



A review of strategies used to retain participants in clinical research during an infectious disease outbreak: The PREVAIL I Ebola vaccine trial experience

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ARTICLE INFO

Keywords:

Follow-up
Retention
Participant trackers

ABSTRACT

Introduction: This article describes a retrospective review of participant follow-up and retention strategies in the Partnership for Research on the Ebola Virus in Liberia (PREVAIL) I Vaccine Trial. It illustrates and analyzes strategies used to retain participants in an emergency clinical research response vaccine trial conducted during the 2014 Ebola outbreak in Liberia.

Methods: An anecdotal review of participant retention strategies developed and employed during the PREVAIL I vaccine trial.

Results: Though other factors likely contributed to the high retention rate of trial participants, the unique PREVAIL I follow-up process described resulted in an exceptionally high participant retention rate (97.8%) through 12 months of follow-up, increased the ability to obtain meaningful trial results, and provided a platform through which to respond to social issues in an emergency clinical research response setting.

Conclusion: Successful strategies were developed and employed in the PREVAIL I vaccine trial that resulted in extraordinarily high participant retention and follow-up rates during an infectious disease outbreak. This review illustrates that employing host country social mobilization concepts within a modified clinical research management framework is highly correlated to elevated rates of retention and minimal loss to follow-up. These strategies also contributed to increased data quality and enhanced adherence to protocol requirements. The increased ability to respond to social issues such as stigma, job retention and relationship conflicts was an additional and significant benefit of this follow-up methodology.

1. Background

In August 2014, eight months after the initial Ebola cases were identified in Guinea, the World Health Organization (WHO) declared the Ebola outbreak in West Africa a public health emergency of international concern [1]. A robust multilateral response followed from governments, non-governmental organizations, private industry and others as it became clear that the pandemic would grow to an unprecedented scale.

The Liberian Minister of Health (MoH) requested assistance from the United States (US) government in developing an accelerated clinical research program on promising Ebola vaccines and therapeutics. The US Department of Health and Human Services accepted the request, and in November 2015, The Liberia-US Joint Clinical Research Program, known as Partnership for Clinical Research on Ebola Virus in

Liberia (PREVAIL), was formed. A team organized by the Division of Clinical Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, U.S. Department of Health and Human Services worked collaboratively with the Liberian Ministry of Health and Liberian clinical research staff to establish the capacity, protocols, ethical approvals, national and international consensus, and other research components enabling the initiation of a trial of two leading Ebola vaccine candidates 4 months later.

2. Introduction

Infectious disease outbreaks are increasing in our progressively interconnected global environment. During an infectious disease outbreak, the primary focus is, understandably, on treating those who are sick and preventing transmission of infection to their contacts.

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However, by simultaneously conducting well-designed clinical trials, clinical researchers can provide the global public health community clear evidence on the safety and efficacy of candidate treatments, vaccines, and other preventive measures and ultimately offer the best opportunity to lessen the severity of disease outbreaks and save lives both during the outbreak and afterwards.

Clinical research is a relatively new pursuit in the context of outbreak settings. Traditionally, during an outbreak, available resources and human capital have been largely concentrated on epidemiology, contact tracing, and clinical management of affected individuals. However, it has become increasingly evident that rigorous clinical research to characterize novel emerging infectious diseases, such as Ebola, influenza H1N1 pdm09, and Zika, is a critical element to informing effective response efforts and developing medical countermeasures to end outbreaks and prevent future ones.

It was of critical importance to employ local Liberians as integral partners in a clinical research response in this setting. Knowledge regarding social mobilization concepts, particularly in a country still reeling from civil disruption and curtailment of civil liberties, was paramount. The Liberian team gave counsel on many facets of the clinical research management process to include engaging community leaders in problem-solving and using continuous bidirectional dialogue with clinical research volunteers by Social Mobilization Committee staff with various community stakeholders.

This paper outlines trial participant retention strategies employed in an Ebola vaccine trial conducted during an infectious disease outbreak in a resource-poor, population-dense setting in urban Liberia.

3. The trial

The trial, titled “A Phase II/III Trial to Evaluate the Safety and Efficacy of the ChAd3 and the rVSVΔG-ZEBOV Investigational Ebola Vaccines in Liberia,” was designed to test two vaccine candidates and a placebo for safety and the prevention of EVD over a one-year period. A Phase 2 sub study was embedded to evaluate safety and immunogenicity of the vaccine candidates. The trial was launched on February 2, 2015. As Ebola cases declined in Liberia in the ensuing months, the Phase 3 component was deemed not feasible. Original plans for the expanded trial were to recruit 28,000 participants from several sites, starting at Redemption Hospital in Monrovia, Liberia. When the Phase 3 component was eliminated, recruitment was restricted to enrollment of a smaller number of participants only at the Redemption site.

4. The timeline

Inclusion criteria for this trial included testing positive for EVD. Therefore, a rapid response was required to optimize trial results. As depicted in Fig. 1, Liberia and the United States agreed to a clinical research partnership in October of 2014. PREVAIL commenced recruitment at Redemption Hospital in February of 2015.

5. The setting

The vaccine trial was conducted at Redemption Hospital in New Kru Town (NKT), a densely populated community of Monrovia, Liberia and one of the hardest hit by Ebola. According to the Chairperson, District 6, New Kru Town [2], New Kru Town has a population of 82,696 with 10,200 dwelling structures. Redemption Hospital is a no-cost, government-subsidized medical facility and was chosen because of its large population base, a willingness to partner in clinical research, and its high-performing clinical staff. When the PREVAIL I trial began, Redemption was closed to the community because of the general fear of Ebola and the deaths of healthcare workers in the facility resulting from Ebola infection. Redemption Hospital clinical staff had no previous experience with clinical research.

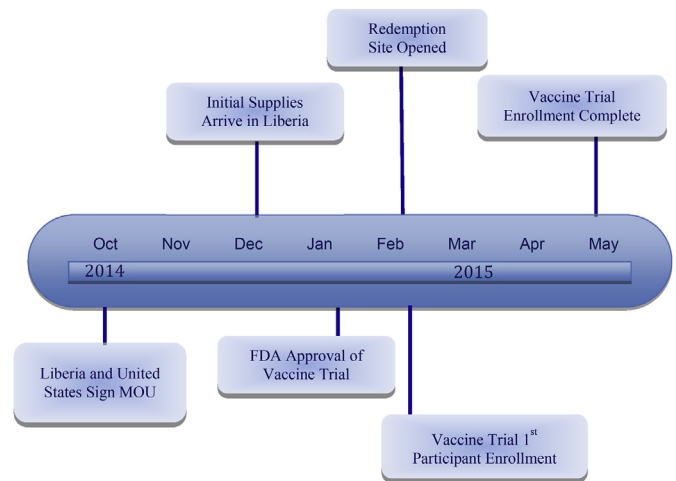


Fig. 1. Evolution of Ebola response, PREVAIL.

Adding to these complexities, the NKT community is characterized by:

- No official street names and home addresses
- High rates of poverty
- Dense population
- High mobility
- Inherent distrust of the Liberian government, medical science, and clinical research trials

6. The myths and the challenges

There were several community myths surrounding Ebola, including those listed in Table 1, which was generated by the PREVAIL SMC team. Reinforcing the validity of one of these myths articulated below, Idoko, et al. noted “... in certain parts of West Africa blood is considered sacred and children are thought to be made ill by blood sampling.” [3].

The trial team recognized that conducting a vaccine trial under these circumstances would be extremely challenging and require a great deal of support and input from social mobilization experts in Liberia. Educational backgrounds of PREVAIL SMC experts include sociology, biology, and epidemiology. Professional experiences include mobilizing communities, providing health promotion education, case investigation, and contact tracing. The U.S. members of this team added clinical research education and experience to the team skillset. An extremely robust and culturally confident team was engaged in PREVAIL to address social fears and stigma. Building trust would be critical, as noted in Hurd et al., “Trust is the cornerstone of clinical trial recruitment and retention.” [4].

The logistical setting in which PREVAIL I was conducted posed a significant challenge. Davis et al. touted a comprehensive database as an effective method of retention and noted, “In addition to participants' mailing address and phone contact numbers, the names, addresses and phone numbers of family members, neighbors, friends, information on the participant's birth date, occupation, and social security and driver's license numbers, should be noted.” [5]. In New Kru Town, there are no street addresses, limited numbers of cell phone users, no home phones, and minimal birth information or identification of any sort. The PREVAIL I trial team needed to be creative and work intimately with their PREVAIL social mobilization counterparts to surmount these issues.

7. Methods

This is an anecdotal review of participant retention strategies developed and employed during the PREVAIL I vaccine trial. Due to the urgent nature of initiating this vaccine clinical trial during the

Table 1
Myths about Ebola, vaccines, and clinical research prevalent in the community in Monrovia, Liberia where the PREVAIL I Ebola vaccine trial was conducted.

Ebola-Related Myths	Vaccine-Related Myths
Ebola is a man-made virus	Ebola vaccines were used to transmit Ebola to more Africans
Ebola was brought to West Africa by Westerners to make money	Ebola vaccine trials were scams invented to infect Africans with the end aim of reducing the African population
Ebola was a conspiracy by the Liberian government to receive funds from the international community	Plasma collected from participants was used for commercial purposes
Health workers were the ones responsible for spreading Ebola	Clinic or hospital visitors would be given an injection meant to accelerate death
Health workers were using Ebola to collect organs and blood	Vaccine trial participants would contract Ebola during the rainy season
Those who drink alcohol are immune from Ebola	The vaccine trial was just a money-making scheme for government, NGOs, and pharmaceutical companies
Ebola normally spreads during the rainy season	Vaccines will kill participants during the rainy season
The Ebola virus can be eliminated by taking a saltwater bath	Participants will experience sudden deaths after six months
Ebola is a death sentence—nobody survives Ebola	The vaccine will turn participants into monsters
Ebola can be cured by traditional herbs alone	The vaccine is made for animals and not human beings

outbreak, the study team was not able to conduct a controlled study of these procedures. This review explores the successful methods employed to track and retain participants in the PREVAIL I clinical research vaccine trial.

In addition to engaging social mobilization experts, other retention strategies used included creating an identity/brand so that participants and community could quickly identify the trial. This included creating a logo and naming the project PREVAIL – Partnership for Research on Ebola Vaccines in Liberia. This strategy was extremely successful and has resulted in being able to readily implement additional studies as the communities can easily identify what it means to participate in a PREVAIL trial.

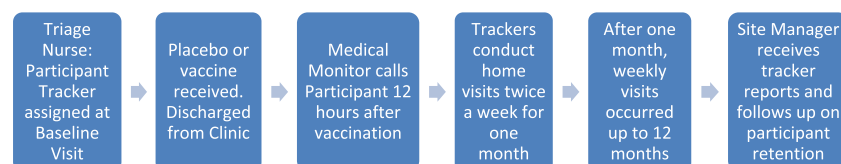
Ensuring optimal participant comprehension of the research trial by developing high-quality information and consent materials was an added retention strategy. Abshire et al. notes that in studies with high retention rates, it often takes time to explain the trial requirements, which include the benefits and risks [6]. Information sessions were conducted for PREVAIL I potential candidates to explain the trial requirements, risks, benefits, and compensation. These sessions lasted 45 min to 1 h depending on the number of questions asked. During these sessions, the trial information was presented by trained Liberians in local dialects, thereby eliminating potential ethnic distrust and reducing misunderstandings. Flipbooks were created with clear illustrations and guidance related to the trial for added visual comprehension. Private informed consent sessions were conducted after the main information sessions to inform participants and allow them to ask additional questions confidentially. This strategy, coupled with community information sessions by the SMC team, resulted in increased knowledge that participants used to make an informed decision to enter the trial, thus facilitating higher retention.

8. The participants

The trial enrolled a total of 1500 participants, most of whom were from the 25 communities within NKT, between February 2- April 30, 2015. Of the 1500, 549 (36.6%) were females. Ages ranged from 18 to 90 years old (median 30 years).

9. The retention and follow-up procedures

Similar to conventional clinical research trials, the Redemption



Hospital clinical site management team consisted of nurses, physicians, phlebotomists, and laboratory technicians. Particularly in an outbreak situation, it is critical to recruit participants as quickly as possible and to retain as many of those recruited as possible. Focusing on the retention angle, a great deal of emphasis was placed on embracing cultural norms to increase the ability of tracking participants. Thus, the Liberian SMC team was instrumental in leading the effort to provide counsel in this area. Many clinical team role functions were supplemented to include social mobilization efforts. This can be evidenced by the role of the PREVAIL nurses. The nurses reinforced the messages given by the SMC team in the various communities in which participants resided. Additionally, participants often reported rumors and perceptions of the community dwellers regarding the trial to follow-up nurses, triage nurses, and medical monitors. Several participants mentioned how they were being stigmatized by some members of the community. Nurses and medical monitors took the opportunity at those times to reinforce messages relayed in the community by the SMC team. This action not only supplemented the efforts of the SMC team, SMC but also helped to alleviate participant fear and doubt.

Participant follow-up visits were scheduled at 1 week, 1 month, and 2 months post-randomization, and every 2 months thereafter through 12 months. Fig. 2 illustrates the clinic participant flow:

10. The participant trackers

Emulating the contact tracers concept used by the Liberian Ministry of Health during the Ebola outbreak to track close contacts of persons who had contracted EVD, the PREVAIL I clinical research team developed a participant follow-up system in which 25 Liberians living in the New Kru Town communities were hired as participant trackers. Each trial participant was assigned to one participant tracker. The trackers worked in communities in which they live and thus were familiar with the local culture and population. They possessed an extensive knowledge of the geographic area, as well as the various community leaders and residents. Their primary role was to follow up with the participants in their community to ensure any medical issues such as vaccination reaction were reported, to remind them of their next clinic visit, and to survey for potential adverse social or community perceptions regarding the trial. Additionally, trackers were trained in infectious disease control procedures because they were working in an outbreak situation.

There are several anecdotes illustrating the creativity of this follow-

Fig. 2. Participant Flow Process in PREVAIL I Ebola vaccine trial.

up method including:

1. At the baseline visit, participants would give their full family name. The trackers quickly realized that communities often only know residents by nicknames (e.g. “Playboy” or “Ma Tete”). As a result, the trackers suggested the trial team also gather at baseline any nicknames by which the participants were known in their communities. This allowed for quicker and more effective follow-up.
2. As mentioned previously, there are no street addresses in New Kru Town. Trackers were assigned to the community in which they live as they possessed intimate knowledge of their community. At the baseline visit, the tracker would ask the participant to describe the area in which he/she lived. Having familiarity with the neighborhood allowed the trackers to know and find that location.
3. Many people in Monrovia are extremely mobile and do not reside from day to day in the place they call “home.” The trackers had to talk with family/friends to discover where the participant might be located.
4. Several different strategies were needed in case the participant did not have a cell phone or access to a telephone. If a group of participants came in together and knew each other, one phone contact was collected to cover all in that respective group. Trackers would call the lead participant and he/she would ensure contact was made with other members of the group. In other situations, the phone number of a community store was given, and the person answering the phone would find the participant.

During visits with participants, the trackers interviewed them for medical symptoms or problems. This included whether the participant was hospitalized, had any social or personal issues, and what community perception was regarding the trial. After the visits with participants, the trackers reported this information to the site manager, the medical monitor, and the SMC team.

The trackers obtained information initially by means of oral conversation. A form was later developed to aid in data collection (Fig. 3).

11. Results

The PREVAIL I clinical research team achieved an overall follow-up visit rate of 97.8% (See Table 2) through 12 months, and nearly all participants attending their visits had their blood drawn for immunogenicity testing (99.9%). The design for PREVAIL I assumed a loss to follow-up rate of 1% per month. With this assumption, we would expect to have lost approximately 160 of the 1500 participants. The PREVAIL I follow-up exceeded this by approximately 120 participants.

Additionally, the participant trackers accounted for 374 participant medical symptoms uncovered (in 24.9% of the trial population) and exposed twelve social-related issues that required intervention (in 0.8% of the trial population). Additionally, community perception anecdotes were collected allowing for PREVAIL I SMC intervention. Tracker follow-up also accounted for 35 hospital admissions.

In their article, Rachlis et al. [7] described reasons for disengaging from clinical care in western Kenya that included:

1. Felt well so didn't need care
2. Transport was too difficult or expensive
3. Work or need for money interfered with picking up medicine

The PREVAIL I participant trackers addressed all three of these reasons by:

1. Visiting participants at their homes to see how they felt. It is believed that participants were more willing to share medical issues during a home visit by a community member.
2. Using a provided transportation allowance to visit the participants.
3. Scheduling visits at times convenient to the participants, allowing

them to remain actively employed.

12. Discussion

Though other factors were likely influential, the PREVAIL I retention and follow-up procedures described contributed to extraordinarily successful participant retention, less-than-expected losses to follow-up, increased data quality, enhanced adherence to protocol requirements, and enhanced attention to social issues.

However, it must also be mentioned that participant compensation for inconvenience was given and may be a contributing factor to retention. The baseline visit compensation was \$40.00, follow-up blood draw visit was \$20.00, and the close-out visit was \$150.00. The Liberian trial team assigned these dollar amounts and felt this was appropriate for this trial in this setting.

We believe a strong correlation exists between personal contacts and successful clinical trial outcomes. In their research, Senturia et al. conclude, “Face-to-face may have contributed to participants' investment in the project and facilitated collection of information on alternate contacts, which we found to be significantly related to the likelihood of complete follow-up.” [8].

Conducting high-quality research (i. e., low loss to follow-up, high-quality data, attention to adverse events, etc.) in an outbreak situation can lead to an increased ability to identify viable vaccines and treatments while providing the global health community with clear data on best approaches for responding to emerging infectious diseases. In addition, conducting high-quality clinical research could result in an increase in financial and educational opportunities. For example, Liberia could receive additional clinical research opportunities from outside funding such as grants or participation in pharmaceutical trials, thus contributing to global health knowledge related to Ebola and other diseases, as well as providing essential information for outbreak procedures in other settings.

13. Limitations

There were several limitations to this research. The results may not be generalizable because of the urgency of the situation and the intense commitment of the community to finding a solution to a lethal outbreak wreaking havoc in their country. It must also be noted that participants were given compensation at each visit to defray transportation and inconvenience costs, and this likely contributed to the high retention rates.

Participant trackers in Liberia received an appropriate salary in this setting as well (the trackers monthly salary was \$575). However, paying trackers in a more developed country setting might not be cost effective.

14. Conclusions

We believe the extremely high rate of participant retention and trial adherence in the setting of the PREVAIL I Ebola vaccine trial was largely the result of the specific creative participant follow-up strategies employed, including:

- PREVAIL branding
- Comprehensive, culturally sensitive, visual informed consent
- Traditional clinical research team roles, such as triage nurse, site manager and medical monitor, modified to include local and cultural retention strategies
- Utilization of participant trackers

The trial data collected illustrate an extremely high participant retention rate, particularly for this research-naïve setting, that facilitated the optimized capture of trial results, including adverse events. The increased ability to respond to social concerns of participants—such as



Liberia – US Joint Clinical Research Partnership

Participants Tracking Form

Participant PID: _____ Community: _____

Have you experienced any side effects? YES NO

If yes, please specify: _____

When did this start? _____

Have you taken any medication? YES NO

If yes, please specify: _____

Have you experienced any form of stigma / discrimination? YES NO

From:

Family Members Friends Neighbors Community

What are they saying? _____

Are you affected by what people are saying? YES NO

How? _____

Community Rumors: _____

Participant Signature: _____ Participant Cell #: _____

Form Completed by: _____ Date: _____
TRACKER

Approved by: _____ Date: _____
SUPERVISOR

Fig. 3. Prevail 1 participants tracking form.

Table 2
Trial Visit Attendance for PREVAIL I Ebola vaccine trial.

Trial visit	# expected	# attended	%	Sample collected	%
Week- 1	1500	1487	99.1	1487	100%
Month – 1	1499	1477	98.5%	1476	99.9%
Month-2	1496	1460	97.6%	–	–
Month-4	1495	1455	97.3	–	–
Month-6	1494	1459	97.7%	1457	99.9%
Month-8	1491	1444	96.8	–	–
Month-10	1488	1436	96.4%	–	–
Month-12	1488	1463	98.3	1460	99.8
Over all	11951	11681	97.77%	5880	99.9%

stigma, job retention and relationship conflicts—was an additional significant benefit of this intensive follow-up methodology. This analysis underscores the criticality of community involvement in clinical research efforts.

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