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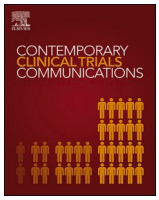

ClinicalTrials.Gov: Pitfalls for pregnant women looking to enroll in studies

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ABSTRACT

The common exclusion of pregnant women from clinical HIV research warrants inquiry into those few studies that do include pregnant women. This commentary highlights some of the pitfalls of the ClinicalTrials.gov platform for its intended users–study participants, particularly pregnant women–and investigators looking to use its data for study. Some of the pitfalls include missing information; lack of historical reporting enforcement; difficulty searching for studies focused on pregnant women versus the fetus; inability to consistently find studies targeted at specific stages of pregnancy; and lack of information relating to whether a study intervention is investigational or previously approved by the FDA.

Pregnant women are often excluded from clinical research, resulting in a lack of scientific understanding of the risks and benefits for women and developing fetuses associated with the use of many medications during pregnancy [1]. While there is a need to include pregnant women in clinical trials generally, there is a particular need for inclusion in research for HIV therapies as pregnant women are two times more likely to acquire HIV than non-pregnant women and since HIV infection during pregnancy can increase the likelihood of mother to child transmission by 15 times [2].

As professionals working in health law and policy, we sought out three years ago to conduct a systematic review of ClinicalTrials.gov ("the platform") to provide greater understanding and context for the interpretation and application of the laws and regulations relating to the platform, specifically the quality and quantity of information submitted by clinical trial sponsors and/or investigators, in the context of HIV research with pregnant women. Congress enacted legislation creating ClinicalTrials.gov through Section 801 of the Food and Drug Administration ("FDA") Amendments Act of 2007 ("FDAAA" or "the Act") to "increase the availability of information to the public" and to "communicate the risks and benefits of drugs" in order to "help patients, providers and investigators learn new information and make more informed health care decisions." [3] The sponsor or designated principal investigator of a trial must register certain clinical trials and submit basic information to the National Institutes of Health ("NIH") for inclusion on ClinicalTrials.gov. Requirements include a registration deadline; a description of the enrolled patient population and primary and secondary outcomes; and study results. FDAAA also created enforcement mechanisms to ensure that responsible parties comply with clinical trial reporting obligations, including issuing Notices of Noncompliance and civil monetary penalties.[1]

Given the need to include pregnant women in research relating to HIV therapies, we specifically sought to identify and characterize clinical research studies registered on ClinicalTrials.gov that included pregnant women for the purpose of studying HIV prevention or treatment. To do so, we identified interventional trials that were aimed at HIV and HIV-related conditions, enrolled pregnant study participants, and were initiated between September 27, 2007 (the date of enactment of the FDAAA) and September 30, 2016. Of the 60 trials that were registered that met our criteria, we assessed the use of pregnancy-related terms, such as those relating to gestational age and trimester, within each trial's description that could potentially be useful to pregnant women looking to enroll in clinical research for HIV treatment or prevention as well as whether study results were reported for completed studies, and other study characteristics (e.g., sponsor type, phase, and study site(s)). Ultimately, we could not move forward due to methodological concerns and lack of consistent reporting to the platform. We thought it worthy to share some of the pitfalls of ClinicalTrials.gov that contributed to our inability to perform the study and our lack of confidence in our planned study findings. While our research was specifically focused on HIV research in pregnancy, we believe the difficulties we

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[1] The FDA issued its first Notice of Noncompliance for failure to comply with the reporting requirements of the FDAAA on April 27, 2021, nearly thirteen years after the enactment of the FDAAA and nearly five years after the Act's implementing regulations were issued in 2016. The FDA has since issued two additional Notices of Noncompliance [13]. However, no civil monetary penalties have ever been imposed by the FDA [14].

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Abbreviations

FDA	U.S. Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
HIV	Human Immunodeficiency Virus
REMS	Risk Evaluation and Monitoring Strategy

encountered in using the platform are generalizable to any pregnant woman who utilize the platform and are looking to participate in clinical research. We want to highlight the pitfalls of ClinicalTrials.gov for pregnant women and their health care providers who are likely to encounter similar barriers when using the platform to identify clinical research in which to participate and to obtain study results from completed research involving pregnant women.

1. Missing information and a lack of reporting enforcement prevent the platform from being a reliable source of information for pregnant women, health care providers and investigators

For our research, we wanted to capture the number of HIV-related studies in pregnant women that reported research results on ClinicalTrials.gov to understand the extent to which pregnant women, health care providers, and investigators might be able to identify HIV-related studies in pregnant women or obtain easy access to the published findings of completed HIV-related research in pregnancy through ClinicalTrials.gov, as required by the FDAAA. Of the 60 studies registered during the study period that met our criteria, only 8 studies (13.3%) reported basic results. This substandard reporting of results is in line with a recent court decision that determined that an HHS regulation that exempted reporting of certain clinical trials conducted between September 2007 and January 2017 was invalid, resulting in nearly a decade's worth of missing clinical trial results.[2] This also may confirm prior, well-documented examples showing that ClinicalTrials.gov has not been an effective platform to help patients and providers make informed decisions about potentially participating in clinical research due to the lack of studies and study data actually registered on the platform [4–6]. Completed studies that have no reported results could be seen by pregnant women and their providers as studies that were poorly disseminated or studies that cannot be validated. Moreover, the uncertainty about the completeness of the platform and the integrity of the data available raises concerns over whether ClinicalTrials.gov is a reliable data source for research.

2. Pregnant women may have difficulty determining if studies are meant to benefit the woman or the fetus.

We also sought to capture the terms investigators used to describe their study endpoints as an analog for whether the investigators intended the research to benefit the pregnant woman or the fetus. Appraising the relative risk of a study to participants is common to all studies but is more complicated for research involving pregnant women, given that the research also poses potential risks and benefits to the fetus. Pregnant women may express more reluctance to participate in research than other types of study participants, particularly where they perceive any risk to the fetus [7–9]. This was based on the hypothesis that a pregnant woman might assess her willingness to participate in a study based on whether anticipated outcomes used terms more associated with the pregnant woman or with the fetus and our hypothesis that studies are more likely to have outcomes focused on the fetus, not the pregnant woman.[3] However, our search revealed the inconsistency with which investigators refer to pregnant women and fetuses. The terms used to refer to pregnant women included not only our anticipated terms ("woman/en," "maternal," "mother," "children," "fetus/al," and "infant") but also vaguer terms ("participants," "subjects" and "patients") that obscure the focus of measured outcomes. The inconsistent use of terms complicates the ability of pregnant women and/or their providers to search for and identify studies on the ClinicalTrials.gov platform to which the results of such studies may improve informed health care decisionmaking. The myriad terms used to describe the pregnant woman and fetus also obscures the purpose of the study, and for whom it is meant to benefit: the woman, the fetus, or both.

3. Inconsistent use of descriptors regarding the stage of pregnancy for study eligibility makes it challenging for pregnant women to find studies to which they may be eligible to enroll

To understand how investigators described the stage of pregnancy where pregnant women are eligible to participate in clinical trials, we scanned study eligibility criteria for references to trimester, gestational age, general references to pregnancy without any reference to trimester or gestational age, or the absence of such descriptors in the eligibility section. Our search results showed the myriad ways investigators may refer to eligible stages of pregnancy. For example, results included text entries such as "18–26 weeks," "<22 weeks," and "more than 30 weeks, less than 30 weeks." Further, most entries did not clarify whether the criteria referred to gestational or fetal/conceptual age. The lack of a standard descriptor for the eligible stages of pregnancy (i.e., trimester OR gestational age OR fetal/conceptual age) requires pregnant women to search the platform blindly and determine the appropriate search terms, using a combination of numbers, words and mathematical symbols, that allows them to find studies in which they may be able to enroll.

4. Lack of information on interventional products make it hard to determine whether the product has already been approved for use in the general population

Lastly, we scanned the entries to determine whether any indicated that the intervention of study was approved by the FDA. Nearly all prescription drug use by pregnant women is off-label, and 97% of pregnant women take at least 1 prescription drug during the first trimester [10]. However there are several reasons the sponsor of an already-approved drug, biologic and/or device might initiate a study of their therapy in pregnant women post-approval. From the pregnant woman's perspective, she may be more amenable to participate in clinical research if the intervention is an already-approved product rather than purely investigational [6]. From the research enterprise perspective, sponsors may attempt to satisfy a post-marketing requirement, known as a Risk Evaluation and Monitoring Strategy (REMS), imposed by the FDA to monitor off-label use in pregnant women due to a high probability that pregnant women might use the product, or to seek a future supplemental indication for use during pregnancy. As we searched the platform, we noted that of the 60 interventions we found, none of them indicated whether the interventional product had already been tested and/or approved for use by the FDA. While this information

[2] The FDAAA Final Rule declared that sponsors who conducted clinical trials after the enactment of FDAAA in September 2007 but before the effective date of the Final Rule on January 18, 2017 for products that had not received marketing authorization at the time of trial completion were not required to submit results to ClinicalTrials.gov [15].

[3] The terms we chose to identify were "fetus", "fetal", "child", "children", "infant", "woman", "women", "maternal", and "mother" (other terms used in outcome measures that we identified post-hoc included "babies", "female", "mother participants", "female participants", "newborn", "neonate", and "offspring").

may be important to the general population to apprise the risks and benefits of joining a study, this may be even more important for pregnant women, given that most FDA-approved products that are not specifically indicated for use during pregnancy have not been studied in pregnant women, as has been reported in research and popular media [11,12].

Conclusion

ClinicalTrials.gov is intended to facilitate the public dissemination of clinical study information to better inform health care decisionmaking for patients, providers and investigators. We attempted to conduct a systematic review of the platform to better understand the quality and quantity of information submitted by clinical trial sponsors and/or investigators in the context of HIV research with pregnant women but believe our findings could be generalizable to any pregnant woman who is looking to participate in clinical research and to their providers who aid in this decisionmaking process. The roadblocks we encountered in our review of the platform call into the question ClinicalTrials.gov's utility as a resource intended to increase access to clinical study information and results, especially for pregnant women and their providers looking for clinical studies for which they may be eligible to enroll. Policymakers should further examine the platform's data reporting gaps and question the enforcement strategy as it relates to the platform.

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Research data

The following search terms were used to produce our data results from ClinicalTrials.gov: ("pregnant" OR "pregnancy") [ELIGIBILITY] AND ("HIV" OR "AIDS" OR "human immunodeficiency virus" OR "acquired immunodeficiency syndrome") [DISEASE] AND ("09/27/2007": "12/16/2016") [FIRST-RECEIVED-DATE]

Declaration of competing interest

The authors report no conflicts of interest.

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