An overview of the current status of clinical trials on endometriosis: issues and concerns

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Objective: To examine and compare differences, if any, between industry- and nonindustry-sponsored clinical trials on endometriosis and to evaluate the effect of prior published positive preclinical results, or lack thereof, on trial status.
Design: Cross-sectional study of clinical trials on endometriosis that evaluate drugs/biologicals registered at ClinicalTrials.gov as of July 3, 2013.
Setting: University-affiliated hospital.
Patient(s): None.
Intervention(s): None.
Main Outcome Measure(s): Trial status, size, phase, and duration; use of comparator groups; drug classes, number of arms, targeting conditions; and presence or absence of prior positive preclinical results before the launch of the trial.
Result(s): Eighty trials were identified. The trials sponsored by industry and non-industry have distinct features, differing in trial status, phase, comparator, drug classes, number of arms, trial size, and duration. The phase II/III trials are predominantly industry supported, but these trials frequently use placebo as the comparator. Trials launched without prior published preclinical results do not seem to fare well, although the presence of such studies is no guarantee for success.
Conclusion(s): Questions as to whether the drug on trial is truly superior to the best available drug or of its cost-benefit profile are overlooked in most cases. There seems to be a deluge of "me-too" drugs with equivocal superiority over existing drugs and cost-benefit profiles. Because clinical trials are time-consuming, no blockbuster drug for endometriosis seems to be on the horizon yet. (Fertil Steril® 2014;101:183–90. ©2014 by American Society for Reproductive Medicine.)
Key Words: Clinical trials, drug, endometriosis, issues, sponsorship, status

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In the last four decades, the number of Medline-indexed publications on endometriosis has increased exponentially (Supplemental Fig. 1, available online). As the ultimate goal of disease-focused research, such as that focused on endometriosis, is to provide better clinical care, the discovery and successful development of truly innovative drugs represent the culmination of research. Therefore, one hallmark of success in the endometriosis research endeavor is the development of novel, differentiated medicines for patients.

An important intermediate link in basic research and clinical practice is the use of clinical trials to evaluate the safety and efficacy of the compounds deemed to be promising in preclinical research. Results from clinical trials are considered to be level I evidence, and the results from successful trials may be submitted to regulatory agencies to obtain approval for marketing.

Thanks to legislation enacted in the United States and Europe, clinical trials are now required to be appropriately registered in publicly accessible registries. ClinicalTrials.gov, the largest trial registry in the world, has 148,066 registered studies with locations in 185 countries, 164 of which concerned endometriosis (as of July 3, 2013). This number is 7.1 times larger than

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that in the second largest registry, the European Union Clinical Trial Register (www.clinicaltrialsregister.eu), which has 20,782 studies on file (25 on endometriosis, as of July 3, 2013). Thus, for any particular disease such as endometriosis, ClinicalTrials.gov should provide a rather comprehensive overview of the current status of the related clinical trials.

A survey conducted 4 years ago found that 57 endometriosis trials were registered at ClinicalTrials.gov (1). Among the 15 completed phase II or III trials that evaluated the efficacy of various promising compounds, only 3 (20%) had published their results; the remaining 12 (80%) did not. A more recent analysis of trials registered at ClinicalTrials.gov found that the situation had changed very little (2). Among the 35 completed trials on endometriosis, only 11 (31.4%) published their results, well below the 66.3% reported in a recent survey of nonendometriosis trials (2). More disturbingly, the trials sponsored by the pharmaceutical industry were about four times *less* likely than those sponsored by nonindustry researchers to publish their results. Industry-sponsored trials that did get published were those that led to regulatory approval for marketing. Remarkably, so far no trials with negative results sponsored by industry have been published.

The latter analysis, though it unveiled the pervasive lack of transparency in endometriosis trials and characterized the differences between published and unpublished trials, still left many stones unturned. What similarities or differences, if any, do industry- and nonindustry-sponsored trials have? Do trials of one particular class of drugs fare better than the others? As the number of endometriosis trials has increased almost threefold since 2009, what are the popular drugs that have undergone trials? Does the presence or absence of prior published positive preclinical data have any effect on the trial's fate? This article attempts to address these questions.

MATERIALS AND METHODS

Data Source

All registered trials were retrieved on July 3, 2013, into an Excel file after searching the ClinicalTrials.gov site using the key word "endometriosis." The included trial had to be interventional in nature, but interventional trials to study procedures, diagnostics, behavior, or devices (excepting drug-eluting intrauterine systems or IUS) were excluded. Interventional trials on drugs, biologicals, or medicated intrauterine devices were included. In addition, trials that focused explicitly on diseases or conditions other than endometriosis or adenomyosis, such as fibroids or hot flashes, were also excluded. Three trials that focused on healthy women as subjects but tested drugs or biologicals that were used in endometriosis trials such as Proellex (telapristone), Adhexil (tranexamic acid), and CDB-2914 (ulipristal acetate), were included. For some trials that listed more than a single phase (e.g., phase I and II), phase II was determined by examining the context and the intention of the trial (e.g., efficacy).

By the definitions provided at ClinicalTrials.gov, a trial that has a recruitment status of *suspended* means that "the clinical study has stopped recruiting or enrolling participants early, but it may start again." A trial that is *terminated* means that "the clinical study has stopped recruiting or enrolling participants early and will not start again. Participants are no longer being examined or treated." A trial that is *withdrawn* means that "the clinical study stopped before enrolling its first participant." A trial's recruitment status is *unknown* when it has a status of "recruiting," "not yet recruiting," or "active, not recruiting" but the status has not been confirmed within the past 2 years.

For each particular drug or class of drug, such as statins, further PubMed queries were made to see whether there had been any published positive preclinical efficacy studies. I used the combination of the drug name (or name of the drug class, such as "statin") and words such as "endometriosis," and/or "mouse," "rat," or "baboon." These results were also entered into the Excel file. Because this study used only data extracted from a publicly accessible registry and had no access to any patient data, it was exempted from ethics approval from the institutional ethics review board of Shanghai Obstetrics and Gynecology Hospital.

Study Sample

On July 3, 2013, the search yielded 164 trials on endometriosis registered at the ClinicalTrials.gov site. After removal of the trials that met this study's exclusion criteria, 80 trials remained, which were included in this study.

Study Variables

For each trial, this study recorded its status, phase, drug name (and thus class), targeting conditions, sample size, sponsorship (industry, National Institutes of Health, or others), number of arms, duration of the trial (time elapsed between start date and completion date). Trials that had a status of "enrolling by invitation" were recoded as "recruiting" for ease of analysis. For each drug or drug class, information on the presence or absence of prior published positive preclinical results before the launch of the trial (or the first trial on the same drug class) was also used.

Statistical Analysis

The difference in frequency between two or among more groups was evaluated using Fisher's exact test. The comparison of medians between two or more groups was made using a Wilcoxon rank-sum test and Kruskal-Wallis test, respectively. A multiple linear regression analysis was performed to determine factors associated with the trial size and trial duration (both log-transformed to improve normality) using sponsorship (industry versus nonindustry), whether or not it is a phase II/III trial, whether or not it is a phase IV trial, number of arms, disease category, and drug category (neoclassic versus classic, and other versus classic) as covariables. The definition of different drug categories—classic, neoclassic, or other—will be provided.

$P<.05$ was considered statistically significant. All computations were made with R 3.0.0 (www.r-project.org) (3).