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Moving targets: The challenges of studying infectious diseases among pregnant women in resource limited settings

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ABSTRACT

Conducting clinical trials to prevent and treat infectious diseases in pregnancy is essential to saving maternal and newborn lives, though it is fraught with challenges. We have been conducting research in malaria treatment and prevention in children and pregnant women in Blantyre, Malawi for over a decade. Here, we review some of the unique challenges that we have faced in leading research studies that with rigor and integrity and maintaining the highest ethical standard. We conclude with concrete strategies to overcome some of the apparent obstacles that frequently focus on building trust through bidirectional communication with local health workers and communities. We also highlight the key role of local and international investigators to advocate for the health of the communities in which they work.

1. Introduction

Most clinical researchers would have had the experience of a disease sharply decreasing in prevalence, or even virtually disappearing, while the disease is under study. The conditions of a clinical trial often alter the natural history of diseases and the prevalence of adverse outcomes. These complicating factors limit the ability to conduct ethical studies that provide generalizable information, especially in resource-limited settings, where the reality of access to health care and disease prevention is often much less than the stated standard of care [1]. In addition, it contributes to the failure to conduct adequately powered studies to detect differences between treatment and control groups because the overall rate of either the disease or adverse outcome of interest decreases significantly due to the conditions of the clinical trial.

The challenges of conducting clinical studies among pregnant women have been well articulated in previous reviews [2,3]. Our review focuses on unique challenges of clinical trials in resource limited settings using illustrative examples; our research group has encountered conducting studies to evaluate strategies to prevent and treat malaria among pregnant women in Malawi. We highlight common issues that would apply to a wide range of diseases. We end the discussion with several key lessons learned from our experiences and strategies that have overcome some of the challenges that we and others have faced. This discussion is not intended to be exhaustive but rather a framework in which to consider and trouble-shoot the unique obstacles.

2. Typical scenario

In clinical trials, to treat or prevent infectious diseases in pregnant women, the study design is typical. Pregnant women at risk of an infectious disease are enrolled at a standardized and often early point in their pregnancy when they are assumed to be uninfected. At baseline, all participants are expected to be at a similar risk of an incident infection over the course of their participation. They are randomized to receive either the intervention or a placebo or standard of care. The primary aim is to measure the effect of the intervention on the incidence of an infection during pregnancy or in the infant or on the cure rate. The additional key aim is often to assess the safety of the intervention by measuring its impact on maternal, perinatal and fetal outcomes.

Prospective participants undergo a screening process to ensure that they meet specified eligibility criteria and to exclude women who may be at increased risk of harm through study participation. In many cases, the women and their pregnancies are scrutinized and followed carefully. Accurate and complete capture of perinatal

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outcomes is often essential to assessing the safety of interventions during pregnancy [4].

3. Study design

3.1. Sample size considerations

Studies are designed based on baseline data, collected through previous studies or public records. The prolonged process from grant writing to start of the study virtually ensures that baseline data will be outdated by the time the new clinical trial begins. This is true for designing clinical trials in all settings as secular and seasonal variations are the hallmark of communicable diseases. In resource limited settings, the added elements of sporadic and unpredictable availability of resources lead to changes in preventive strategies available in the general community. As an example, in our continuous surveillance of malaria prevalence in pregnant women and in communities, we have consistently found that a single bed net campaign may decrease malaria prevalence dramatically for one year and then return to the previous baseline level subsequently (Boudova and Laufer, unpublished data). Public records are also unreliable and inconsistent. Definitions that distinguish stillbirths from miscarriages and growth restriction from preterm birth require accurate antenatal assessment of gestational age, which is rarely available [5].

Another unique characteristic of research in the most resource-limited environments is the disparity between standard of preventive and curative treatment policies and the access that most women have to those treatments [1,6]. As discussed below, investigators are obligated to provide clinical trial participants with, at least, the basic care to which they are entitled. While this obligation is essential, when such services are not available to the population at large, such care alone will likely have an effect on the natural history of a wide range of infectious diseases and also the incidence of adverse perinatal and neonatal outcomes. A significant decrease in baseline rates of these key outcome measures can limit the power of clinical studies. In our studies, the provision of bed nets to prevent malaria is a key element of the antenatal care package, though the local government clinic frequently experience stock outs. Active detection and treatment of anemia, hypertension, urinary tract infections and sexually transmitted diseases that often does not occur in busy public clinics, likely improves the perinatal and infant outcomes among all participants.

3.2. Eligibility criteria

To ensure some uniformity in the study population, gestational age windows are specified in the eligibility criteria [2]. Assessment of gestational age of the pregnancy is typically performed by calculation based on last menstrual period or measurement of the fundal height. Even when implemented correctly, these techniques do not provide consistent results [7–9]. In our experience, women often do not recall their last menstrual period and busy midwives often do not have time to measure the fundal height or do not have measuring tapes. Visual inspection and palpation of the abdomen are used to give a rough estimate of gestational age. For a clinical trial, more precise measurements are required and the use of ultrasound dating is essential. Portable and inexpensive ultrasound machines are now available for use in resource-limited settings [10]. However, this capacity to accurately date pregnancies requires training and supervision as described below.

When participants are expected to be enrolled prior to the third trimester, recruitment may be difficult. Reaching women during the early stages of their pregnancy poses a challenge. There are social concerns about revealing ones pregnancy "too early". Women typically present for their first antenatal visit late in their second or even in their third trimester [11–14], limiting the ability to capture data during early fetal development.

3.3. Follow up

The ability to maintain the follow up schedule through pregnancy has been identified previously as a barrier to obtaining adequate safety data [2]. Follow up fatigue often sets in. The World Health Organization recommends a minimum of four antenatal care visits. For active case detection, administration of interventions and monitoring for adverse events, participants are often asked to attend more antenatal visits than this commonly-accepted minimum. Although, transportation costs are reimbursed for participants at all scheduled visits, increased antenatal visits compete with other obligations for participants as well as the physical fatigue of pregnancy, all contributing to the risk of reduced adherence to follow up schedules over time.

There are local traditions that encourage women to deliver their infants at health facilities located close to their extended families. These customs are essential because family members provide all care for pregnant women and their newborns. Although, we only included women who agreed to deliver their infant at the study designated health center; we found that delivery plans changed over the course of the pregnancy. As the first antenatal visit coincided with the first public statement of the woman's pregnancy, negotiations about details of the delivery, especially, for women who are pregnant for the first time, evolve over the subsequent months.

Changes in participation as a result of adverse events experienced during the study significantly threaten the integrity of the study. We have observed a wide range of responses. Most often, when complications related to pregnancy occur, participants are grateful to the study team members for the medical care, logistical support and advocacy they provide. Research clinicians and nurses are able to help navigate the often complex health system and provide care that is better than what is available through the typical public health infrastructure. However, adverse events, even when clearly unrelated to study intervention, often elicit suspicion and fear. As a result, women who experience complications of pregnancy either choose to discontinue study participation or withdraw due to pressure from family members who attribute the complication to research participation. In these cases, loss to follow up is strongly associated with pregnancy outcomes.

3.4. Detection of baseline illnesses and exclusion criteria

The eligibility criteria, especially, for trials of new interventions that may have unanticipated risks, are often strict. Potential participants undergo extensive evaluation, often well beyond the standard screening offered to women in the antenatal settings, to assess their eligibility for the study. Thus, women who would have underlying illnesses that would otherwise remain undetected at an early stage will be systematically excluded from the clinical trial. This is undoubtedly essential for the protection of the welfare of those who enroll. However, conclusions about safety and efficacy in a real life population are severely limited. Outcomes will be demonstrated in women with or without conditions, which were identified through screening tools that may never be available in routine setting, so a conclusion, for example, that a drug is safe as long as a pregnant women do not have hypertension may not be relevant in the setting where blood pressure is not carefully monitored.

3.5. Capturing endpoints

Deliveries are unpredictable. They occur day and night, though typically more often in the night [15]. This trend has not been