

Reasons for and associated characteristics with early study termination and: Analysis of ClinicalTrials.gov data on pregnancy topics

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Abstract

Prematurely terminated studies are unlikely to provide data for evidence-based practice. This study investigated the reasons why studies on pregnancy topics are terminated and the associated characteristics with early termination. A total of 3,623 studies (332 terminated and 3,291 completed) were retrieved from ClinicalTrials.gov registry. Reasons for termination were grouped into four categories, including accrual difficulty, research operation issues, data-related recommendations, and external factors. Study characteristics were statistically compared between terminated and completed studies. Accrual difficulty (44.6%) and research operation issues (21.4%) were most frequently cited reasons for termination. Study design characteristics of intervention, randomization, masking, treatment and drug trial, and low funding from federal agencies were significantly associated with early termination. Population tailored subject recruitment strategies, scientifically sound research protocols, and well-planned research operations may mitigate premature study termination.

Highlights

- Accrual difficulty was a major reason for study termination.
- Terminated studies were more likely to be randomized intervention trials.
- Tailored study-specific recruitment strategies may mitigate study termination.

Reasons for and associated characteristics with early study termination: Analysis of ClinicalTrials.gov data on pregnancy topics

The US Department of Health and Human Services (2020) has recently announced a call for improving maternal health before, during, and after pregnancy. Sound therapeutic or behavioral research is needed to improve maternal health outcomes. One phenomenon that impedes advancement of research is the early study termination. When studies are terminated before planned completion, time and resources allocated to the research are wasted and data needed to advance the development of evidence-based practice may become unavailable.

Early termination of studies is a common problem. Three percent of studies on dental health topics (Sivaramakrishnan & Sridharan, 2016) and about 18% of drug trials were discontinued before study completion (van den Bogert et al., 2017). Johnson et al. (2019) examined the dissemination of results of randomized controlled phase 3 and phase 4 trials on head and neck cancer and found that the results of discontinued trials were less likely to be published than completed trials (31.6% vs 59.8%).

Recruitment challenges are a major factor that contribute to early study termination. One study found that only 55% of the 73 multi-site randomized controlled trials on various health topics (mental health, orthopedics, OB/GYN, primary care, cardiology, incontinence, HIV, etc) funded by the UK National Institute for Health Research-Health Technologies Program and UK Medical Research Council achieved their targeted sample size (Sully, 2013). Using data from the ClinicalTrials.gov registry, Bernardez-Pereira et al. (2014) found that 54% of 684 cardiovascular interventional trials were prematurely terminated due to low recruitment. Also using data from the ClinicalTrials.gov registry, Carlisle et al. (2015) analyzed phase 2 and phase 3 interventional trials and found 43% of 363 terminated trials cited poor accrual of study participants as the

reason for study termination.

Another factor leading to early study termination is interim trial data regarding efficacy, toxicity, safety, futility, and/or superiority (van den Bogert et al., 2017). Stensland et al. (2014) found that among 935 adult cancer phase 2 and phase 3 interventional trials that were not completed, 18.1% were terminated to toxicity or poor efficacy data. Williams et al. (2015) examined 905 terminated trials registered in ClinicalTrials.gov registry and found 21.3% were terminated because of interim trial scientific data and 68.4% were due to other reasons. Migrino and Topol (2003) stated that the use of endpoints, prespecified stopping rules, and cautious statistical requirements could influence interim data analysis and therefore the decision to continue or stop a trial before the trial's planned completion date. Essentially, interim data analysis is to estimate efficacy in relation to the ratio of benefit and risk. Migrina and Topol (2003) used the Women's Health Initiative to illustrate benefits and risks. The Initiative was terminated early because the risks of developing invasive breast cancers outweighed the benefits of preventing myocardial infarction or cardiac death from conjugated estrogen plus medroxyprogesterone among postmenopausal women. On the other hand, when benefits outweigh risks, a trial can also be terminated early. In the 1990s, for example, the AIDS Clinical Trial Group Protocol 076 on HIV-infected pregnant women was terminated before study completion because the interim analysis showed favorable efficacy of Zidovudine treatment regimen in reducing vertical transmission of HIV infection from the mother to the fetus and infant, which outweighed the side-effects from antiviral treatment (Cooper et al., 1996).

Researchers have also described an array of logistic factors that contribute to early study termination, such as cancelation by a sponsor, inadequate budget, unavailability of study agent, and departure of principal investigator from the institution (Stensland et al, 2014). Bernardez-

Pereira et al (2014) identified several characteristics of cardiovascular trials that were terminated due to low enrollment including parallel design, safety/efficacy as end points, phase 4 trial, diagnostic assessment as primary study purpose, and funding from mixed sources.

External factors may also lead to early study termination. For instance, a clinical trial to test the efficacy of an asthma education program as an adjuvant to good medical care for Hispanic children was stopped three months after the trial had begun because a high percentage of children and their families did not have adequate medical care and insurance (Lewis et al., 1994). Continuing the trial without helping families in both the experimental and the control groups deal with housing, medical care, and poverty related issues was deemed to be unethical.

Preventing early termination of studies for pregnant women could ultimately improve the health of this population. These women were historically viewed as a vulnerable population and often excluded from participating in clinical research involving investigational therapies or treatments so as to prevent unexpected harm to them and/or their developing fetus (Mastroianni et al., 1994). Recently, federal regulatory and professional organizations have considered pregnant women a scientifically complex rather than vulnerable population (ACOG, 2015; USFDA, 2018). Pregnant women are encouraged to exercise autonomous decision making even for clinical research participation. Even so, recruiting pregnant women into research remains a challenge. In one study, researchers enrolled only 16 of a proposed 306 pregnant women who were obese or overweight for a weight management trial study in 18 months (Sutton et al., 2017). While many pregnant women are willing to take part in clinical research because they like to “help the future of medicine” (Meshaka et al., 2016), risks and safety of the fetus and the pregnant woman are major concerns influencing the decision of pregnant women to participate in research. These same risks often discourage healthcare providers and researchers from

encouraging pregnant women to participate in intervention trials (Wada et al., 2018).

Because recruitment of pregnant women is difficult, it would be important to determine if enrollment, as well as other factors, contribute to early termination of studies among this population. Such information could avoid delays in development of innovative interventions for this population due to early termination of studies. To our knowledge, there has been no systematic reviews that analyze reasons for premature study termination on pregnancy-related research. The purpose of our study therefore was to (1) investigate reasons for early termination of studies on pregnancy topics registered in the ClinicalTrials.gov, and (2) compare characteristics between terminated and completed studies on pregnancy topics registered in ClinicalTrials.gov.

Methods

Study selection

ClinicalTrials.gov is the largest registry in the World Health Organization International Clinical Trials Registry Platform (Valkenhoef et al., 2016). The ClinicalTrials.gov registry is publicly accessible and is managed by the U.S. National Library of Medicine. Both interventional and observational studies are included in the registry. Since 2007, clinical trials to study drugs, biologics, and devices to be approved by the US Food and Drug Administration are required to register in the registry (Zarin et al., 2016). Although permission to use the registry data is not required, for this study we obtained approval from the U.S. National Library of Medicine (case number CA-616319-W0C4H0).

According to the ClinicalTrials.gov registry, a terminated study is one that “has stopped early and will not start again” and “participants are no longer being examined or treated.” A completed study is one that “has ended normally” and “participants are no longer being examined or treated (that is, the last participant's last visit has occurred)” (U.S. National Library

of Medicine, 2020).

We retrieved studies from the ClinicalTrials.gov on October 13, 2020. We entered the term “pregnancy” to the condition or disease box on the registry website to search all relevant studies. This search yielded 7,746 studies. In the advanced search location, which contained several filters (e.g., not yet recruiting, recruiting, enrolling by invitation, active not recruiting, suspended, terminated, completed, withdrawal, and unknown), we selected the “terminated” option. This yielded 332 studies, which was about 4.3% of all studies related to pregnancy. We then selected the “completed” option, and this yielded to 3,291 studies, which was about 42.5% of all studies related to pregnancy. These two sets of studies combined included 3,623 studies.

Analysis framework for reasons for study termination

We developed four categories to group various reasons for study termination. These categories were derived from the literature review, particularly from published studies based on the ClinicalTrials.gov data (Bernardez-Pereira et al., 2014; Stensland et al., 2014; van den Bogert et al., 2017; Williams et al., 2015). The four categories were (1) accrual difficulty (e.g., low numbers of subjects, medical charts or specimens); (2) research operation issues (e.g., personnel issues; inadequate support of testing drugs, equipment, facilities, or funding; protocol changes; unable to obtain IRB approval; measurement issues; coordination difficulties; and sponsors’ decisions to stop a study); (3) data-related recommendations (e.g., futility analysis, safety or efficacy data, and interim analysis); and (4) external factors (e.g., changes in market demand, business decisions, practice guidelines, laws, and standard of care; similar results reported by others; changes in disease prevalence or COVID impact; and competing trials on the same population).

Data analysis

To analyze reasons for study termination, we retrieved narratives provided on the website

from each terminated study. These narratives were very short often in one or a few sentences. Most studies cited a single reason, which was assigned to one of the four categories: Accrual difficulty, research operation issues, data-based recommendations, and external factors. Eight studies provided multiple reasons. We used a chronological order to list multiple reasons as they appeared on the website (e.g., accrual and operation issues or external and accrual issues) and created an additional category named multiple reasons to group combinations of reasons. One research team member coded all reasons first. A second research team member checked the already coded categories against definitions for each category. The interrater agreement was 92.8%. Disagreements in coding were resolved first through verification of category definitions by the two coders and then discussion between the two coders to reach consensus. For instance, the reason of “high incidence of fraudulent enrollment” was coded differently (accrual difficulty vs. research operation issues) by the two coders. After definition check and discussion, this reason was coded under the category of accrual difficulty.

For comparisons between terminated and completed studies, we used the 26 data elements in the registry for each study. Data elements included national clinical trial number, study title, conditions, intervention type, study type, study design, phases, enrollment number, sponsor, funding agency, first and last postdates, start and completion dates, results first posting date, study locations, and other information such as gender, acronym, other study identification number, website of each study, etc. Some data elements from the website that were in text format were recoded as numerical or categorical data. For instance, we counted number of sites listed for the studies and included this number as numerical data, whereas the geographical locations of continents/regions of the study sites was recoded as categorical data. We did not include

enrollment data in our analysis because some studies included actual enrollment numbers and others included estimated enrollment data or did not specify.

Study characteristics between terminated and completed studies were compared. If there were a large number of categories for any characteristic, they were combined to make the statistical comparison feasible. For instance, 16 categories of funding agency were combined to become three categories when we performed comparative analysis for terminated and completed studies. Categorical characteristics were compared by chi-square or Fisher's exact tests. For characteristics (first to last postdate in years, start to completion date in years, and number of study locations) measured with numerical data, nonparametric Wilcoxon rank sum test was used to test for a statistical difference in the distributions.

Results

Reasons for termination

Data are provided in Table 1. Of the 332 terminated studies, over three quarters ($n = 264$, 79.5%) were interventional studies and less than a quarter ($n = 68$, 20.5%) were observational studies. The most frequently cited reason for study termination was accrual difficulty ($n = 148$, 44.6%) followed by research operation issues ($n = 71$, 21.4%), data-related recommendations ($n = 33$, 9.9%), and external factors ($n = 28$, 8.4%).

Table 1 also lists within category findings. Personnel, funding, and facility/material were major issues contributing to study termination in the category of research operations issues ($46/71 = 64.8\%$), whereas unfavorable outcomes from interim or futility analysis was the major issue contributing to study termination in the category of data-related recommendations ($23/33 = 69.7\%$). Of the 332 terminated studies, only 7 (2.1%) reported study termination due to safety concerns. External factors for study termination included changes in disease prevalence, laws,

practice guidelines, and business/market plans (21/28 = 75.0%) and results of similar studies were reported or competing trials were conducted by other researchers (7/28 = 25.0%).

Additionally, 13.3% of the terminated studies did not cite any reasons and 2.4% cited multiple reasons for study termination.

Table 1. Reasons for Study Termination by Designs

	Total N = 332 n (%)	Interventional N = 264 n (%)	Observational N = 68 n (%)
Accrual difficulty	148 (44.6)	120 (45.5)	28 (41.2)
Research operation issues	71 (21.4)	55 (20.8)	16 (23.5)
Personnel	18 (5.4)	11 (4.2)	7 (10.3)
Funding	15 (4.5)	12 (4.5)	3 (4.4)
Facility and material	13 (3.9)	12 (4.5)	1 (1.5)
IRB/protocol	9 (2.7)	7 (2.7)	2 (2.9)
Resource/support	7 (2.1)	6 (2.3)	1 (1.5)
Study design issues	5 (1.5)	4 (1.5)	1 (1.5)
Sponsor decision	4 (1.2)	3 (1.1)	1 (1.5)
Data-related recommendations	33 (9.9)	30 (11.4)	3 (4.4)
Unfavorable interim or futility data	23 (6.9)	20 (7.6)	3 (4.4)
Safety concerns	7 (2.1)	7 (2.7)	0 (0.0)
Favorable interim data	3 (0.9)	3 (1.1)	0 (0.0)
External factors	28 (8.4)	25 (9.5)	3 (4.4)
Disease prevalence/COVID-19	9 (2.7)	9 (3.4)	0 (0.0)
Laws/practice guidelines	7 (2.1)	7 (2.7)	0 (0.0)
Business/market	5 (1.5)	3 (1.1)	2 (2.9)
Results already reported by other	5 (1.5)	4 (1.5)	1 (1.5)
Competing trials	2 (0.6)	2 (0.8)	0 (0.0)
Multiple reasons	8 (2.4)	8 (3.0)	0 (0.0)
Accrual & operation issues	3 (0.9)	3 (1.1)	0 (0.0)
Accrual & external issues	1 (0.3)	1 (0.4)	0 (0.0)
Accrual, operation & external issues	1 (0.3)	1 (0.4)	0 (0.0)
Operation & accrual issues	1 (0.3)	1 (0.4)	0 (0.0)
External & accrual issues	2 (0.6)	2 (0.7)	0 (0.0)
Missing	44 (13.3)	26 (9.8)	18 (26.5)

Comparisons of characteristics between terminated and completed studies

The majority of terminated and completed studies were interventional trials with randomization without masking, took 1 to 5 years to complete and the same amount of time to post study information on the registry website, had an intervention type as drug trial, a primary study purpose of treatment, information on study phase as not applicable or missing, and results not available, and were conducted in a single site in US and funded by individuals, universities, or community-based organizations (details in supplemental Table 1).

Table 2 shows comparison results. Terminated studies had a significantly longer timeframe [median 3.6 (0.0, 15.4) years vs. 2.3 (0.0, 20.1) years] between the first and the last post of study information on the registry website than completed studies. As compared to completed studies, a significantly greater percentage of terminated studies had results available (19.0% vs. 11.6%), were intervention studies (79.5% vs. 67.3%), used randomization (71.4% vs. 53.8%), had treatment as the primary study purpose (50.0% vs. 28.8%) and intervention type as drug trial (45.9% vs. 33.7%), had some degree of masking (39.2% vs. 30.4%), and were conducted solely in the US (50.2% vs. 37.3%). A smaller percentage of terminated than completed studies received some or all funding from federal agencies (8.1% vs.13.6%).

Table 2. Comparisons of Study Characteristics of Terminated and Completed Studies.

		Terminated N = 332	Completed N= 3291	P-value
Start to Completion (yrs)	N	318	3193	0.4545
	Mean ± SD	2.7 ± 2.1	2.8 ± 2.5	
	Median (Min,Max)	2.4 (0.0, 14.7)	2.2 (0.0, 24.2)	
	N	332	3291	
	Mean ± SD	4.3 ± 3.3	3.2 ± 3.3	

First to Last Post (yrs)	Median (Min,Max)	3.6 (0.0, 15.4)	2.3 (0.0, 20.1)	<.0001
Number of Study Locations	N	317	2907	0.3242
	Mean \pm SD	2.7 \pm 5.5	3.1 \pm 11.1	
	Median (Min,Max)	1.0 (1.0, 50.0)	1.0 (1.0, 222.0)	
Results Available	No	269 (81.0)	2908 (88.4)	0.0001
	Yes	63 (19.0)	383 (11.6)	
Study Type	Intervention	264 (79.5)	2214 (67.3)	<.0001
	Observational	68 (20.5)	1077 (32.7)	
Randomization	No	94 (28.6)	1494 (46.2)	<.0001
	Yes	235 (71.4)	1743 (53.8)	
	Missing	3	54	
Study Purpose	Not treatment	162 (50.0)	2279 (71.2)	<.0001
	Treatment	162 (50.0)	922 (28.8)	
	Missing	8	90	
Intervention Type	Drug trial	134 (45.9)	923 (33.7)	<.0001
	Non drug trial	158 (54.1)	1818 (66.3)	
	Not provided (Missing)	40	550	
Phase	Phase 1 or 2	37 (29.4)	305 (33.8)	0.3208
	Phase 3 or 4	89 (70.6)	597 (66.2)	
	Missing or not applicable	206	2389	
Masking	No	200 (60.8)	2247 (69.6)	0.0010
	Yes	129 (39.2)	981 (30.4)	
	Missing	3	63	
Multi-Site Studies (>1 site)	No	79 (24.9)	657 (22.6)	0.3499
	Yes	238 (75.1)	2250 (77.4)	
	Missing	15	384	

Funding	Some or all federal funding	27 (8.1)	449 (13.6)	0.0092
	Some or all industry funding	47 (14.2)	372 (11.3)	
	Other*	258 (77.7)	2470 (75.1)	
Study Location in US only	No	158 (49.8)	1823 (62.7)	<.0001
	Yes	159 (50.2)	1084 (37.3)	
	Missing	15	384	

*Other includes individuals, universities, or community-based organizations

Discussion

Using ClinicalTrials.gov registry data, we analyzed 332 terminated studies and another 3,291 completed studies on pregnancy topics. We found that accrual difficulty followed by research operation issues were the most frequently cited reasons for early study termination. Studies were also terminated less often due to data-related recommendations and external factors. Several study characteristics were associated with study termination. As compared to completed studies, terminated studies were more likely to involve intervention with randomization and some masking, had treatment as the primary study purpose and intervention type as drug trial, and were conducted in US but less likely to have some or all federal funding support.

We found that 4.3% of the studies on pregnancy topics were terminated early. Study termination rates of 3% to 20% among studies focused on dental health, drug trials, cancers, and various health issues have been reported (Siraramakrishnan & Sridharan, 2016; Stensland et al., 2014; van den Bogert et al., 2017; Williams, et al., 2015). The difference in termination rates could be that we included both interventional and observational studies in our analysis and previous researchers performed analyses on interventional studies only. Nevertheless, our study findings indicated that early study termination could occur in both interventional and observational studies.

In our study, accrual difficulty was the major reason for early study termination, which was in concert with findings from previous studies. Difficult subject recruitment and low enrollment were common in studies investigating non-pregnancy subjects and contributed to early study termination (Bernardez-Pereira et al., 2014; Carlisle et al., 2015; Sully 2013). The findings of accrual difficulty imply that careful recruitment designs, innovative strategies, and tailored methods are needed for recruiting and enrolling target population such as pregnant women into a study. We propose four approaches to mitigating accrual difficulty in the following paragraphs.

The first approach is developing tailored study-specific recruitment strategies. Some successful recruitment strategies have been reported, which may be useful for investigators to adopt. Researchers in one study experiencing low enrollment of pregnant women changed passive recruitment (e.g., posting study flyers and waiting for women to call the study) to active recruitment approach (e.g., consented women to be contacted and actively engaged follow-up communication with the women) and were able to improve enrollment (Sutton et al., 2017). Using social media to reach out to pregnant women and to interact with the women during recruitment and consent processes has been adopted by researchers. Herbell (2019) recruited from antenatal classes 25 pregnant women in 75 days into a study about psychophysiological stress and mental health but 62 participants from the Facebook private groups in 48 days, indicating social media could be a useful venue to improve recruitment. Other researchers successfully recruited pregnant Black and African American women from OB/GYN clinics in multiple states by developing a good relationship with clinic staff to gain collaboration, avoiding disruption of clinic flow, and escorting pregnant women to another part of the clinic building as the support for the women and the clinic staff (Vaughan et al., 2021). Use of technology to

collect sensitive information may also improve subject recruitment. For instance, recruitment specialists used an Audio-Computer-Assisted Self Interview (A-CASI) method to screen pregnant African American and Latina women for a behavioral and counseling randomized controlled trial (El-Khorazaty et al., 2007). Pregnant women listened to digitally recorded questions about depression, smoking, and intimate partner violence on headphones and provided their answers on a touch screen. The A-CASI method along with matching recruitment specialists' gender and ethnicity to the study population, providing recruitment training for recruitment specialists, and offering subjects financial incentives for study participation led to a high recruitment rate of 90%, calculated as 1,070 of the 1,191 women consenting to participation completed the baseline interview and were randomized into the study.

The second approach is advancing the science of recruitment by developing recruitment theory and testing efficacy of recruitment intervention. Investigators may take part in recruitment focused research to advance theoretical development of subject recruitment. Recruitment research may focus on the participant, the recruiter, and the recruitment process. For instance, researcher may use a qualitative methodology to study personal factors (e.g., education, interest in the research topic), contextual factors (e.g., influence from family and friend), and study characteristics (e.g., ethical issues, study burden) that could facilitate study participation among pregnant women (Ayoub et al., 2018). Researchers may also use a qualitative evidence synthesis method to study the recruiter's perspectives when recruiting pregnant women into clinical trials (Hanrahan, Gillies, & Biesty, 2020). Investigators are also encouraged to test and evaluate recruitment intervention. Donovan et al. (2016) described a two-phase Quintet Recruitment Intervention (QRI), which was developed from recruitment strategies used in several randomized controlled trials. Phase 1 of the QRI was to understand the recruitment process achieved by

implementing several measures such as interviewing trial team members, mapping eligibility and recruitment pathways, and analyzing audio-recorded recruitment encounters between the recruiter and the participant. The goal of phase 2 in the QRI was developing and implementing recruitment strategies based on findings from phase 1. Goff et al. (2016), using a health equity framework, developed a three-component recruitment intervention, including team preparation before recruitment, process-optimized recruitment, and patient-centered study procedures. Investigators may adopt these intervention models or develop a modified recruitment intervention for a specific population and assess the efficacy or effectiveness of the intervention on recruitment improvement.

The third approach is increasing funding to support recruitment focused research. Funding support could be used to develop a feasibility study, test a full-fledged recruitment focused intervention, or evaluate a recruitment intervention embedded, as a main part, in a randomized controlled trial with other aims. Funding support is especially needed for trials that recruit anticipated difficult to reach pregnant subjects. Terminated studies in our analysis were significantly less likely to receive some or all funding from federal agencies as compared to completed studies. Having extramural funding to support recruitment focused research has the potential to improve subject recruitment.

The last approach is enhancing recruitment knowledge and skills among investigators-to-be. Subject recruitment should be included in formal research training either in a PhD curriculum or a post-doctoral fellowship program. The training could be delivered through a course to increase trainees' theoretical and methodological knowledge of subject recruitment or as research practicum to foster trainees' hands-on ability to test and evaluate recruitment methods.

Preparing future researchers in developing and evaluating recruitment methodology and intervention may mitigate potential study termination in their future studies.

Interestingly, among the 18 studies terminated due to personnel reason (most common cause in the category of research operation issues) 11 cited principal investigator's (PI) departure causing study termination. These 11 studies were funded by universities or community-based organizations. Many institutions do not allow a PI to take intramural grants to another institution when the PI leaves a position. However, some systems wide mitigation plans, such as transferring a grant to a co-investigator within an institution to facilitate study completion or enhancing university/school centralized research administration and management support, may be necessary. Many other research operation issues found in our study could also be improved by processes of hiring, training, and evaluating personnel, purchasing study equipment/material, monitoring budget and expenditures, establishing work relationship with internal and external collaborators, and preparing research reports.

Safety, futility, and efficacy data in our study, to some degree, were attributable to early study termination. This finding was different from that in a previous study. Johnson et al. (2020) identified recommendations based on safety, efficacy, and toxicity data as the most common reason for study termination. Their study, however, included terminated, withdrawal, unknown, and suspended studies in ClinicalTrials.gov and focused only Phase 3 and 4 randomized controlled trials on head and neck cancer.

In our analysis, several study characteristics associated with termination were related to study designs, such as intervention, randomization, masking, and drug trial as intervention type. These characteristics imply that successful study completion requires a rigorous research

protocol with scientific merit. Researchers who plan for a randomized control trial are encouraged to know the study population well and have sufficient knowledge in trial design.

Drug trial in our analysis was an associated study characteristic with early study termination. Among the terminated drug trials in our analysis, 47% cited accrual difficulty as the reason for study termination (data not reported in tables). Healy et al (2018) recommended involving clinicians in subject recruitment by normalizing trials as part of clinical care, which may be suitable for drug studies for pregnant and lactating women in patient care settings. However, more research is needed to assess how integrating trial and clinical care may facilitate recruitment and subject enrollment in a drug trial.

Limitations:

Many studies in our analysis had missing data, and although missing data were expected in some cases (e.g., observational studies would not have data on randomization or masking), some findings from our study might be biased due to missing data. The registry did not have data on retention of study participation. Our finding on accrual difficulty was mostly based on recruitment data and did not include retention information. Lastly, the accuracy of data entry in the ClinicalTrials.gov registry was managed by a principal investigator or assigned study personnel. We were unable to know if data for each study were entered correctly. Some errors might have occurred from the entered data, but systematic errors were not likely to occur.

Conclusions

We investigated reasons for early termination for studies focused on pregnancy in the ClinicalTrials.gov registry and compared characteristics between terminated and completed studies. The most frequently cited reasons for study termination were accrual difficulty and research operation issues. Factors associated with early termination were related to research designs and intervention types, such as randomization, masking, and treatment and drug trials.

Several recommendations are addressed to improve subject recruitment and study completion, such as advancing recruitment focused research, funding to support testing and evaluating recruitment methodology, and developing rigorous research protocols and research operation plans.

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