

Recruitment and Retention of Pregnant Women Into Clinical Research Trials: An Overview of Challenges, Facilitators, and Best Practices

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Pregnant women are a vulnerable group who are needed in clinical research studies to advance prevention and treatment options for this population. Yet, pregnant women remain underrepresented in clinical research. Through the lens of the socioecological model, we highlight reported barriers and facilitators to recruitment and retention of pregnant women in studies that sought their participation. We trace historical, policy-based reasons for the exclusion of pregnant women in clinical studies to present-day rationale for inclusion of this group. The findings highlight why it has been difficult to recruit and retain this population over time. A body of literature suggests that integrative sampling and recruitment methods that leverage the influence and reach of prenatal providers will overcome recruitment challenges. We argue that these strategies, in combination with building strong engagement with existing community-based organizations, will enable teams to more effectively promote and retain pregnant women in future longitudinal cohort studies.

Keywords. pregnant women; clinical research trials; recruitment; retention; vulnerable populations.

Pregnant women represent a vulnerable segment of the population at risk for significant medical conditions such as pain and infections. Women in their childbearing years have been historically excluded from participation in clinical research studies due to the potential for harm to fetuses and infants including unforeseen teratogenic effects and adverse pregnancy outcomes. Consequently, there is a dearth of information on best practices for recruitment and retention of pregnant women in clinical research studies [1]. Yet, there is a growing need in clinical studies for 2 populations of pregnant women: those with and those without illnesses.

Studies often seek pregnant women who are not sick to serve as a comparison group and to assess “routine” problems that happen to occur during pregnancy and need intervention, such as pain control, common infections, and other conditions. Recruitment of this population into clinical studies may be particularly challenging as participants may perceive no direct benefit to themselves.

As policies have shifted toward inclusion of this population in recent years, evidence has emerged on how to promote study involvement among pregnant women and retain cohorts in longitudinal research. Recent studies have emerged globally on the recruitment of pregnant women into clinical research trials (CRTs) exploring a variety of biomedical and socioecological issues specific to this population, including tolerance and resistance to antiretroviral medications (eg, single-dose nevirapine), prevention of mother-to-child transmission of human immunodeficiency virus (HIV) [2], and antidepressant treatment resistance [3], as well as

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pandemic influenza vaccine uptake and pregnancy outcomes [4–6]. Despite these strides, shortages of new medications approved for safe use during pregnancy [7–9] pose a significant barrier to treatment of women during pregnancy. The increased numbers of prevention and treatment studies reflect a strong need for participation of pregnant women in CRTs.

The aim of our study is to synthesize the body of literature that details challenges, facilitators, and best practices toward recruitment and retention of this underrepresented population [1, 8]. The socioecological model of health promotion is a comprehensive, well-established approach to understanding the multi-level factors impacting individual and community health behavior [10–13], particularly among traditionally underrepresented and hard-to-reach populations [14–16]. To examine intersecting factors that help explain how to improve recruitment and retention of pregnant women, we adopted the socioecological framework to analyze the dynamic reverberation across individual, spouse/family/social network, and community/societal levels that contribute to recruitment and retention challenges. We view these challenges as entirely surmountable and present how these can be reframed as opportunities for the development and implementation of novel outreach strategies in a global context.

METHODS

The authors conducted a comprehensive literature search using PubMed, Google Scholar, and other scientific publication databases in advance of a consultative meeting at the National Institutes of Health (NIH) in 2013. The team reviewed the literature from the past 2 decades and used a consensus approach to theoretically and thematically organize the material into a summary format. An oral presentation was delivered by the team leader to the broader consultative group for input and subsequent discussion.

Following the NIH meeting, study team members and a partner contracted from Technical Resources International, Inc, conducted concurrent searches using online database sources (eg, PubMed/Medline). Only publications written or translated into English were included in the database searches. These iterative approaches yielded 106 publications from study team members, and 23 publications from an assisted literature review conducted by the contracted partners from Technical Resources International. From these 129 articles, study team members identified 86 articles directly relevant to the thematic content of this paper (ie, recruitment, enrollment, and retention of pregnant women into CRTs).

Structural and Policy Issues

As of 2011, 15 “non-pregnancy related” medications were approved for use during pregnancy by the US Food and Drug

Administration (FDA) [7], with 91% of the drugs approved in the United States between 1980 and 2000 having an “undetermined” safety status with respect to risk to the fetus [8,9]. In the past century, investigators and pharmaceutical companies were reluctant to include pregnant women and women of childbearing age in CRTs due to concerns of legal liability, potential risks to the unknown fetus, and negative publicity. The NIH defines clinical research as that which is “patient-oriented” and has an epidemiologic, health service, or behavioral focus to evaluate the safety, utility, and effectiveness of biomedical or behavioral interventions [17]. The history of unsafe novel drug use among pregnant women (eg, thalidomide, diethylstilbestrol) and publicity of scandals involving improper drug use in pregnant women influenced administrative boards and the FDA to reduce drug exposure. Conflicts regarding the balance of maternal benefit against fetal risk, or vice versa, further incentivized potential investigators and review boards to avoid ethical commentary and negative publicity completely by limiting studies in which benefits to a pregnant woman were balanced against risk to the fetus.

Stringent regulation of clinical research protocols has been a significant historical barrier to successful recruitment and retention of pregnant women into CRTs [18]. Exclusionary criteria posed by institutional review boards and federal guidelines have contributed to this challenge [1,8]. As a result, the Code of Regulations Title 45 (45 CFR 46, Subpart B) was established in 2009, stipulating inclusion of pregnant women in CRTs [19]. Nevertheless, despite limited evidence of recent successful litigation against institutional review boards [20], collective memory did not fade with respect to damage produced by thalidomide exposure in pregnancy. Thus, avoidance of significant harm and concern over potential liability have been primary concerns. As a consequence, very few sponsors, institutions, and investigators have been willing to conduct any biomedical interventional studies with pregnant women even to this date.

Providers: Gatekeepers to Clinical Research

In addition to exclusionary policies and study criteria that limit representation of pregnant women in CRTs, eligible women may be reluctant to enroll in a CRT due to a general lack of awareness about research in their community. With so few institutions and investigators conducting studies with pregnant women, only a handful of hospitals and obstetric practices may be aware of a need for referral of pregnant patients [21–28]. Thus, there is evidence that expansion of CRTs in diverse communities will generate greater awareness of studies for which medical providers are a direct conduit for study promotion and effective recruitment [25, 27, 29–32].

Prior studies have demonstrated that lack of investigator/study team outreach to community providers can reduce clinicians’ willingness to promote clinical studies to their patients

and pregnant women's willingness to join studies [33–35]. Without direct community outreach to advise and inform providers about studies, many women express unease and distrust of the research. Even among women of childbearing age, the most cited reason for their unwillingness to join studies was a preference for protocols that enabled them to follow up on study results with their clinician [33]. Accordingly, past research studies have integrated referral to a health provider, if needed, as component to study procedures [23]. Women have also expressed a preference for face-to-face interactions with providers and clinic staff members when participating in research and intervention activities [34, 36]. Preference for such personal encounters indicates that active engagement of medical providers is critical to encouraging the recruitment and enrollment of pregnant women in CRTs.

Clinical staff and providers are the first point of contact into the healthcare system for most pregnant women, and therefore can be strong allies and advocates for study enrollment. They have direct access to patients and, as a component, would be able to facilitate recruitment by identifying and speaking directly to eligible women about study protocols and procedures [37, 38]. Building integrated networks comprised of clinical practitioners who have direct reach into the community and medical providers knowledgeable about study enrollment has proven a successful method of recruiting pregnant women [27]. Additionally, there is evidence pointing to the need for obstetricians and all members of their staff to promote unified messages in clinical settings to encourage pregnant patients to get immunized [39]. Thus, staff education and message training, along with study promotion via clinic media, print material, and interpersonal communication, will enhance patient receptivity to study recruitment.

Despite being constrained by pressing clinical duties [27], the evidence demonstrates that medical and social service providers are uniquely able to serve as patients' first contact with research studies. For example, the National Children's Vanguard Experience study completed rapid accrual of pregnant participants from Detroit (Wayne County, Michigan), including poor and minority women, through direct engagement of healthcare providers and clinic staff to recruit eligible women [25]. This study highlights how clinical/provider sampling approaches, rather than household or probability sampling, can yield impressive geographically and ethnically diverse samples of women in a short period of time [25]. Provider-based sampling methods are therefore feasible and cost-effective in enrolling a nationally representative sample of pregnant women for research purposes [40].

Transportation and Access Barriers to CRT Study Sites

In addition to knowledge and awareness, accessibility of CRTs poses an obstacle to the recruitment and enrollment of pregnant women in CRTs. Transportation and access to study sites was

the most cited barrier to participation (51%) among a sample of pregnant women who declined participation in one clinical research study [41]. Low-income women may not have reliable access to research study sites, particularly if they rely on a friend or family member for transportation, or use of public transportation. Study site locations that are located far away from regions frequented by low-income pregnant women (eg, lacking public transportation stops) further discourage participation in CRTs [42]. Pregnant women cite travel expenses as a reason for refusing enrollment in clinical research [41], raising the issue of affordability and study compensation. However, in a study of opioid dependence among pregnant women, reimbursement in the form of gradually increasing vouchers throughout the course of a research trial did not increase rates of recruitment and retention among this population [43]. Therefore, monetary compensation alone may be insufficient motivation to participate in CRTs, particularly if the study site is inconveniently located or women are poorly informed about the usefulness of the proposed project.

Use of hospitals and obstetric offices has been successful in identifying and enrolling eligible pregnant women for immunization trials [44]. The widespread use of prenatal clinics may exclude pregnant women without regular access to prenatal care; however, a similar community-based method can be applied to not-for-profit social and health organizations, and can help target women from low-resource settings [22, 45]. Visiting community-based organizations (CBOs) and establishing networks with community groups is an effective method of promoting the recruitment of pregnant women into CRTs [46]. Accordingly, similar studies have found that the most effective strategy for both recruitment and retention of eligible pregnant women with resource-constrained living situations was visits to community groups in their geographic area [46].

Clinical research staff who travel to the region of interest directly address the issue of transportation and time constraints. Pregnant women do not need to take additional time out of their day to travel to an inconveniently located study site to make first contact with the study. For example, lay health advisors and community health promoters (*promotoras*) have been effective in promoting pregnancy-related interventions, including those focused on infant nutrition and breastfeeding practices in many parts of the world [47–50]. It has also been used as a recruitment and retention strategy for clinical trials [51].

Similar effects have been observed with lay health advisors engaged in retention of pregnant women in resource-constrained areas [50]. In a study of pregnant South African women living with HIV, 75% of women enrolled in a peer-mentored intervention attended at least one antenatal session, and >50% were retained for postnatal sessions [50], lending support for use of community members as part of outreach and intervention efforts. Despite scant literature regarding peer

recruitment of pregnant women into CRTs, the successful use of peer mentorship programs [50] and CBOs [46] in promoting participation of pregnant women in research studies suggests that peer recruitment methodology may be important for the inclusion of pregnant women in future CRTs.

Normative Support and Social Approval From Friends and Family Members

Normative support and approval from friends and family members play a significant role in pregnant women's health perceptions and behavior [52], and may similarly influence willingness to participate in research studies. A study of recruitment factors among pregnant women found that 82% of young women between the ages of 18 and 30 years cited the husband's opinion as a significant reason for nonparticipation [53]. These results provide preliminary evidence that recruitment methodology may be important. Success is likely with those who leverage the influential role of family members as they mediate pregnant women's CRT participation and their perceptions of research safety and practicality.

Community-based methodology has been shown to encourage research trial enrollment globally [54–57]; studies that employ this methodology typically have very high success rates in recruitment and retention of racial and minority groups [58]. These methods may encourage both pregnant women and their social circles to feel more positively about research that actively attempts to engage the community and improve community well-being. Finally, through these conversations, CRT study members can educate pregnant women, friends, and family members about study practicality and potential benefits [46].

Community-based methods of recruitment may also include ethnically targeted messages, an effective method of improving response to clinical trials [59], as well as vaccine decision-making behavior among pregnant minority women [60]. Culturally competent, targeted recruitment and retention methods have also proven successful in maintaining high rates of CRT enrollment and retention among pregnant minority women.

Given the importance of community- and individual-level factors in mitigating willingness to participate as well as overall recruitment and retention rates among pregnant women, it is critical that CRTs tailor recruitment and retention methods to issues that are most salient to this population. The effect of community-level factors and normative support on women's decision making [52] suggests that recruitment and retention methods must engage the community as well as the individual pregnant woman. Prior studies have engaged CBOs through use of focus groups to identify salient barriers and facilitators to CRT participation [56], targeted messages and promotion materials [52], and community-based participatory research methods [58]. Research partners and community members need to combine knowledge of the research intervention and

community needs with the ultimate goal of promoting participation of the target population in overall research [61]. Ultimately, engaging community members via participation in community advisory boards can open up opportunities for engagement by leveraging existing programmatic activities in which pregnant women are involved [62].

Personal Factors Affecting Recruitment Into Research

Individual-level obstacles to CRT participation include time constraints and pregnancy-related issues [53]. Our recent studies of maternal immunization with influenza vaccine also indicated that messages emphasizing protective benefits conferred to infants was a major motivator for pregnant women to participate in the study and receive a vaccine [60, 63]. In response to the issue of increased time constraints faced by many pregnant women, several CRTs employ the hospital or clinic itself as the main study site [64–68]. Other research trials have attempted to accommodate the time constraints of pregnant women by taking advantage of mobile technology and the prevalence of cellular phone usage [69–71]. The Text4baby (T4B) program, launched in 2011, attempted to improve health behavior and perceptions among pregnant women by employing a text messaging program [71]. Fifty-one percent of women attempted self-enrollment in the program, of which 69% were successful [71], suggesting that online self-enrollment may be a successful method of recruitment when used more widely. A significantly greater portion of college-educated women attempted online enrollment, compared to those with less than a college education ($P = .04$) [71]; therefore, research investigators should consider this method for a more highly educated population. Conversely, if women with less than a college education simply feel less confident with self-enrollment, investigators must consider more aggressive promotion of this method of enrollment to ensure that the demographic characteristics of women enrolled does not differ significantly from those who do not enroll. Successful enrollment was also significantly associated with higher education ($P < .001$) and less than or equal to 3 financial dependents in a household ($P < .01$) [71]. As with other nonmobile methods of recruitment [72], individual demographic characteristics must be taken into account with mobile technology [71].

Nevertheless, mobile technology holds promise for the future of recruiting pregnant women in CRTs. Indeed, at 2-month follow-up, 88% of women expressed intent to continue using T4B [71]. Although primarily intended for health education rather than CRT recruitment and retention, T4B nevertheless promoted intent to continue participating in a research intervention [71], and may therefore be a useful method for retention of pregnant women in CRTs. Programs such as T4B also promise to change pregnant women's hesitancy about the practicality of a research study. T4B successfully changed attitudes toward pregnant women's health behavior [70], and should thus be

considered as a method to alter perceptions of CRT practicality and overall benefits to their health. Disseminating messages via cellular phone usage allows investigators to educate eligible participants without taking additional time out of pregnant women's schedules. CRT education via mobile technology that has promoted significant changes in health behaviors and perceptions may also help providers restrained by clinical duties to reach eligible patients and use a similar program to educate them on available studies.

Social networking sites have been employed as an effective method of increasing recruitment rates among pregnant women [73]. Prior studies indicate that social media, as a supplement to traditional healthcare-based recruitment sources, significantly increases retention of pregnant women into CRTs [73]. Other study findings indicate that Web-based recruitment methods can successfully enroll young women of reproductive age into research studies [74], demonstrating potential for Internet-based recruitment methodology to be used successfully among young pregnant women. Furthermore, online advertisement recruitment methods result in enrollment of higher percentages of traditionally hard-to-reach populations into research studies (eg, racial/ethnic minorities, individuals with less than a high school education) [75], and should thus

be considered a cost-effective method of improving participation of pregnant women in CRTs.

In-person recruitment is also an effective method of recruitment that addresses several important individual-level factors [27, 76, 77]. Through face-to-face interactions, women have the opportunity to address concerns about research safety, practicality, and mistrust in scientific research studies, which are significant barriers to participation of pregnant women and minorities in research [41, 78]. Additionally, several studies indicate that fear about research study findings (eg, abnormal results on a cervical smear test) influence individual willingness to participate in CRTs [33, 79, 80]. Interpersonal communication may help assuage individual worries about CRT results and may also help participants understand the benefit and importance of knowing, rather than avoiding, an unwelcome diagnosis.

Future CRT recruitment methods that employ in-person communication should be aware of the role of fear and anxiety in mediating willingness to participate, and address these issues upfront with pregnant and nonpregnant participants. Finally, in-person recruitment of pregnant women may help to deliver information about the importance of CRTs for population and individual health. A recent report indicated that the majority of participants in a cervical cancer randomized controlled trial believed their participation was worthwhile to cervical screening programs as a whole and beneficial to other women [33]. Considering that other findings have indicated perceived lack of research practicality as a significant barrier to recruitment and retention of pregnant women, improving perceptions of CRTs among individuals and community members through face-to-face interactions may prove a critical component of successful CRT recruitment strategies targeting pregnant women.

As summarized in Table 1, issues of location, research perception, and opinion of partners likely interact to discourage active participation by pregnant women into research studies. Pregnant women may consider a research study particularly impractical if the benefits are uncertain and it is inconveniently located. Additionally, pregnant women may rely on members of their social circle (eg, partners, family members, and friends) for transportation, in which case lack of social support to participate in a CRT becomes particularly problematic. Understanding the interaction of geospatial and psychosocial barriers to CRT participation is indispensable to promoting an improved understanding of how these factors may impact recruitment and retention of pregnant women (Table 1).

Table 1. Factors Influencing Recruitment and Retention of Pregnant Women in Clinical Research

Recruitment	Retention
Socioecological influences	
Institutional, legal, and higher-level factors	
<ul style="list-style-type: none"> Public scandals (eg, thalidomide) Federal guidelines on recruitment of pregnant women Institutional review board provisions Liability issues 	<ul style="list-style-type: none"> Research budget constraints Prevalence of longitudinal studies requiring follow-up
Community and social-level factor	
<ul style="list-style-type: none"> Provider study promotion (or lack thereof) Provider-patient study recruitment networks Clinic/study accessibility and affordability Social network and spouse/partner influences 	<ul style="list-style-type: none"> Clinical accessibility Strong relationship with study team Social network and spouse/partner influences
Individual-level factors	
<ul style="list-style-type: none"> Demographic factors (ie, age, income, and education) Time to participate Pregnancy-related health problems Perceived research relevance Fear 	<ul style="list-style-type: none"> Voucher-based incentives Time to complete study Pregnancy-related health issues Demographic factors (ie, age, income, and education)

Barriers and Facilitators to Retaining Pregnant Women in CRTs

A meta-analysis of effective recruitment methods for population-based studies found that cash or gift incentives were associated with an increase in retention rates [81]. Among face-to-face interventions, cash incentives may be associated with an increase in retention rates up to 85% [81]. Similarly,

financial incentives have been suggested as a method of increasing retention rates among new mothers [72]. Budget planning in research trials concerning pregnant and vulnerable women should include a consideration of cash or gift incentives [82], particularly considering the steady decrease in the purchasing power of research dollars [83] to carry out biomedical research. Budget constraints are further compounded by the popularity of longitudinal designs, which have increased substantially in the past several decades in both social science and medical research [84, 85].

Individual-level (personal) factors mediating recruitment of pregnant women in studies (eg, time constraints, lack of awareness) may also play a role in retention rates. In a study of new mothers recruited to nutrition research trials, women cited common reasons given for nonconsent for subsequent follow-up in the postnatal phase. These included time constraints (64.5%), a need to return to work or school (29.5%), and transportation (18.1%) [72]. Reasons cited for nonconsent at follow-up closely match those given in earlier studies for non-enrollment. Similar solutions may be applicable to improving retention rates, including use of mobile reminders, tailored messages, and social media, in addition to community-based recruitment methods.

Community-level factors are similarly critical in retaining pregnant women in CRTs, and must therefore be incorporated in retention strategies. Culturally appropriate messages and research tailored to the need of participating CBOs were among the 3 most effective strategies contributing to successful retention of pregnant women in research trials [86]. These findings further evidence the importance of incorporating partnering agencies and CBOs into research methodology, as well as recruitment methodology that is carefully tailored to interests and needs of pregnant women (eg, health of fetus) [36].

CONCLUSIONS

In addition to identifying critical barriers and facilitators to recruitment and retention of pregnant women in CRTs, we provide evidence for a new direction in CRT methodology. Specifically, we propose sampling and recruitment methods that make broader use of prenatal providers and general practitioners, as well as aggressive engagement with existing CBOs. Interpersonal communication between research staff and study participants is also integral to overcoming psychosocial obstacles to pregnant women's willingness and ability to participate in CRTs.

Underrepresentation of pregnant women in clinical research is a challenge that contributes to the dearth of evidence-based methods to treat the illnesses and conditions of this vulnerable population. Employing novel methods of recruiting and retaining pregnant women is indispensable to improving future studies' recruitment and retention rates. By understanding

correlates of nonparticipation in research trials, we can effectively craft new interventions for the inclusion of pregnant women in CRTs.

Notes

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