

Design of Clinical Studies of Spermicides for Prophylaxis Against Sexually Transmitted Diseases

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The current concern with acquired immune deficiency syndrome (AIDS) and other sexually transmitted diseases (STDs) has focused attention on prophylactic measures that individuals can take to reduce their risk of becoming infected. Among these measures is the use of vaginal spermicides. None of these products is approved by the U.S. Food and Drug Administration for prophylaxis, and no such use is suggested in the product labeling. Indeed, laboratory and clinical evidence suggests that spermicides provide some protection, but the evidence is not compelling, and the degree of protection afforded by regular use remains unquantified [1-7].

The need for effective prophylactic agents has forced the clinical community to evaluate potentially effective agents in cultural and social settings that have not been used traditionally for drug evaluations. Specifically, measuring the protective effect that a drug or device may have against STDs requires study in a population among whom STDs are relatively prevalent, for example, prostitutes. Otherwise, an unusually large number of study participants and an unacceptably long time are required to complete each study. Unfortunately, individuals who practice behaviors that put them at risk for STDs often do not lead lifestyles that are conducive to participation

in a regimented clinical trial [8]. Too often, problems are encountered with inconsistent product use, irregular and untimely return visits to the clinic, and unreliability of information provided by the study subjects. These obstacles are rarer in studies involving curative treatments for STDs, since such subjects are highly motivated to cooperate with clinic requests. It is the study of prophylactic agents, in which uninfected individuals participate, that these problems characterize.

The present work discusses the experience of Family Health International (FHI) in conducting four clinical trials—one each in Costa Rica and the Dominican Republic and two in Colombia—of spermicides and other compounds for prophylaxis among women at high risk for STDs. Because FHI had limited prior experience with this type of population, initial studies of product acceptability were conducted to gain insight into product preferences and to develop strategies that would maximize the chance for success of a clinical study. The present work focuses on the difficulties encountered in these studies and the problems and possible solutions that can arise with the study design, the subject population, and the clinic and subject follow-up and compliance.

STUDY DESIGN

Great care and attention to detail must be given to research protocol development. As with all good clinical trials, the clinical investigator, and perhaps the staff, should review the protocol before it is finalized to ensure that the requirements, procedures, and data collection forms are logical and clear. Several aspects of the study design, however, require particular attention for studies involving subjects at high risk for STDs.

The two most troublesome aspects of these studies are the lack of compliance with or inconsistency of product use, and the unpredictability of subjects in returning for follow-up evaluations. The first problem largely reflects the convenience and acceptability of the study product. The second, in part, relates to the number and frequency of required return visits to the clinic. Frequent follow-up visits hinder the cooperation of study subjects, but too-infrequent visits make it difficult to estimate the date of infection. Regardless of the follow-up scheme chosen, a balance must be struck that achieves high compliance and follow-up rates while maintaining a follow-up schedule that allows a reasonable estimate of date of infection. Deterioration in the rates of follow-up and compliance is usually more severe in long-term studies. Because of this and other factors in the

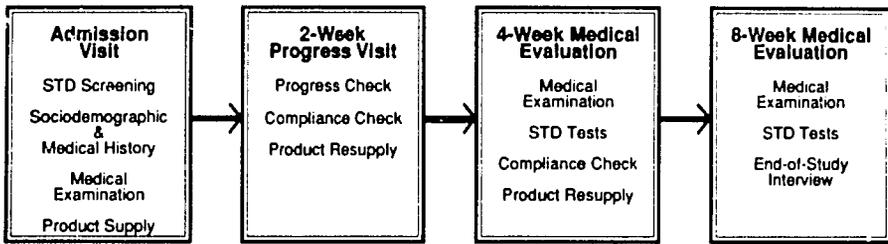


Fig. 1. Suggested scheme for clinical trials involving high-risk subjects at STD clinics.

participant's lifestyle that are discussed below, study participation for each subject should be minimal in length. Although situations differ, FHI has found that 8 weeks of participation are optimal. Figure 1 outlines one scheme for the frequency and activities of follow-up visits.

High-risk subjects frequently fail to return to the clinic for their scheduled follow-up visit. The protocol must include policies to deal with these situations and to define when to discontinue a patient from the study due to loss to follow-up. In our current clinical trials, FHI provides a 4-day grace period within which a subject may return for a follow-up visit and still be retained in the study.

Since many STD clinics are understaffed, the complexity of protocols involving high-risk subjects requires particular attention. In an early clinical trial in Costa Rica, the protocol required that subjects who became infected with an STD be discontinued from the study, cured, and then reentered to complete the full duration of product use. In addition, the protocol stipulated many more laboratory tests than were required to measure product efficacy and ensure the subject's general health. These facets of the study design created administrative and record-keeping difficulties that hindered completion of the study.

POPULATION

Our study definition of an individual at high risk for an STD is one who has had at least one clinically proved and verifiable STD within the past 12 months and also has had two or more sexual partners in the past 30 days. Most individuals recruited at STD clinics, particularly where FHI studies were implemented, exceeded these minimum requirements. Once these criteria have been met, the most critical elements about the study population are lifestyle, attitude, and reliability.

TABLE 1. Interim Data on Selected Sociodemographic Characteristics of 195 High-Risk Women Participating in a 4-Week Trial of Spermicides in Bogota and Ibague, Colombia, 1988

	Mean	Standard Deviation
Age (years)	29.2	5.4
Education (years)	5.3	2.9
Parity	2.1	1.4
Self-reported frequency of intercourse per week in the three months prior to study	14.5	10.6

Table 1 presents sociodemographic characteristics for the women participating in a 4-week trial in Bogota and Ibague, Colombia. These women on average were 29 years of age, had completed about 5 years of schooling, and had borne two children. The women reported frequent sexual activity, averaging over 14 acts of intercourse per week in the 3 months prior to their admission to the study.

When considering the appropriateness of a clinic as a site for any clinical trial, it is obvious that the clinic must have a sufficiently large pool of clients with the disease or diseases to be studied. From this pool, the most cooperative, reliable subjects must be identified. These subjects must also be willing to use the product and return to the clinic once enrolled in the study.

In trials involving individuals at high risk for STDs, the lifestyles and cultural habits of the subjects are of great importance. Many of the women make their livelihood from prostitution and lead a transient lifestyle in which sexual practices are characterized by frequent, sometimes hurried sexual intercourse and a willingness to meet customer demands. These women generally are reluctant to use products that are time-consuming to apply, messy, or otherwise offensive to them or their sexual partners. In addition, reusable applicators, if provided, are not always cleaned between use. In our study in Costa Rica, a cream containing a nonspermicidal, antifungal formulation was applied intravaginally just prior to intercourse by means of a reusable applicator that was filled halfway from a tube of medication. This cumbersome, time-consuming process was believed to have contributed to inconsistent product use. In another example, approximately one in seven women in our study in Bogota reported that their partners generally did not like the spermicidal foam they were using. In the Dominican Republic, a few complaints were made of

excessive vaginal wetness by users of liquid-filled gelatin capsules and of dysuria by foam users. Although the extent to which these factors contributed to inconsistent product use is unknown, some women reported these reasons for nonuse.

The cultural and legal setting of the study site also affects the regularity of follow-up visits to the clinic. In Colombia, where prostitution is unofficially allowed, enforced guidelines require women to report monthly to a clinic to ensure the absence of STDs. In both study clinics in Colombia, follow-up visits were missed infrequently. In the Dominican Republic and Costa Rica, on the other hand, the lack of an enforced contact system contributed to greater difficulties in getting women to return to the clinic. In Costa Rica, frequent migration of the women to rural areas to meet farm workers also contributed to many missed clinic appointments and a high loss to follow-up rate. Thus follow-up rates are higher in settings where the subjects are accustomed to returning to the clinic on a regular basis. The rates can be further enhanced by scheduling follow-up visits that coincide with scheduled nonstudy visits.

STUDY CLINIC

A well equipped facility that is run by an organized, dedicated staff optimizes the success of any clinical trial. Unfortunately, many STD clinics have the lowest priority when government funds are allocated. A facility may be outdated, a clinic housed in inadequate quarters, and staff greatly overworked or undertrained or both. These conditions can damage any clinical trial, but they especially affect a trial that involves individuals at high risk for STDs and that must carefully recruit reliable subjects and give them extra attention during their participation.

FHI has encountered two other problems in clinic studies: the overcommitment of the principal investigator to other obligations and the failure of the diagnostic laboratory to complete the required tests in a timely manner. The first problem can be overcome somewhat by delegating duties to responsible support staff. The second is troublesome because it slows both the admission of subjects into the study and processing of study data. In Costa Rica, the FHI experience was hampered by an overburdened diagnostic laboratory. In addition, the laboratory director worked in a department different from that of the principal investigator and was not obligated to the study. In Zogota, most laboratory tests were done on the clinic premises, and the remaining tests were sent to an efficient laboratory that responded to the clinic's needs. It is important, therefore, to

TABLE 2. Interim Data on Nonoxynol-9 Gel and Foam Product Use and Satisfaction Among 150 High-Risk Women Participating in a 4-Week Trial of Spermicides in Bogota and Ibague, Colombia, 1988

	4-Week visit
Median (range) of biweekly frequency of intercourse	19.0 (0-198)
Median (range) of biweekly number of different sexual partners	13.8 (0-98)
Regularity of product use (% women)	
Always	54.3
Frequent	34.4
Occasional	4.6
Not used	6.6
Product acceptability (% women)	
Very favorable	66.7
Favorable	22.0
Unfavorable	6.0
Very unfavorable	3.3
No response	2.0

consider not only the investigator, the staff, and the facilities but also the competence of collaborating centers and their relationship with the investigator.

COMPLIANCE WITH PRODUCT USE AND REGULARITY OF FOLLOW-UP VISITS

The success of trials in high-risk populations using prophylactic agents depends in part on a good relationship between the investigator or other members of the clinic staff and the study participants. A good relationship optimizes subject compliance and the subjects' willingness to return to the clinic for follow-up visits. The FHI studies in Colombia were successful because almost 90% of the eligible subjects reported for follow-up visits and completed the study using either a nonoxynol-9 gel or foam; by the end of the study, almost 90% reported using these assigned products frequently or always (Table 2). These investigators and their staff established an excellent rapport with their clients because of their personalities and the clinics' philosophy and mission, and this rapport contributed to the high compliance and follow-up rates. The clinics not only provided exam-

**FAMILY HEALTH INTERNATIONAL
DIARY**

Center Number:

 1-4 FHI Admission form number:

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 13-18

Study Number:

 5-8 Date of last visit:

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 day

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 month

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 year 19-24

Patient Order Number:

 9-12 Product: _____

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 25-28

	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	
Day of the Week																						
Calendar Month:																						
Calendar Day																						
Number of Coital Acts:																						5
Number of times partner used condom:																						6
Number of times product not used:																						7
Bleeding/spotting: 0) no 1) yes																						8
	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	80

PLEASE RETURN COMPLETED FORM TO CLINIC DOCTOR.

Fig. 2. Coital log used in clinical trials of spermicides with high-risk subjects at STD clinics.

inations, diagnostic tests, and treatment for STDs but also contraceptives, counseling, and education on reproductive health issues

The consistency and diligence of spermicide use by study subjects are of paramount importance for estimating the clinical efficacy of these products against STDs. With many medications, failure of subjects to comply with the dosing schedule can be uncovered by periodic analysis of blood or urine samples. With the use of vaginal spermicides or other barrier contraceptives, this detection is not possible. FHI often requests that subjects participating in clinical studies of barrier contraceptives complete coital logs (Fig. 2). Although diaries initially were developed to indicate only sexual activity, they evolved into documents that indicate the consistency of product and condom use. The coital logs are an important means of measuring subject compliance, and the candid completion of these documents helps establish the reliability of the follow-up data. For this reason, FHI instructs the clinic to emphasize to the subjects the importance of accurate, truthful logs rather than absolute compliance to product use. It is unreasonable to expect all women to use their assigned product at every act of sexual intercourse, and badgering the subjects to do so is counterproductive. For these women, the threat of being

TABLE 3. Frequency of Spermicide Use Among High-Risk Women Participating in a 4-Week Trial in Bogota, Colombia, 1988

Frequency of use	Percent of women	
	2-Week visit (n = 87)	4-Week visit (n = 78)
Always	30	45
Frequent	43	45
Occasional	23	5
Not used	5	5

dropped from the study if they do not use the study products consistently is, essentially, an invitation to falsify the coital logs. In our earliest study in Costa Rica, many coital logs were believed to have been completed falsely for this reason. On the other hand, under-emphasizing consistent use is dangerous as well. In the Bogota study, the frequency of use improved during the second half of the subjects' participation mainly because the importance of consistent product use was explained more fully during the subjects' return visit (Table 3).

CONCLUSIONS

The issues raised throughout this chapter, summarized in Figure 3, all contribute to the success of a clinical trial with individuals at high risk for STDs. These issues involve five major considerations.

- 1 The subjects' lifestyle and culture must be conducive to the use of the study product and demands of a clinical trial.
- 2 The impositions of study participation upon the subjects must be kept to a minimum.
- 3 The clinic must have a good rapport with its clients.
- 4 The principal investigator and clinic staff must be dedicated to the project.
- 5 The clinic must be adequately staffed and equipped and have good access to diagnostic testing.

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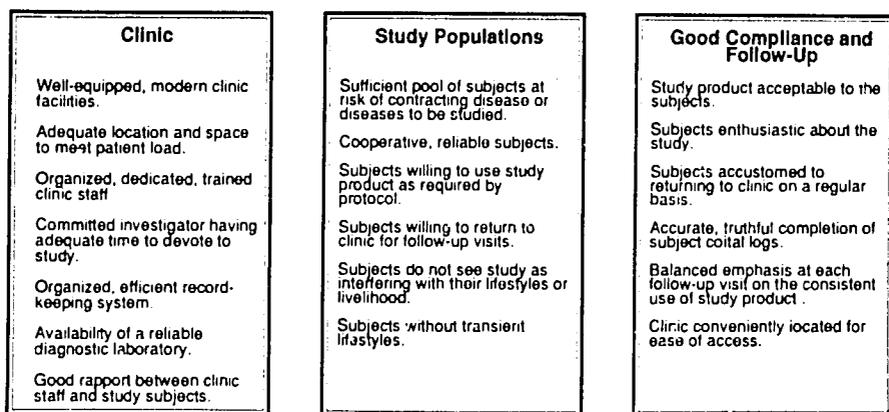


Fig. 3. Characteristics of a model STD study clinic and its population and the factors that influence subject compliance and follow-up.

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DISCUSSION

DR. JOHNSON: One of the problems we have had in practice using nonoxynol-9 in our partner study (and Dr. Cameron has just said he had a similar experience) is that a lot of the women complained of candidiasis, which in itself caused irritation and inflammation. There is some concern about whether this is a sensible product to be advising for people who are at very high risk of HIV transmission.

DR. FOLDESY: Well, nonoxynol-9 is a surfactant, as Dr. Chantler mentioned earlier, and it can cause irritation. I think that the irritation is going to vary with the individual. From the data that I have seen, it seems that just about as many men as women will experience local irritation. Obviously, if you use it more often, say, 10 times a day rather than once a week, you are more likely to experience irritation. I think that in regular use, i.e., a few times a week, the percentage of people who complain of irritation seems to be rather low, maybe in the area of 2-3%.

DR. JOHNSON: My question was, should we be recommending this for people or not? There could be a potentially deleterious effect, with the product causing irritation and abrasion of the vaginal mucosa that could facilitate HIV transmission.

DR. FOLDESY: I think that is a very important consideration and is related to the earlier discussion today. In my mind, the jury is still out on the question of spermicides. There are data to suggest that there is some protective effect, but they are not compelling data.

DR. HEYMANN: I have seen considerable monilial vulvitis from nonoxynol-9-impregnated sponges, but these cases were in women in Nairobi working as prostitutes who put a sponge in all day, every day. It might be a dose-related phenomenon, and may or may not be related to sponge use in other settings.

I would like to ask about attempting to establish a cohort of women to study for incident STDs. Is there a representative community spokesperson who could act as an intermediary between the clinic and the community of women that you would like to study?

DR. FOLDESY: With regard to the latter question, I think it is entirely possible, and, in some of the other work that is being supported by FHI, they have used exactly that strategy.

In the studies we have conducted in Latin America, we have not

found it necessary, because the clients come to the clinic. The clinic is the draw in that situation.

DR. CAMERON: The combination of both has been very successful in Nairobi, and I think that is why in Nairobi that cohort is sustained.

DR. FOLDESY: Thank you very much for that comment. With regard to the monilia, an FHI study was completed a couple of years ago in Bangkok, where prostitutes used the N-9 sponge. It was observed there that an increased incidence of monilia accompanied the use of the sponge.

DR. CATES: Dr. Foldesy, that was a delightful presentation, and, to me, it really reflected on a personal odyssey moving from a family planning field, where clinical trials are conducted with individuals who are there to choose contraceptives and who are generally motivated enough to come back to the clinic on a regular basis to obtain their supplies. Conducting studies with populations who are at an STD clinic because they have a symptom or a particular, one-time need to be treated is something else. How to motivate those individuals to become involved in long-term studies that need to be conducted on AIDS is going to be a continuing challenge as we see this overlap of the two fields. We all have to digest this. This is probably one of the most important points made at this conference.

DR. FOLDESY: You are absolutely right. The real problem is that when people are not well they take their medicine, and as soon as they start to feel better they stop taking it.

DR. CAMERON: You alluded to an interesting sociologic point, and that is that women with STDs are required to report monthly for surveillance, I presume, in some countries. Is there any attention to, or is there any voice directing public policy towards, men with STDs?

DR. FOLDESY: That is a fascinating question. I do not know the answer. I would think, at least from what I have heard in my work in these countries, that the answer is no, but I am really not sure.