public release and dissemination of findings from such trials, which are considered to be key principles in the proper conduct of clinical research.⁴ Indeed, clinicians, policymakers, and even patients learn of evidence-based medicine primarily through peer-reviewed biomedical journals. The apparent opaqueness of endometriosis trials is certainly a disservice to the public.

At the time when there is a palpable disappointment over the slow progress in developing novel therapeutics for endometriosis, this opaqueness is an added hindrance to drug development, because it impacts negatively on basic research scientists. When everybody is holding their cards close to their chests, nobody will benefit from hard-earned lessons, and everybody will be condemned to repeat others’ mistakes, miscalculations, or missteps. It also exposes trial participants to the unnecessary risk of receiving inferior treatment or having an adverse effect since different drug companies may test slightly different drugs that belong to the same class of drug (such as selective progesterone receptor modulators). Above all, it betrays the wish implicitly or tacitly expressed by the trial participants that their participation will generate generalizable medical knowledge that might benefit not only themselves but also society.
but also other and future patients, scientists, and physicians so that collectively the trial and other scientific research will ultimately improve patient care.

Given this apparent opaqueness in endometriosis trials, pressure needs to be kept on to change this situation. More transparency not only is a moral imperative to researchers, sponsors, reviewers, and journal editors alike, but also should help researchers, healthcare providers, policy-makers, drug companies and, above all, patients with endometriosis.

References

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Clinical trials are well-designed studies that collect information about new treatments for diseases and disorders. Most of the time, this means medications, but clinical trials can also test other things, such as stem cell therapies, surgical techniques, tests for diagnosis, medical devices, as well as others. In particular, clinical trials focus on administering an experimental therapy in humans, as opposed to animals, which are conducted first in the lab (known as pre-clinical research). Why do we need clinical trials? Clinical trials are needed for medical treatments to be approved by the regulatory authorities. Despite mounting pressure on more transparency of clinical trials, the current state of transparency, or lack thereof, of clinical trials on endometriosis is worrisome and does not benefit the trial sponsor or women with endometriosis. We need to change this!

Professor Sun-Wei Guo, Fudan University, China. In the last decade, about half dozen books have been published that are very critical of the pharmaceutical industry, some of them scathingly. They include Merrill Goozner’s The $800 Million Pill, Jerry Avorn’s Powerful Medicines, John Aramson’s Overdosed America, Jerome Kassirer’s On the Take.

More transparency of registered clinical trials on endometriosis. Hum Reprod. 2009;24:1247–1254. 3. Guo SW, Evers JHL. Lack of transparency of clinical trials on endometriosis. Gynecol Obstet. Registry based study of clinical trial summaries. ClinicalTrials.gov, searched on 19 January 2011, with cross referencing with Drugs@FDA to determine for which trials mandatory reporting was required within one year. Selection criteria Studies registered on ClinicalTrials.gov with US sites which completed between 1 January and 31 December 2009. Proportion of trials for which results had been reported. The ClinicalTrials.gov registry contained 83,579 entries for interventional trials, of which 5642 were completed within the timescale of interest. Endometriosis is a chronic disease characterized by the presence of functional endometrial glands and stroma in ectopic locations outside the uterine cavity. The ectopic endometrial tissue responds to estradiol and other hormones similarly to the normal endometrium. Endometriosis is one of the most common benign gynecological conditions, as many as 5-10% of women in the reproductive age may be affected. Presently, endometriosis can be reliably diagnosed only by laparoscopy. Since this is an invasive surgical procedure, new diagnostic tools would be warmly welcomed. Furthermore, as the progression of the disease is presently impossible to predict, new markers for the "malignancy" of each case are desperately needed. Traditionally, clinical trials have been kept hidden from the public. The US congress, concerned about this fact, created a publicly accessible internet site with information on trials by enacting Section 113 of the Food and Drug Administration Modernisation Act in November 1997 with the creation of ClinicalTrials.gov. In September 2004, the International Committee of Medical Journal Editors announced that its journals would not publish the results of trials that had not been registered at this or similar websites. Trial registration appears to have only gone one step towards the attainment of transparency in clinical trials on endometriosis by highlighting the gap between research conducted and results reported; the next crucial step is to close this gap with faithful reporting of all results.