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METHODOLOGY ARTICLE

Socio-ecological Model as a Framework for Overcoming Barriers and Challenges in Randomized Control Trials in Minority and Underserved Communities

Hamisu M. Salihu, MD, PhD;[1] **Ronee E. Wilson,** PhD, MPH;[2] **Lindsey M. King,** MPH, CHES, CCRP;[2]✉
Phillip J. Marty, PhD;[3] **Valerie E. Whiteman,** MD[4]

[1]Department of Family and Community Medicine, Baylor College of Medicine, 3701 Kirby Drive, Suite 600, Houston, Texas, 77098, USA.
[2]Department of Epidemiology and Biostatistics, College of Public Health, University of South Florida, 13201 Bruce B Downs Blvd, MDC56, Tampa, Florida, 33612, USA.
[3]University of South Florida Health, Associate Vice Dean for Research, Tampa, Florida, 33612, USA.
[4]Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, College of Medicine, University of South Florida, Tampa, Florida 33612, USA.

✉Corresponding author email: LKing1@health.usf.edu

ABSTRACT

Background: Numerous barriers and challenges can hinder the successful enrollment and retention of study participants in clinical trials targeting minority populations. To conduct quality research, it is important to investigate these challenges, determine appropriate strategies that are evidence-based and continue seeking methods of improvement.

Methods: In this paper, we report such experiences in a registered clinical trial in an underserved minority population in the Southern part of United States. This research study is a randomized double-blind controlled clinical trial that tests the efficacy of higher-strength as compared to low-strength/standard of care folic acid to prevent fetal body and brain size reduction in pregnant women who smoke. A unique approach in this socio-behavioral, genetic-epigenetic clinical trial is that we have adopted the socio-ecological model as a functional platform to effectively achieve and maintain high participant recruitment and retention rates.

Results: We highlight the barriers we have encountered in our trial and describe how we have successfully applied the socio-ecological model to overcome these obstacles.

Conclusions and Global Health Implications: Our positive experience will be of utility to other researchers globally. Our findings have far-reaching implications as the socio-ecological model approach is adaptable to developed and developing regions and has the potential to increase recruitment and retention of hard-to-reach populations who are typically under-represented in clinical trials.

Key words: Participant Enrollment • Recruitment • Genetic-Epigenetics • Socio-Ecological Model (SEM) • Clinical Trials • Retention • Challenges

Background

Clinical trials are considered the "gold standard" in clinical research.[1,2] An effectively designed and properly implemented clinical trial protocol is the most definitive method of determining whether an intervention has a hypothesized effect.[2] Participant enrollment is a critical component of conducting meaningful research. Recruitment and retention of an appropriate and representative study sample enhance the validity of the results and heighten the potential public health impact.[3,4] Despite the benefits of clinical research, many people approached to participate decline to do so because of deeply rooted myths about research.[5,6] Physician-scientists and basic/translational scientists need to work together to dispel these misconceptions so that enhanced participant enrollment can be attained, a step that is vital to conducting a successful clinical trial.[5]

The philosophical underpinnings of conducting clinical trial research are centered around three basic ethical principles: Respect for Persons, Beneficence, and Justice.[7] Respect for Persons requires individuals to be treated as autonomous or independent agents. Those unable to act autonomously should be considered vulnerable populations, including children, prisoners, persons with physical handicaps/mental disabilities, and pregnant women.[8] The informed consent process is vital to protecting human subjects by ensuring that subjects enter into research voluntarily and with complete information.[8] The Beneficence principle assesses the risks and benefits of research protection with the two principles: Do no harm and Maximize benefits and minimize harms.[8] These principles require researchers to secure the well-being of subjects. The Justice principle is related to the selection of research subjects, addressing the question of who should bear the burden of research and who should benefit. An injustice occurs when a benefit is denied without good reason or when there is an unfair burden.[8] The Justice principle prohibits exploiting disadvantaged populations for the benefit of other more advantaged populations. Additionally, the principle prohibits researchers from selecting samples that are easily accessible (college students), in compromised positions (prisoners, those confined to institutions) or those easily manipulated rather than choosing a population directly related to the study. This principle also requires that everyone benefit from research, not just those who are able to afford it.[8] All three principles must be adhered to during every phase of clinical trial design and conduct in order to safeguard participants and preserve research integrity.[9]

Enrolling patients into a clinical trial is clearly an important step in the success of a research protocol. Frequently the inclusion/exclusion criteria make recruitment even more difficult. Demographic characteristics of potential populations also complicate enrollment efforts. Many individuals mention some mistrust about their willingness to be involved in a clinical trial. To counter this issue, financial and other incentives have been more frequently used to recruit subjects into clinical trials. When patients come from disadvantaged or low-income populations, this practice clearly raises questions about coercion, manipulation and concerns about true informed consent. Institutional Review Boards are tasked to review these concerns and have rigorous criteria in which to determine acceptance of the use of financial and other incentives in the conduct of research trials, especially related to minority and underrepresented populations.[6]

Beyond the challenges of patient recruitment exists the issue of participant retention and ensuring that those individuals who enroll successfully complete the study. Low retention rates can impair the accuracy of study results and undermine fiscal and human resources; therefore, emphasis must be placed on maintaining high levels of participation.

It is widely known that special barriers and challenges affect the successful enrollment and retention of study participants in clinical trials targeting minority populations. One way of dealing with these issues is to investigate related challenges, consider action plans or strategies that represent evidence-based research and continue seeking methods for improvement.

In this paper, we report such experiences in a clinical trial that we are currently conducting in an

underserved minority population in the southern United States. A unique approach is that we are utilizing the principles of the socio-ecological model (SEM) to effectively achieve and maintain high participant recruitment and retention rates. Although previous literature[10-12] has described the use of the SEM to promote study recruitment, limited information exists which explores the utility of this model in participant retention, especially, in a minority and socio-economically disadvantaged setting.

Description of the Clinical Trial

This research study is a randomized double-blind controlled clinical trial that tests the efficacy of high-strength (4mg) as compared to lower-strength/ standard of care (0.8mg) folic acid to prevent fetal body and brain size reduction in pregnant women who smoke. Experimental (4mg) and control (0.8mg) groups are assigned (165 pregnant women to each arm). The specific aims of this study are to:

a. Assess folic acid reserves in women who smoke during pregnancy; and
b. Determine whether higher-strength folic acid in combination with smoking cessation programs will prevent reduction in fetal body and brain size among smoking mothers.

We hypothesize that higher-strength folic acid in combination with a smoking cessation program will prevent reduction in fetal body and brain size. This 5-year clinical trial is being implemented within an underserved minority community in Florida, USA and is now in its fifth year. To our knowledge, this is the first human study to determine the utility of higher-strength folic acid in preventing smoking-induced fetal body and brain size reduction (clinicaltrials.gov registration #NCT01248260). Pregnant women are recruited from a community health center affiliated with a local university. Women who receive care at this community health center and deliver at the affiliated hospital are typically of low socioeconomic status. Very few patients have private health insurance and most are either uninsured or covered by Medicaid, the public health insurance program in US that covers the poor and underprivileged members of the society.[13] The racial/ethnic distribution includes 42% blacks, 30% Hispanics, and 28% whites. About 15% of the women at the study site smoke actively during pregnancy without quitting, thus, prenatal smoking is a common addictive behavior in this study population.

This study is approved by the University of South Florida Institutional Review Board and each participant signs an approved informed consent form. Eligible consented women are enrolled ≤20 weeks gestation and screened for smoking habits. Maternal blood is drawn at baseline for assessment of biomarkers including folate, vitamin B12, homocysteine levels, and maternal Methylenetetrahydrofolatereductase (MTHFR) enzyme polymorphism. Women in both study groups are enrolled in a smoking cessation program. Survey instruments are administered to participants during three subsequent antenatal study visits to assess changes in smoking habits, dietary factors, quality of sleep, stress levels and other antenatal psycho-social markers.

All study participants are followed until delivery at which time fetal body and brain growth anthropological measures are collected. Maternal blood is drawn again for assessment of folate biomarkers. Umbilical cord blood is also collected for genetic and epigenetic tests on markers of fetal brain growth and development. Non-smokers are also randomly selected for blood draw to compare baseline folate levels. Non-smokers are not followed past baseline visit. Figure 1 presents the RCT CONSORT flow diagram of the trial.

The Socio-ecological Model as Conceptual Framework

Previous literature has proposed the use of the SEM in examining barriers related specifically to enrollment in clinical trials.[10-12] The SEM provides a very useful theoretical framework for addressing the numerous and varied obstacles in participant recruitment and retention. The SEM[14] suggests that an individual's behavior is integrated in a dynamic network of intrapersonal characteristics, interpersonal processes, institutional factors, community features and public policy. The model assumes that interactions between individuals and their environment are reciprocal, implying that an

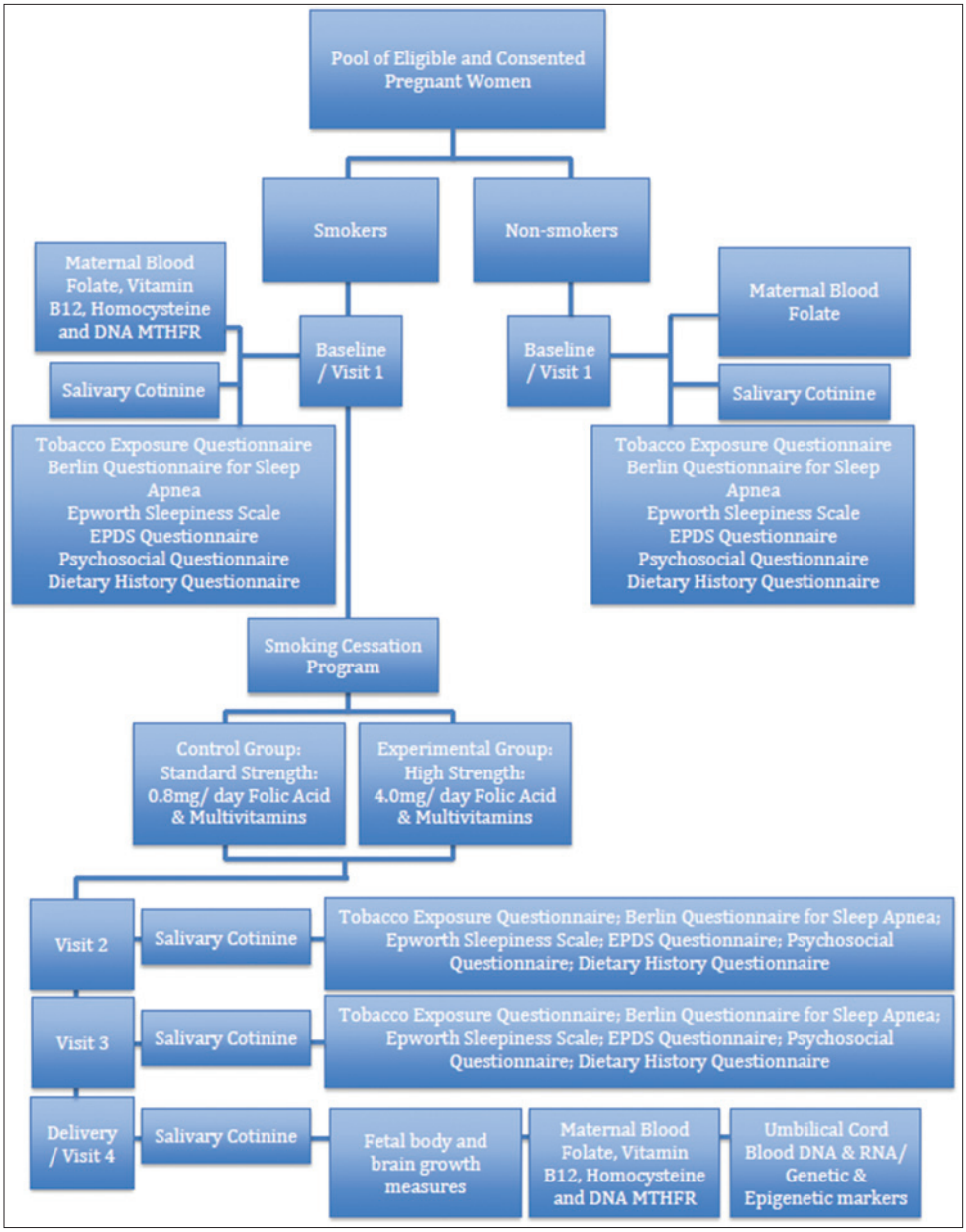

Figure 1. RCT CONSORT Flow Diagram

individual is influenced by his/her environment and the environment is influenced by the individual. It is also assumed that the environment is comprised of several overlapping levels. The intrapersonal level encompasses the research participant's knowledge, awareness, attitudes, beliefs and perceptions. These factors are influenced by the individual's physical and social environments. The participant's family, friends and health care providers comprise important components of the interpersonal level. The healthcare institution's rules, regulations and general attitude toward research shape the institutional level

within the model. Features of the community that may influence participant retention include convenience and acceptance of prenatal care, local cultural attitudes about smoking, the availability of public transportation and safety of the neighborhood. The public policy level is shaped by local, state and federal laws regarding socio-behavioral and biomedical research. The SEM takes into account socio-cultural factors, as well as environmental factors, and their linkages to biologic factors.

In order to effectively examine factors that influence participant recruitment and retention in our socio-behavioral, genetic-epigenetic clinical trial among pregnant smokers, we have adopted the SEM as a functional platform. We will identify the barriers we have encountered in our trial and use their placement within the SEM to identify the reasons for these obstacles (perceived and/or real) and viable solutions. Taking into account all these level-specific influential factors will help ensure our success in assessing the efficacy of higher-strength folic acid in preventing the fetal body and brain growth inhibitory effect of prenatal smoking.

Application of the SEM to Clinical Trials

Swift identification and remediation of issues is critical to the success of any clinical research study. Based on our knowledge of the SEM, we were able to anticipate several areas of concern from the onset. First, we were aware that our study population, because of its nature, may be experiencing higher levels of stress, depression and other markers of psychosocial dysfunction. With this in mind, the trial was designed to collect information on and provide referrals for individuals who suffer from abnormal levels of stress, depression and sleep disturbances (factors found on the intrapersonal level of the SEM). Additionally, we question women about their nutritional intake or access to nutritious food (community level factor). As the trial progresses, each issue we encounter is identified and addressed using the SEM in the following sections and in Figure 2.

Intrapersonal Factors

The intrapersonal level of the SEM is made up of individual knowledge, attitudes, beliefs and perceptions that influence behavior.[15] Fear, distrust, and/or suspicions of research have proven to be substantial barriers to participation in research.[5,6,10] There is the belief among many prospective participants that entering a randomized trial will mean a loss of control because they will not be able to choose their treatment[5] or that clinical research will cause them harm[16] Others fear being treated like "guinea pigs" or distrust of the medical community due to past experiences, particularly in racial and ethnic minority populations.[5,17] Many believe signing the informed consent provides legal protection to physicians or researchers rather than study participants.[18] The National Cancer Institute reports that African Americans are less likely to participate because of knowledge of historical mistreatment of research participants such as the Tuskegee syphilis study.[5,17,19] One study reported that one-third of African-American women avoided participating in clinical trials because they believed that scientists could not be trusted.[20] These intrapersonal characteristics determine the individual's likelihood of participating in the clinical trial.[10] Educating the public and health professionals on human subjects' protection and legislation is essential to eliminating this mistrust and demonstrating how the Tuskegee incident would be prevented today.[17] Health care providers and research staff should communicate safety measures to patients to help build their trust and overcome suspicions.

The target population for the project is comprised of minority socio-economically disadvantaged individuals and a mistrust of research could be a reason for declining to participate. We are aware of these challenges and are developing strategies to limit this as a recruitment barrier. Study staff has held meetings with clinic staff to discuss ways to eliminate mistrust of researchers, particularly among minority patients. Currently, some clinic providers explain the trial to their patients prior to referring them to our study. In order to ease potential suspicions, research staff gives a potential participant time to read through the informed consent document and to discuss with her partner or family. Additionally, trained research staff reviews the consent document section by section with each prospective participant.

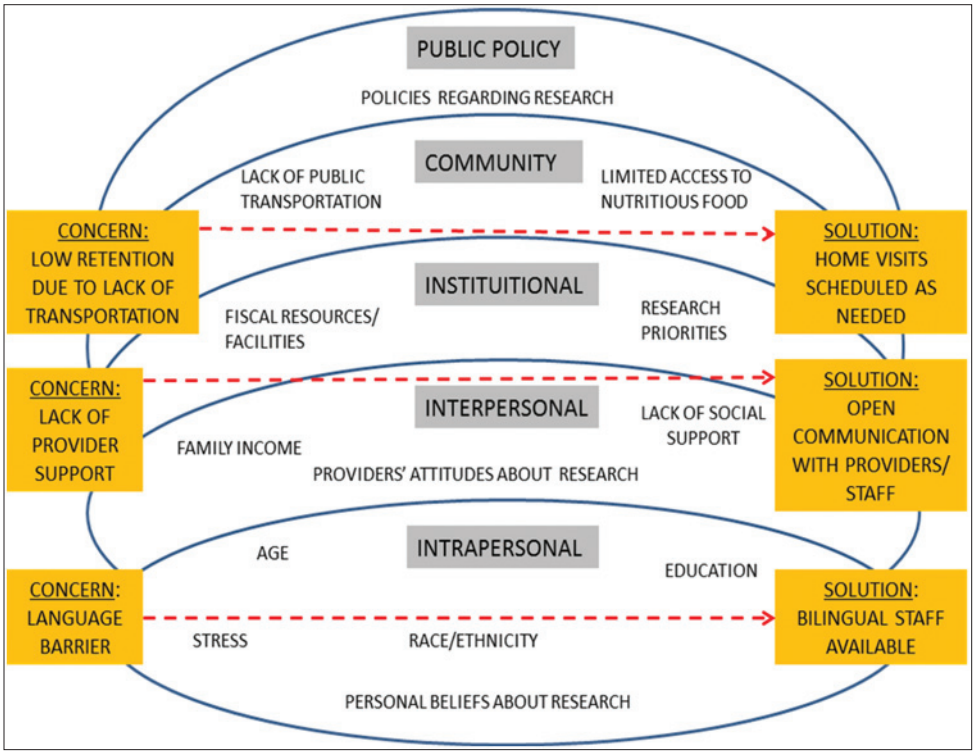

Figure 2. Application of the Socio-Ecological Model (SEM) to enhance participation in a clinical trial

Participants' questions are answered throughout the recruitment process. The research staff is careful to explain fully the following issues: the voluntary nature of the research, its distinction from clinical care, the right to withdraw without penalty at any time, and the steps to be taken to protect confidentiality of information. Research staff also confirms the participant's correct understanding of each of these issues through appropriate questioning. To reduce social and psychological consequences about answering questions on high risk behaviors (smoking) during pregnancy, participants are assured that responses are kept confidential and are for research purposes only.

Language or literacy barriers may also create obstacles to participation[21] which also fall under the intrapersonal level of the SEM. In order to address this issue in our study, only trained research staff is permitted to recruit participants. Study recruiters answer the participants' questions throughout the entire recruitment and enrollment process. The participant's thorough understanding of the informed consent form is confirmed through appropriate questioning. Additionally, two of the study staff members speak Spanish and English, which is extremely useful because of the high population of Spanish-speaking patients at the study site. All study questionnaires and the informed consent documents are available in Spanish and English.

Medication compliance also falls under the intrapersonal level of the SEM. Folic acid/multivitamin compliance has been a concern in the clinical trial. Although the majority of patients have reported taking their folic acid on a regular basis, a few have reported unwelcome side effects such as nausea and/or constipation. Literature has suggested that counseling women to understand that side effects will subside is one way to prevent side effect-related non-compliance.[22] In our trial, we suggest that participants take their multivitamins with food to prevent gastrointestinal discomfort and to increase their water and fiber intake. Such issues should

not be ignored and steps can be taken to reduce noncompliance.

Individuals of various ethnic and racial backgrounds are influenced by cultural views and beliefs. One particular belief that is most common in Latino cultures is that an individual must accept "God's will" and that their health is in God's hands.[23] Individuals who hold this belief may be less likely to take actions to promote their health,[23] such as taking folic acid/multivitamins in a research study. Although we have not investigated individual health belief models and how they impact compliance to medication during pregnancy, we believe understanding the patient's intrapersonal perspective within the SEM framework is a potential solution to medication adherence. A strong point of the study design is that both self-report of dietary folic acid intake as well as biologic blood levels are measured and assessed in the analysis.

Interpersonal Factors

The interpersonal level of the SEM comprises the participant's social network including family, friends, peers, and health care providers. Several sociodemographic factors such as maternal age and household income influence multivitamin use. Provider influence can have a significant impact on patient enrollment. The extent to which the patient trusts her doctor can influence whether she will participate in the study.[24] Patients' unwillingness to defy a physician's wishes can serve as a recruitment barrier.[5] Physicians must recognize these concerns, teach the patient that the decision to participate is entirely that of the patient, not the doctor, and confidently recommend the most suitable studies. Some physicians may feel they are losing control of their patient's care by referring a patient to a clinical trial.[5] Provider attitudes and perceptions, such as mistrust of researchers and provider lack of awareness of the study are the leading barriers that prevent providers from referring or enrolling patients in clinical trials that target minority populations.[25,26] We have encountered many providers at the clinic who seem to have a mistrust of research and do not want to refer their patients to our study. This obstacle was addressed by setting up a formal meeting with the Medical Director and Clinic Manager to discuss our study objectives and open the lines of communication. During the meeting, additional topics of discussion included patient flow, the average wait time for new obstetrical appointments, and the most effective use of the patient's wait time. In addition, due to limited space in the clinic, discussions covered the most ideal days for recruitment particularly, days with the highest numbers of new appointments.

Providers may believe that referring patients to trials will add burden to their work.[5] Educating staff and demonstrating that they will not face additional burden is important, however, this is easier to accomplish in theory than in practice. Prior to initiating recruitment, research staff presented the study objectives to nursing personnel at a clinic staff meeting. Gaining the support of the Medical Director and the Clinic Manager was very instrumental in bridging the gap between research and clinic staff who were initially less cooperative. Study staff provides monthly emails to the Director and Manager about recruitment numbers and/or any important updates. Establishing and maintaining these open lines of communication has provided a strong foundation for recruiting in the clinic.

Institutional Factors

The institutional level of the SEM involves the health care system, policies, and structures working together to assist or hinder the clinical trial. One barrier we have had to overcome at this level includes policies and structures in place within the health care system that influence or limit participation.[15] During the initial phase of participant recruitment, many lessons were learned about the most ideal timing for recruitment. One challenge was to find the best time and place to consent and interview participants that afforded adequate privacy without interrupting clinic flow. For instance, although women spend more time in the waiting room than in the examination room, there is little privacy to complete the interview process in this setting. Research staff quickly discovered that the most ideal opportunity to consent and interview women is following triage when the women are sitting in the examination

room waiting for the provider. The examination room allows for privacy and the window of time is lengthy enough to answer the potential participant's questions regarding the study and to complete the consenting process. Depending on clinic flow, the recruiter is usually able to complete the interview process during this time as well.

Biological specimen collection for research use can be a complicated process and requires detailed protocols. Collection of blood, urine, saliva, and extracted DNA and RNA should be carefully planned prior to research initiation, closely monitored, and handled consistently to guarantee samples will provide maximum value to the study.[27] Most of the challenges related to biological specimen collection fall under the Institutional level of the SEM.

When establishing collaborations with the laboratories, we discovered that the RNA had to be extracted within four hours of draw if collected and transported to the lab in regular EDTA tubes. This proved to be a major institutional barrier when working with a lab that is only open during normal business hours, as women can deliver at all hours of the night and on weekends. This problem was remedied by purchasing PAXgene® blood RNA tubes, which contain an RNA preservative. These tubes are about eight times the cost of regular tubes, but allow the blood to be kept at room temperature for up to three days. Therefore, these tubes are ideal for our study and allow for RNA extraction at a later date. Another institutional challenge relates to appropriate study infrastructure. We have had to put the necessary logistics in place at the hospital. It was challenging to introduce new research staff members into a unit that has limited space. We hired a staff member who spends time daily on the labor and delivery unit. After establishing our presence, the cooperation of the hospital staff has been more forthcoming and is improving with time.

Finally, the transition of the hospital medical record system from paper to an electronic system as well as a change in hospital leadership also falls under the Institutional level. Prior to this change in health information systems, it was difficult to collect the appropriate samples and identify when patients would arrive at the hospital for their delivery. After the transition, the new electronic medical record system has become a continuous link of patient information from the antenatal period through delivery to the postnatal period. This new system has facilitated the conduct of the study by enabling identification of patients at delivery and timely biological specimen collection. Without this cohesion of institutional systems working together, we would not have been able to successfully retain as many patients or collect as many biological samples.

Community Factors

Although we anticipated barriers in recruiting minority participants into the trial, we quickly realized that the true challenge would be retaining the women's interest in participating over multiple study visits. We understood that in addition to providing a small monetary incentive to compensate them for their time, we also had to ensure that their participation did not create an additional burden. With this in mind, study visits are combined with routine prenatal appointments to reduce the scheduling hassles for participants. This effort helps keep our retention rate high and our loss to follow-up rate low. Currently, our loss to follow-up rate is less than 6% and this can be attributed to our understanding of the factors that influence participation in research studies based on the SEM community level.

Another community factor relates to study participants' limited access to nutritious food. Because our study population is comprised of socio-economically disadvantaged individuals, access to nutritious foods is often limited. Folic acid is important for fetal development and the prevention of neural tube defects. Since many women do not obtain the recommended daily intake (RDI) of folic acid, the Food and Drug Administration began folic acid fortification of cereal and other grain products. In spite of this, many women still do not meet the RDI for folic acid. Non-Hispanic Black women and Hispanic women are less likely to meet the RDI, regardless of folate source, than Non-Hispanic white

women. Both arms of the study are likely to be exposed to these sources of dietary folic acid since the study design employs randomization.

Conclusion and Global Health Implications

This paper describes a clinical research study utilizing a population made up primarily of minority, socio-economically disadvantaged individuals. This population is often poorly represented in clinical research studies.[20] Due to the heterogeneous nature of the global population, it is vital to have an equally significant number of participants enrolled in clinical research from different ethnic and racial groups.[28] Additionally, inclusion of underrepresented groups in clinical trials is important because sex, race, and co-morbid conditions could play vital roles in intervention studies, especially those related to response to medications/drugs.[18] As is the case for this study, using different dosage levels of folic acid to prevent fetal body and brain size reduction in pregnant women who smoke is important for a variety of reasons. Certainly, babies born with reduced body and brain development have many challenges early in their lives and can continue into adolescence and adulthood. Secondly, determining more efficacious drug dosages has significant preventive outcomes and financial implications for this and other populations. Finally, folic acid is an inexpensive intervention that has minimal risk and is easily available. It is important to determine patient compliance issues to maximize the likelihood of this population taking folic acid during the entire pregnancy but especially as early as possible after the pregnancy is identified and diagnosed. The population in this study is often seen with poor nutritional behaviors. Providing a folic acid supplement is again an important way to enhance the health of the neonate. With the challenges evident in this population to consider folic acid supplementation, a clear analysis of the challenges and barriers with such an intervention is essential.

Using the SEM as a theoretical framework, we have been able to address many barriers and challenges that could have reduced the effectiveness and utility of our intervention. We have faced barriers but have succeeded in overcoming them through a thorough analysis of the intrapersonal, interpersonal, institutional, and community levels. From this analysis, the implementation strategies have evolved with greater anticipated outcomes in patient adherence to folic acid and to retention in the study. This is important because we continue to have insufficient data about what works and does not especially related to drug efficacy in individuals of various racial and ethnic backgrounds.[29] If sufficient populations of minority subjects are underrepresented in the trial, that subset's information on drug use and efficacy are not valid and therefore, the study may not be generalizable to the entire population.[30] This success is due mostly to an understanding of the usefulness of a theoretical model for structure and problem solving, strong leadership, cohesion across study staff, and excellent insight into the relationship dynamics that exist in the clinical research setting including clinic staff, research personnel and study participants. Our experiences have widespread implications as the SEM approach is adaptable to developed and developing regions. The principles of the model can be used to address challenges related to religious, cultural or political considerations. Effective implementation of this approach has the potential to increase recruitment and retention of hard-to-reach populations who are typically under-represented in clinical trials. With the use of the SEM, we believe we have laid the groundwork for continued success for effectively securing valid and reliable outcomes for the clinical trial research study we currently have underway.

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Key Messages

- Despite the benefits of clinical research, many people approached to participate decline to do so because of deeply rooted myths about research.
- It is vital to have an equally significant number of participants enrolled in clinical research from different ethnic and racial groups.
- Using the SEM as a theoretical framework, we have been able to address many barriers and challenges that could have reduced the effectiveness and utility of our intervention. We have faced barriers but have succeeded in overcoming them through a thorough analysis of the intrapersonal, interpersonal, institutional, and community levels.

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