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Enrolment practices and outcomes by gender for HIV prevention trials in Southern Africa:

Challenges and Best Practices

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1. EXECUTIVE SUMMARY

UNAIDS-WHO (2007) specifically identifies *women* as an important population for inclusion in HIV prevention trials – both for scientific reasons and because they are likely to be the beneficiaries of successful products/interventions. However, there are various challenges to the recruitment, enrolment and retention of women in trials; these have been extensively outlined in the literature (e.g. IAVI, 2004; Kapoor, 2004; 2005; Wassenaar & Barsdorf, 2007).

Enrolling women in HIV prevention trials is a scientific, social and ethical imperative, given their heightened vulnerability on the basis of biology and their social position. Furthermore in order for them to benefit from successful interventions they must participate in trials. Women have been largely under-represented in vaccine trials, and even when they are successfully recruited there are many obstacles to their retention in trials. Given that HIV vaccines show great promise in abating the epidemic, the factors that promote and hinder recruitment, enrolment and retention of women in these trials need to be thoroughly researched.

This study emerged from the recommendation for research "to identify the enrollment practices and outcomes by gender for HIV vaccine trials in developing countries, generally, and in southern Africa, specifically" (Wassenaar & Barsdorf, 2007). This study aimed to 1) identify and examine recruitment and retention outcomes by gender at HIV vaccine trial sites; 2) to identify the strategies used at several types of HIV prevention trial sites across Africa (focusing particularly on Southern Africa) to overcome challenges regarding female participation in research; and 3) describe these strategies or "best practices" as a basis for a resource guide.

Eleven respondents, representing 10 HIV prevention trial sites across Africa [8 from South Africa, one from Uganda, one from Botswana, and one from Rwanda] were sent an email questionnaire dealing with recruitment and retention practices at sites, as well as outcomes by gender. Respondents could choose to respond via email or to be contacted for a telephone interview. Only one respondent opted for the telephone interview.

Responses dealing with enrolment, recruitment and retention outcomes by gender, suggested that the recruitment of women into trials was easier than the retention of women in trials. Responses dealing with challenges and best practices were coded inductively to find common themes.

Barriers identified by respondents were clustered into four broad categories, namely, care responsibilities, economic barriers and concerns around financial incentives, socio-cultural barriers and trial requirements.

Strategies and best practices which were identified as successful in overcoming these barriers to women's recruitment, enrolment and retention in HIV prevention research included:

- The provision of supervised child-care and family friendly waiting areas on-site
- Scheduling clinic hours to accommodate women's time and employment pressures; providing reimbursement of expenses and possibly compensation for time and inconvenience
- Community and participant education about their rights, research, research ethics, HIV, healthcare and the study in question.
- Ongoing community engagement and the establishment of partnerships with communities in order to establish trust; address concerns as they arise; to overcome potential stigma and discrimination; and to maintain interest in and support for the study.
- Facilitating access to healthcare, contraception and family-planning services in order to ensure that women meet the study requirements.
- Acknowledgment of women's participation and contribution to the study.

Generally, the obstacles identified by our respondents, as well as the steps taken to overcome these obstacles, correspond with those identified in the literature. In line with the recommendation for collaboration, cooperation and resource sharing between HIV vaccine and microbicide fields (Wassenaar and Barsdorf, 2007), women-only HIV prevention trials, such as microbicides and cervical barrier trials were strategically sampled to provide important insights into useful mechanisms for including and retaining women in trials.

2. BACKGROUND

UNAIDS-WHO (2007) specifically identifies *women* as an important population for inclusion in HIV prevention trials. While women are noted to be vulnerable to potential abuses, it is argued that they should not necessarily be excluded from research on this basis, as there is enormous social value in their involvement (Emanuel et al., 2004; UNAIDS-WHO, 2007). Guidelines assert that research aiming to enrol vulnerable populations should include a description of "the social contexts of [the] proposed research population that create conditions for possible exploitation or increased vulnerability among potential trial participants, as well as steps that will be [or can be] taken to overcome these" (UNAIDS-WHO, 2007, p. 31). Furthermore, these guidelines have highlighted the value of anticipating, addressing and overcoming barriers to women's participation in trials (UNAIDS-WHO, 2007).

Women in developing countries, and particularly in Southern Africa, are at heightened risk for HIV infection (Ramjee, 2000; WHO/UNAIDS Expert Group, 2005) to the extent that almost 60 percent of HIV infections in sub-Saharan Africa are in women (UNAIDS, 2008). In addition, young women in sub-Saharan Africa, aged 15–24 years have an HIV prevalence of three to four times higher than young men of the same age (WHO-UNAIDS Expert Group, 2005). The feminization of the HIV epidemic is indicative of women's greater social and biological vulnerability to HIV (Quinn & Overbaugh, 2005). Biological, socio-cultural, economic and legal factors all contribute to the heightened vulnerability of women. Social determinants of female vulnerability to HIV include gender inequities, poverty, cultural and sexual/gender norms, a lack of education, and violence against women (Quinn & Overbaugh, 2005).

Largely, but not exclusively, it is the behaviours of husbands and male partners rather than the women themselves that place women at increased risk for HIV (Kapoor, 2005). However, access to proven prevention technologies is inadequate and women are often not empowered to negotiate safer sexual practices with their partners. Further, women's economic dependence on men "increases their vulnerability to HIV by furthering their dependence on men and constraining their ability to refuse sex, negotiate the use of a condom, discuss fidelity with their partners, or leave risky relationships" (Gupta, 2002, in Kim, Prony, Barnett & Watts, 2008, p. S58). Current prevention strategies, such as condoms, fail to provide adequate protection for women as they require negotiation with men. At present the female condom is the only available female-controlled method for HIV prevention. However, uptake of the female condom has been disappointingly low due to cost, availability (Padian, Buvé, Balkus, Serwadda, & Cates Jr, 2008) and the fact that female condom use cannot always be clandestine (Kapoor, 2005). Furthermore, "for every person placed on antiretroviral treatment in 2006, another six people became newly infected with HIV" (UNAIDS-WHO, 2007, p. 9), with access to treatment in Africa being notably poor (Wassenaar & Barsdorf, 2007). Therefore, it

is pertinent that attempts are made to better use currently available prevention strategies and identify new ones (Lagakos & Gable, 2008). Female-controlled methods such as vaccines and microbicides remain the greatest hope for abating the epidemic.

In order to evaluate the safety and efficacy of an HIV vaccine (or other prevention products), candidate products must be tested in the populations most affected by HIV. This means increasing the involvement of women in trials, especially those in sub-Saharan Africa who bear a disproportionate burden of HIV infections (UNAIDS, 2007). For product licensure, regulatory authorities will require that products are tested in the populations in which they will be used. Therefore, for women to have access to successful products, sufficient numbers of women will need to be enrolled in HIV prevention trials. Given that women are at heightened risk of exposure to HIV, they stand to benefit most from an effective HIV vaccine (Wassenaar & Barsdorf, 2007) or other products designed for use in women, such as microbicides.

To date, women in Africa have generally been under-represented in trials of HIV vaccine candidates (Mills et al., 2006; Wassenaar & Barsdorf, 2007). Even when enrolment targets for women are met, recruiting women into trials appears more challenging than recruiting men (Ashburn et al., 2008). Hence, gender-sensitive approaches are important in the design of recruitment procedures in HIV preventive trials (WHO-UNAIDS Expert Group, 2005; Wassenaar & Barsdorf, 2007). Previous studies have demonstrated that recruitment, enrolment and retention are gendered, that is, experienced differently by men and women (Ashburn et al., 2008). Efforts to recruit, enrol and retain women thus need to be cognisant of factors that facilitate and those that impede these processes. To this end, Wassenaar and Barsdorf (2007, p. 46) recommended that "the AAVP/UNAIDS commission a study to identify the enrollment practices and outcomes by gender for HIV vaccine trials in developing countries, generally, and in southern Africa, specifically". They also recommended that this study should be conducted with sites identified as having the best enrollment strategies in order to identify the key factors associated with optimal recruitment and retention outcomes by gender - these "best practices" could be developed into a resource guide for HIV prevention studies that aim to enroll women (Wassenaar & Barsdorf, 2007).

3. AIMS AND OBJECTIVES

In response to the above recommendations by Wassenaar and Barsdorf (2007), this study aimed to:

1. Identify and examine recruitment and retention outcomes by gender at HIV vaccine sites.

2. Identify and examine optimal recruitment and retention strategies and challenges to recruitment and retention for women at several types of HIV prevention trial sites across Africa, focusing particularly on Southern Africa.
3. Develop a resource guide on best practices in recruitment in HIV prevention studies.

4. METHODOLOGY

Ethics approval was obtained from the University of KwaZulu-Natal, Faculty of Humanities, Development and Social Science research ethics committee.

4.1 Sample

The sample consisted of 11 respondents representing 10 trial sites across Africa. Eight respondents were from South Africa, one from Uganda, one from Botswana, and one from Rwanda. Respondents represented various research areas including HIV vaccines, microbicides, herpes suppression, diaphragm studies, pre-exposure prophylaxis (PrEP) and couples counselling interventions. Respondents comprised trial site staff (community liaison officers/recruitment officers, directors, investigators and study co-ordinators) dealing with recruitment of participants at HIV prevention sites across Africa, and especially in Southern Africa. Respondents were purposively sampled or selected via snowball sampling, where respondents were recommended by other respondents.

We sent an email describing the study to 26 potential participants across Africa (many of whom were staff at the same site). We received expressions of interest to participate from 13. We then sent the email questionnaire to all 13 participants and got responses from 11 respondents. Two of the potential respondents opted not to complete the questionnaire because another site staff member had already completed it.

4.2 Procedure

An information sheet describing the research was distributed to all potential respondents, along with a cover letter and invitation to participate. Potential respondents were identified from an AAVP database of staff at trial sites across Africa. Respondents were asked to indicate whether they would prefer to complete an email survey or to be contacted for a telephone interview. Once potential respondents agreed to participate, the email questionnaire was forwarded to them. Only one respondent opted for the telephone interview.

4.3 Instruments

An email questionnaire (Appendix 1) was developed that aimed to elicit information about enrolment practices at sites, recruitment outcomes by gender at the sites, challenges and best practices regarding recruitment, and barriers to the recruitment and retention of women. The email interview questions were used as the basis for the semi-structured telephone interview.

4.4 Data analysis

Given the descriptive and exploratory nature of the study, the email survey and telephone interview transcript were analysed using a descriptive thematic analysis. The telephone interview was selectively transcribed (cf. Halcolmb, Cert & Davidson, 2006). Responses dealing with enrolment, recruitment and retention outcomes by gender, were arranged in a table (see table 1 below) for ease of comparison across sites. Responses dealing with challenges and best practices were coded inductively to find common themes. Themes were grouped and regrouped in analytically relevant ways.

5. RESULTS AND DISCUSSION

5.1 Recruitment, enrolment and retention outcomes by gender for trials enrolling men and women

	Studies	Recruitment	Enrolment	Retention
Site 1	Couples VCT	Couples recruited	84% of eligible couples enrolled	Couples released; 90% of couples retained at year 1
	Herpes Suppression	Couples recruited	Couples enrolled	Couples released
	HIV vaccine trial	No data	63% men and 37% women enrolled	No data
Site 2	HIV vaccine trial	More women than men recruited	65% women and 35% men enrolled	Similar rates of retention between men and women
Site 3	HIV vaccine preparedness study	33% women and 66% men recruited	55% of recruited women were enrolled and 54% of recruited men were enrolled	99% of women retained compared to 55% of men
	HIV vaccine trial	45% women and 54% men recruited	23% of recruited women were enrolled and 18% of recruited men were enrolled	66% women and 100% men retained
Site 4	HIV vaccine trial	Slightly more women than men recruited	More men than women enrolled: Study 1: 13% women Study 2: 38% women	Retention rates were similar for men and women in both studies
Site 5	HIV vaccine trial	No data	35% women enrolled compared to 65% men	Women were more difficult to retain than men
Site 6 2 respondents	HIV vaccine trial	Recruitment rates are similar between men and women	44% women enrolled compared to 55% men	Retention rates are similar for men and women
Site 7	No data provided	Recruiting women is easier than recruiting men	No data provided	No data provided

Table 1: *Recruitment, enrolment and retention outcomes by gender* (Grey shading indicates those instances where outcomes for women are better than men)

Seven sites reported conducting trials with both men and women. In terms of recruitment, outcomes by gender varied across sites. Two studies reported that recruitment of women are easier than that of men; two reported that recruitment rates are similar between men and women; two reported that recruitment rates are lower for women than men, and two studies

did not provide any data on recruitment.

In terms of enrolment, only one site reported higher rates of enrolment of women compared to men. Five sites reported lower enrolment rates for women than for men and one site did not provide any data. Similarly in terms of retention, only one site reported higher retention rates for women. Two sites did not provide any data, three sites reported similar retention rates among men and women and two sites reported that women were more difficult to retain. This data suggests that for the seven sites represented women are easier to recruit than they were to enrol and be retained in trials.

5.2 Challenges and best practices around the recruitment, enrolment and retention of women

Respondents, across all HIV prevention trials, identified several impeding factors to women's recruitment, enrolment and retention in HIV prevention research. Barriers identified by respondents are clustered into four qualitative categories, namely, care responsibilities, economic barriers and concerns around financial incentives, socio-cultural barriers and trial requirements.

Sites identified strategies and best practices which have proved successful in overcoming the barriers to women's recruitment, enrolment and retention in HIV prevention research. These best practices and strategies were clustered as responses to the challenges outlined in the categories above.

5.2.1 *Care responsibilities*

Clinical trials typically recruit women between the ages of 18-35 years. Therefore, many eligible women are mothers to young children, they may be responsible for taking care of the elderly, and are wives and homemakers. Women are faced with multiple responsibilities including childcare, household duties and earning an income. There are consequently limits on women's time to make frequent study visits or attend information sessions (Mills et al., 2006; Singh, 2008; Kapoor, 2005). This impacts on their participation in trials.

Many respondents identified women's care responsibilities, especially the care of children, as a barrier to their participation in HIV prevention trials:

> *"Women are met with the usual challenges of childcare, household chores and a society that expects them to give birth to as many children as possible"* (Respondent 5).

> *"They also have limited time to spend at the research site because … they always need to be back at home by the time the children/husbands are back from school/work. Some women look after babies"* (Respondent 1).

In addition to limiting women's available time to spend at sites, childcare responsibilities create the added burden and expense of finding someone to look after their children while they are at the site: *"[a] lack of where one can leave their small children could be one of the barriers to participation"* (Respondent 3) and *"women had to travel to the site, spend time for study procedures, take time off work, getting someone to look after their children…The effort involved and commitment was greater than the financial compensation"* (Respondent 4).

Care responsibilities: Best practices/ Strategies for overcoming challenges

The provision of child-care facilities for women participants who have children as well as creating a welcoming, family-friendly waiting area, has been suggested in the literature as an important aspect of establishing a gender-sensitive, women-friendly site (IAVI, 2004; Kapoor, 2004; 2005). Several respondents reported that the provision of child-care facilities at the clinical trial site had proven a useful strategy in meeting the challenges related to women's care responsibilities and their participation in research: *"We also provide on site child care which allows women to attend visits more easily"* (Respondent 5) and *"we have a 'children corner' within the research clinic to encourage mothers with small children to come with them as they attend their study visits"* (Respondent 3).

It was suggested that it is important for women to feel comfortable with the child-care provided and for the experience to be pleasant for the children too:

> *"We have tried to make it easier for women with children, by introducing a child friendly area in our clinic. Women are then able to bring their children along to the clinic for their study visits. Children are supervised while the mother attends to the information sessions. They are entertained with educational toys"* (Respondent 9).

5.2.2 Economic barriers and concerns about financial incentives

a. *Economic barriers*

Most of the respondents identified economic factors that hinder women's participation, particularly that women could not negotiate time off work. This is further complicated for women who provide the sole source of income for their families, *"Some women are the only breadwinner in the family and cannot afford to take time off work to attend study visits"* (Respondent 9).

On enrolment many female participants are unemployed and therefore may be flexible

regarding their time. However, given the extended follow up periods of large-scale trials, these women often become employed during the course of the trial: *"They may have enrolled when they are unemployed, but when they start work their employer may not understand their need to take leave regularly or they have not accrued leave"* (Respondent 2). Respondents noted that women may be less empowered to negotiate time away from work with their employers. Therefore, clinic hours that run in parallel with office hours, make it difficult for employed women to participate in trials.

Economic barriers: Best practices/ Strategies for overcoming challenges:

Several consultations regarding the involvement of women in HIV prevention trials have recommended running clinic hours that suit the work schedules of participants, as well as considering the convenience of the site location (IAVI, 2004; Kapoor, 2004; 2005).

Most respondents noted extending clinic hours to accommodate the needs of participants as a best practice adopted in response to the challenges around employment commitments. Often this has involved extending clinic operating hours to outside working hours in the week and on Saturdays for those who may be unable to attend during the week. Some respondents reported the provision of transport to participants to minimize time away from work, as a useful strategy:

> *"For women that found it difficult to take time off work to attend the study visits, we have a transport service available. We arrange with the participants to collect them from work during lunch time or after work and return them to work after the visit, if required. We also extend our clinic hours to try and accommodate the participants either before going to work in the morning or after work in the afternoons"* (Respondent 9).

Another useful strategy reported was accommodating participants by performing only absolutely necessary procedures (for study validity) at visits which were impacted by employment and time pressures:

> *"We may also do the most relevant procedures for a visit rather than miss the visit. E.g. we may not complete long behavioural questionnaires instead we will collect the biological specimens, blood, swabs, and urine) because they measure 'hard' end points viz. Seroconversion, STI or pregnancy"* (Respondent 2).

b. *Concerns around financial incentives*

Several respondents also raised concerns about financial incentives, many of which are in line with the usual concerns about the payment of trial participants raised in the literature (cf. Koen et al., 2008). Respondents discussed the potential for payment to undermine altruistic

motives and to encourage co-enrolment in multiple studies:

> *"Personally I think this is a big incentive for some women. Evidence emerged from the co-enrolment of women in multiple trials. We discovered women were enrolled in more than one trial at a time. Some travelled great distances. This is an extreme example but it does demonstrate the point"* (Respondent 2).

Payment was *"the main reason why they co-enrolled"* (Respondent 7).

Respondents also noted the difficulty of establishing a fair financial incentive (for a more complete discussion of the fair payment of trial participants, see Koen et al., 2008):

> *"The problem is the MCC has benchmarked the reimbursement at R150, 00. This amount may be fair compensation for time and travel expenses; however, it is an incentive if someone has no job. Altruistic reasons for participation can only occur when the reimbursements are almost negligible"* (Respondent 2).

> *"Women had to travel to the site, spend time for study procedures, take time off work, get someone to look after their children; as well as contact the site. The effort involved and commitment was greater than the financial compensation"* (Respondent 4).

Value of Financial incentives

Respondents also commented on the issue of financial incentives and the role they play in the enrolment and retention of women in trials. Several noted that financial incentives *"play a huge part in women's participation in the trial as most are unemployed and the reimbursement is their only source of income"* (Respondent 10) and that these incentives helped to give women some independence:

> *"It helps women to know that they don't have to ask their partners for money for transport or childcare. They are also able to buy airtime to contact site-staff should they have problems or concerns. It also helps with retention because women know that they can borrow money for transport because they will be able to pay it back with what they get from the site"* (Respondent 11).

Overall, respondents noted that the provision of some sort of financial incentive was important, particularly where the purpose would be the reimbursement of expenses. "*They appreciate transport re-imbursement*" (Respondent 8). Respondents suggested that these incentives should not be emphasised in recruitment but that they do play a role in ensuring

retention of women in studies, particularly given the economic barriers they face.

1.2.3 *Socio-cultural barriers*

Research in developing countries is conducted within unique socio-cultural contexts which may variably impact on women's participation in HIV prevention studies.

a. Informed and autonomous consent

In many contexts, women may not be able to exercise true autonomy in making decisions (c.f. UNAIDS, 2007; Wassenaar, Barsdorf & Richter, 2005). Often they rely on their partners/husbands (Kapoor, 2005) and significant others such as family, friends, community members and social networks (Ashburn et al., 2008; Singh, 2008). Therefore, women may be pressurised to disclose sensitive information, such as their HIV status and contraceptive use, to partners (Singh, 2008). Many women, in many cultures, have little autonomy to make decisions themselves, and very often run the risk of coercion by family members to either participate in or withdraw from a trial. Prevalent gender norms make women vulnerable to influence and even coercion from their husbands/partners, family, community and health care providers, to either participate in or withdraw from a trial (IAVI, 2004). This limited autonomy may impact on recruitment, enrolment and retention of women in trials. For example, a South African site staff member observed that partner objections to participation do occur and related that in one study, *"…the partner actually phoned us up to tell us that she had fits and things, you know, and she's not had fits. But he was so put out about her…taking part in this trial, um, that he would do anything to get her out of this trial"* (Essack et al., in press).

In resonance with the literature, our respondents noted that the need for approval of partners for trial participation or various components of trial participation, such as contraceptive use, is a major deterrent to women's trial participation. Most respondents noted that women's decisions to enrol are externally influenced particularly by their husbands/partners, and to a more limited extent by their peers and community: *"When approached, most women were interested but the main challenge was involvement of their male partners – some of them had to seek consent from partners*" (Respondent 6) and *"due to the cultural climate we are recruiting in, we have found that some women need to get permission from their husbands/partners before they are allowed to participate in a study"* (Respondent 9). In some cases women do not disclose their participation to their partners which means that *"they also have limited time to spend at the research site because half the time they do not disclose their participation in the studies therefore they always need to be back at home by the time the children/husbands are back from school/work"* (Respondent 1).

When husbands/partners unwittingly learn of the participation of a woman, there may be serious negative consequences and social costs to female participants such as abandonment,

withholding of financial resources, violence, divorce and/or stigma, among others: *"The absence of partner support or risk of violence or abandonment by the partner are others challenges they face"* (Respondent 5). Even when women seek the permission of their husbands/partners, they may object to the women's participation. Partners/husbands also have significant influence on whether women are retained in trials. Many respondents observed that women may withdraw from trials due to influence from their husbands/partners: *"A few women have withdrawn their consent. The reason some give is their new partner objects to them using the product"* (Respondent 2) and *"If a husband/partner decides that the woman needs to discontinue participation, it influences retention"* (Respondent 9).

One respondent noted that negative peer influence is also a major challenge to recruiting and enrolling women: *"There seem to be peer influence amongst women. We received some reports of females who were talking each other out of study participation"* (Respondent 3).

As a result of the above barriers, women often do not provide reliable contact information to recruiters as they do not want to be enrolled in the trial or be followed up for fear that their husbands/partners may negatively react to their participation.

Informed and autonomous consent: Best Practices/ Strategies for overcoming challenges

In order to meet the goals of successful recruitment and retention of (women) participants in trials, the literature suggests that informed consent cannot be reduced to the signing of a piece of paper, but should rather be viewed as a multi-step process (IAVI, 2004; Kapoor, 2004; 2005). The informed consent protocol should take into account the complexity of decision-making processes in various contexts and should include consideration of the factors affecting this process. Investigators must be cognisant of the power dynamics and the prevalent gender norms which may raise concerns about the potential for compromised voluntariness of women regarding decisions about their participation in trials, and should adopt measures to support each individual's right to make voluntary and independent decisions about research participation (IAVI, 2004; Kapoor, 2004). To this end community engagement in research should not be a substitute for individual consent processes.

In contexts where women lack autonomy to make independent decisions regarding trial participation, it would be unrealistic to expect successful female recruitment, enrolment and retention in HIV prevention trials where communities and families have not been educated and mobilised around the value of their participation (Kapoor, 2004). In line with general recommendations in the literature that trial-related information be provided in accessible and understandable language, and that the autonomy and voluntariness of individual informed consent be emphasised (cf. IAVI, 2004; Kapoor, 2005), respondents noted that ensuring

voluntary and autonomous informed consent involved the following: A process of education and information dissemination about HIV; research, ethics and the trial to potential participants and at a broader community level. This information was noted to be available both in English and the local language:

> *"Community entry is key. Talking to relevant key stakeholders including traditional leaders ensures a smoother buy-in. Keeping the community informed and engaging in frequent dialogues with them brings about trust and confidence in service rendering. Respecting participants and allowing them enough time to make an informed consent to participating has proven successful as well"* (Respondent 8).

> *"The sites have dedicated recruiters who provide information on the trial together with pamphlets in both the English and local language (isiZulu). Information generally on HIV prevention, research study, ethics of research in terms of voluntary participation is provided."* (Respondent 10)

Furthermore, the literature suggests that the informed consent process should be structured in order to empower participants to be fully aware of their rights, and the risks and benefits of trial participation (cf. IAVI, 2004; Kapoor, 2005). It was noted that the informed consent process involved information provision regarding the ethical and regulatory oversight of the study, the partners involved in the study, as well as the right to voluntary participation and withdrawal:

> *"Women are informed that the trial has been approved by regulatory bodies, such as the Institutional review body of the University X[1] and the Medicines Control Council. Additionally, participants are informed of funding partners and that the trial is required to be approved by these partners. Women are also informed that should they wish to discontinue participation, the staff will assist them in trying to understand barriers and facilitate ongoing participation. If they still wish to discontinue, their decision will be supported." (Respondent 10)*

Partner influence:

One of the key strategies for overcoming some of the challenges posed by the need for partner consent for women's enrolment in HIV prevention trials, and the potential for partner objections to negatively affect retention, noted by respondents in this study, was the inclusion of partners in the education, recruitment, enrolment and retention processes:

> *"Though it wasn't a strategy that we specifically employed, some females came with their spouses for the seminars and informed consent and these females appeared*

[1] The name of the university has been omitted to protect confidentiality.

more receptive of the study. I believe couple education, counselling and enrolment would be an effective strategy" (Respondent 3)

"We do believe that our most effective strategy is to recruit couples, provide the information to both partners, allow time for questions, answers and discussion and finally obtain consent from both with one partner providing support to the other… Regarding the consent of partners we emphasized the need to invite partners to the presentations or to just refer an individual partner to study staff and for those who agreed the strategy worked well because some partners ended up supporting and helping in the retention process, they would actually make sure that they encourage their women to honour their visits by accompanying them to their study visits." (Respondent 5)

Certain respondents noted that the involvement of couples in VCT provided an entry point into educating partners around the research. This strategy was argued to "*facilitate couple communication and mutual support*" (p.176), and to create a 'safe' environment for disclosure of HIV status and trial participation and therefore to mitigate negative partner reactions (IAVI, 2004; Kapoor, 2004; 2005):

"We encourage all women to bring their partners to the clinic. We do couple counselling and test both partners for HIV. If a partner comes in we also explain everything about the trial" (Respondent 2).

Furthermore, to avoid the possible negative consequences of a partner discovering a woman's enrolment in a trial, without his prior knowledge or approval and to support women in disclosures to their partners, *"Women are encouraged to disclose participation to their partners and to bring their partners to the clinic site if possible for further discussions, where one on one sessions [can be] facilitated"* (Respondent 10).

Peer influence:

Respondents also described peer influences on women's decisions to participate in research as an important consideration. While the potential for negative peer influence on women's participation decisions was noted, most respondents reported that peer-influence and support could form a part of a successful information dissemination, recruitment and retention strategy:

"Many women also talked to others about the study and word of mouth significantly contributed to recruitment" (Respondent 3)

> *"Women are better accessed through friends and colleagues who they take time to discuss participation with before responding to invitations to participate"* (Respondent 11)

Respondents also noted that women seemed more willing to trust information about HIV and about trial participation from women who were participants compared to research staff:

> *"We train participants to educate other women about HIV and their participation in the trial. These women become the 'voice' of the trial in the community. When the other women are interested in participating in the trial, they approach our staff and we take them through the whole informed consent process."* (Respondent 2)

> *"We have also found that women in studies also recruited other women through word of mouth. It seemed to be more acceptable for women to receive the information from other women already participating in a study. They could share their experience with other interested women."* (Respondent 9)

> *"We use enrolled women as a point of referral for other potential participants – we give them information about the trial and get them to refer others to the trial."* (Respondent 11)

Responses in this study support the argument in the literature that informed consent could include individual and group process (cf. Kapoor, 2004).

A respondent from one site reported group discussion sessions as an important basis for informed decision-making regarding study participation and as a successful recruitment strategy:

> *"We have implemented discussion groups for interested women to attend. These sessions are held in a very relaxed, informal atmosphere. It allows them to ask questions as a group and do not put pressure on them as individuals. We also arrange these discussion groups in the different sub-districts of X[2], to make it easier for them to attend. Through this strategy we ensure that the women have enough information about the studies to be able to make an informed decision regarding participation in these studies."* (Respondent 9)

Contrary to the reported success of group discussions for female participant recruitment and decision-making noted by this respondent, and the observation in the literature that women in

[2] The name of the district has been omitted to protect confidentiality.

certain contexts discuss sensitive issues more openly in group contexts than in one-on-one sessions (Kapoor, 2004), certain of the other respondents in this study reported that group sessions were some of the less effective strategies in recruiting and retaining women in studies. *"In discussion groups women don't ask questions as readily as men"* (Respondent 11) and women may be concerned about privacy and confidentiality in large groups:

> *"Group sessions were found to be less effective as some women have not felt comfortable to issues/questions as there is less privacy. Our groups generally comprise of a maximum of 8 women. However, following every group session women are offered individual sessions especially for those not feeling comfortable to take the opportunity to ask questions and concerns"* (Respondent 10).

These opposing views on methods best to facilitate female recruitment and retention in trials and of obtaining voluntary and meaningful informed consent for women participants suggests that informed consent be seen as process-oriented, rather than prescriptive (cf. Kapoor, 2004), and that methods of accessing potential participants should be responsive and sensitive to the context from which investigators are recruiting.

b. *Distrust and myths about the research*

Kapoor (2004, pp.15-16) notes that "fear and misinformation - about the vaccine and testing - is a huge barrier" to enrolment and retention in HIV vaccine trials in general, "but [that] women also fear the consequences of potential violence and conflict from their partners if they enroll in a trial or if they test positive during the screening process."

Furthermore, in many contexts, particularly those in which there is a history of abuse, there may be a general distrust of medical research (Barsdorf & Wassenaar, 2005), and this may have a significant impact on participation (IAVI, 2006; Stadler, Delany & Mntambo, 2008). Omnipresent myths and misconceptions about trials mean that fears of mistakenly being identified as HIV infected (cf. Mills et al., 2006) are not misplaced, especially given high levels of stigma associated with HIV/AIDS (cf. Kapoor. 2004). In addition, various myths and misconceptions are perpetuated that instigate a wariness of HIV research such as that HIV vaccines cause HIV.

Some of the respondents reported that mistrust of research is an obstacle to women's participation in trials. Specifically, respondents suggested that women expressed concerns about the safety of the product and that the study product may cause HIV. There is also some wariness around new research and new research sites, *"As a new research site, [there is] uncertainty and lack of trust"* (Respondent 4).

Some of the respondents also noted that negative media reporting about the early closures of trials of HIV prevention products could potential fuel rumours about and distrust of research, and contribute to poor enrolment and retention of participants. Such concerns are also noted in the literature (cf. Mills et al., 2005; Ramjee et al., 2007). These respondents referred specifically to the closure of the Cellulose Sulfate microbicide trial - a trial of a female-initiated method of HIV prevention. Media reporting around this trial suggested that the investigational product contributed to increased susceptibility of the women in the trial, to HIV infection.

> *"[Challenges preventing women from enrolling in HIV prevention research include] distrust for research: some women are sceptical about the process of evaluating a product. Negative media reports relating to cellulose sulfate still appear."* (Respondent 2)

> *"When the cellulose sulfate results were available there was overwhelming negative publicity on these results."* (Respondent 10)

Distrust and myths about the research: Best Practices/ Strategies for overcoming challenges

Respondents noted the development of trust and understanding between the study population, the community and the investigators as critical in overcoming fears and misinformation related to trial participation. It was emphasised that investigators must be aware of any rumours or misunderstandings and should address these as they arise. As noted in the literature (cf. Kapoor, 2004; UNAIDS-AVAC, 2007), this involves intense and ongoing community engagement and dialogue, open and honest dissemination of information in accessible and understandable forms; and enabling staff to address community concerns and to dispel prevalent myths and misperceptions.

Respondents reported community participation and engagement as critical in the development of trusting investigator-community relationships:

> *"[Community Participation] is a vital part [of the recruitment and retention of women in HIV prevention trials]. Most of our sites have been in the community for a few years. Through our various meetings and other initiatives we have a strong community presence. The community trust our staff and therefore they have no problems enrolling in our trials. We pay particular attention to rumours or misperceptions in the community. We address them immediately. We have close relationships with traditional leaders, local government and other community leaders to facilitate this process."* (Respondent 2)

> *"Community engagement activities are important to clear the myths in the community*

and it also plays an important role in recruiting women. It also gives face to the community and creating ownership of the research in general. It also creates transparency leading to trust." (Respondent 4)

"Establishment of trust is …critical. Our recruitment process ensured that contact was established multiple times over [a short period of time]. This strategy made it possible for the research team to have time with potential participants, answer their questions and dispel myths and misconceptions… The strategy of multiple contacts during the recruitment process to build trust and ensure that females' questions and concerns are addressed has been particularly useful." (Respondent 3)

Suspicions about clinical research (that investigators are purposefully concealing information relevant to participation decisions) might arise because confidentiality procedures may be perceived to indicate secret or shameful experimentation. Keeping information hidden may be seen to imply that the research is ethically questionable and in contravention of cultural norms (cf. Essack et al, 2009 in press). Essack et al. (2009 in press) recommend transparency abouttrial procedures and information, as well as ensuring that communities understand the importance of maintaining individual confidentiality. In this study it was noted that a means of achieving this transparency and ensuring understanding was community engagement:

"[Community engagement] better re-assures them in that there is nothing "secretive" about trials especially when they see visibility in their community." (Respondent 8)

Suspicions about research may be heightened by negative media reporting on research. In order to overcome the potential impact of these negative messages on recruitment and retention in other similar trials, investigators must recognise and respond to emerging issues in the research context (UNAIDS-AVAC, 2007). In relation to the negative reporting about the Cellulose Sulfate trial, one of the respondents noted the critical importance of ongoing community engagement and of using such issues as tools for building research literacy in communities:

"Ad hoc meetings are set up for purposes of providing information on recent developments on trial results, e.g. when the cellulose sulphate results were available there was overwhelming negative publicity on these results. Whilst this was not our trial we had to ensure that the communities through the CAB members were provided with true accurate information. Additionally together with CAB members we reviewed the newspaper quotes which were grossly inaccurate and reinforced what is usually being done in trials, understanding research and interpretation of results."
(Respondent 10)

The *UNAIDS-AVAC (2007) Good participatory practice guidelines for biomedical HIV prevention trials* list 'building research literacy' as one of the core principles for ensuring meaningful community participation in research and for overcoming conflicts, confusion and mistrust and misconceptions of research. Research literacy involves education around research methods, design, terminology and ethics. Several respondents reported that building research literacy was a successful strategy for improving female recruitment and retention in trials and for overcoming concerns and confusion:

> *"We have a strong community engagement and education component. A broadly knowledgeable base will ensure that potential participants are not negatively influenced by friends, spouses and peers who do not understand research."* (Respondent 3)

Educating women about HIV and clinical trials was noted as a strategy for overcoming low recruitment as a result of a lack of interest because of a poor understanding of research. Furthermore, a successful strategy for overcoming concerns about the safety of the product was the provision of information about the product, including clear descriptions of what was known about it on the basis of literature and experience and what was still unknown about it. Clear information about the possibility of vaccine-induced HIV seropositivity was noted to be an important component of these explanations:

> *"What they appreciated most was the thorough explanation of the possibility of testing false positive after receiving a vaccine, once they were satisfied and were reassured, they started to come in large numbers."* (Respondent 5)

c. *Stigma and fear of testing positive for HIV*

Women may also be concerned about stigma and discrimination associated with both testing for HIV and participating in a trial. In many contexts women are blamed for the spread of HIV, and for bringing the disease into their families (Kapoor, 2004). Given that HIV/AIDS is linked to socially stigmatised behaviours like commercial sex-work, promiscuity, intravenous drug use; and is inextricably tied to fears about disease and death, any association with HIV/AIDS is likely to trigger high levels and broad spectrum stigma and discrimination (Campbell, 2003; Kapoor, 2004). "HIV/AIDS-related stigma and discrimination faced by women reinforces pre-existing economic, educational, cultural and social disadvantages and unequal access to information and services that they are subject to in their everyday lives" (Kapoor, 2004, p. 19). Women who test positive may be subjected to severe social harms such as violence and abandonment (Dunkle et al, 2004) and rejection from their family and community (Wakasiaka, 2005). Therefore many women are reluctant to be tested for HIV (Wakasiaka, 2005).

A few respondents identified stigma and the fear of testing positive for HIV as disincentives to women's participation: *"women are concerned that people will think they are HIV positive if they participate in trials"* (Respondent 11) and *"they were afraid if they tested positive they would be physically assaulted or abandoned by their partner"* (Respondent 2). While these issues may also deter men from participating, women are more vulnerable to negative social consequences such as violence and abandonment (cf. Dunkle et al, 2004).

Stigma and fear of testing positive for HIV: Best Practices/ Strategies for overcoming challenges

The literature suggests that ensuring confidentiality about trial participation and of the results of HIV-tests goes some way to avoiding potential HIV/AIDS-related stigma and social harms (IAVI, 2004; Kapoor, 2004; 2005). Several respondents noted the importance of supplementing group information sessions with private, one-to-one opportunities for participants and potential participants to raise questions and concerns and to make autonomous and voluntary, informed decisions about research participation:

> *"One on one information sessions were found to be more effective as compared to group sessions as the participant is comfortable to talk and openly discuss her issues confidentially"* (Respondent 10)

Establishing research sites in neutral locations and not emphasising their link to HIV/AIDS or STIs is recommended in the literature as a means of averting potential stigma and discrimination (IAVI, 2004; Kapoor, 2005). A respondent noted that women's recruitment and participation in HIV prevention trials was packaged in terms of general health:

> *"Women's discussion meetings and recruitment messages were not specific to HIV or vaccines because these issues are stigmatising. Invitations to attend the meetings or participate in the study were packaged in terms of general health concerns."* (Respondent 11)

Research teams should adopt a sensitive, compassionate and supportive stance when communicating HIV-status to participants and should support and facilitate disclosure of results or trial participation to others, where the participant so desires (IAVI, 2004; Kapoor, 2004). Respondents reported: *"Encouraging women to know of their HIV status and options available to them"* (Respondent 4) and encouraging women *"to disclose participation to their partners and to bring their partners to the clinic site if possible for further discussions"* (Respondent 10). Involving partners in the recruitment and retention of women, and encouraging couple communication and risk-reduction through offering VCT to women and

their partners, is a recommended strategy for overcoming the risks of stigma and other social harms (Kapoor, 2004; 2005). As already noted, respondents reported partner involvement and couple-counselling as a successful strategy for enhancing female participant recruitment, enrolment and retention, and for ameliorating negative reactions to women's participation.

Many respondents reported that access to healthcare benefits was *"an important factor in maintaining and encouraging [women's] participation"* (Respondent 1) and that *"access to HIV counselling, testing and referrals and access to care has significant influence"* on enrolment and retention of women (Respondent 3). Furthermore, the healthcare services provided at research sites *"are viewed as more available than in the public sector"* (Respondent 1) and are *"a very important benefit for women. They manage to receive [regular] general medical care and advice, without having to go sit in queues for very long time periods at the [public] clinics"* (Respondent 9). *"It was also important to women to receive high quality care and continue access to good quality care women to avoid queues at the local clinics"* (Respondent 10).

The establishment of high quality and women-friendly health provision is recommended to offset and overcome potential social harms related to stigma and discrimination (IAVI, 2004; Kapoor, 2004). *"They appreciate the benefit of a well presented health care facility that makes them feel welcomed and are treated with dignity* (Respondent 8).

The literature also suggests the importance of facilitating and supporting participants to access care and treatment for HIV/AIDS and related illnesses (Heise, Shapiro & West Slevin, 2008). It was reported that:

> *"Volunteers are tested for HIV on a three monthly basis and assessed and treated for STI's. They do receive prophylaxis and treatment for opportunistic infections if found HIV positive and are referred for HAART when necessary"* (Respondent 5).

In line with suggestions in the literature (cf. Heise et al., 2008), the importance of providing ongoing care and support to participants, even those who may, for reasons like pregnancy, no longer be eligible for participation was noted in responses. A respondent suggested that there may be value in *"establishing HIV support groups in the trials* and in continuing *"providing care for the seroconverters and pregnant participants that cannot continue with the study product"* (Respondent 4).

In addition to this, several respondents reported that the provision of health-care services to the partners and families of women participants played an important role in enhancing female enrolment and retention in trials and in gaining partner and family (and by extension

community) support for women's participation. Access to high-quality STI treatment for participants and their partners was reported as an incentive to enrolment and retention. A respondent observed that: *"If [the care provided to female participants] was to be extended to family members, I suppose more women would participate"* (Respondent 3). Another of the respondents reflected that access to healthcare for participants and their families was a successful retention strategy:

> *"Access to healthcare benefits for themselves and their families plays an important role in our retention strategies. We do provide an annual health scheme card that covers primary and secondary healthcare for the whole family"* (Respondent 5).

This extension of care beyond the study participants is consistent with the recommendation in the literature that stigma and discrimination can, in part, be addressed by positive messaging around volunteers regarding their altruism and contribution to science and society (cf. Kapoor, 2004).

In designing and implementing gender-sensitive recruitment and retention strategies, investigators must take cognisance of prevalent gender-norms and factors which could potentially result in social harms to women participants (Kapoor, 2004; Wassenaar & Barsdorf, 2007). Addressing misconceptions and gender-stereotypes which lead to AIDS-related stigma and discrimination requires *"community education and engagement [to] ensure a knowledgeable community base to support female participation"* (Respondent 3). It is argued that taking such steps might lead to "further social emancipations" (Wassenaar & Barsdorf, 2007, p. 47), like addressing gender-discrimination at a broader societal level. This again highlights the importance of meaningful community participation and engagement as described regarding addressing the challenges of establishing trust.

d. <u>*Relocation, migration and loss to follow-up*</u>

A few respondents noted that relocation and migration are relevant impediments to retention of participants. HIV prevention trials require lengthy follow-up which may not be amenable to mobile populations, particularly young women. One respondent observed that enrolled women may relocate when they marry and in order to continue/further their studies. Another respondent noted that "*many [participants] are migrants seeking work in the city and whilst work schedules may allow them to participate, many will be returning home for extended periods of time*" (Respondent 10). Several respondents also noted that a major challenge involved in retaining women in studies was unreliable contact information for female participants: "*Women relocate to different cities or away from the research site. They are hard to trace if we do not have a reliable cell phone number"* (Respondent 2) and *"Some women don't provide reliable contact details and address information at enrolment because*

they don't trust the research staff" (Respondent 11). One of the respondents observed that some of the reluctance of women to provide accurate contact details to site staff was tied up with fears around partners and others discovering their participation in the study.

Relocation, migration and loss to follow-up: Best Practices/ Strategies for overcoming challenges

Challenges to retention as a result of relocation and migration and loss to follow up, seemed to be some of the more difficult to address. Some respondents suggested: *"work[ing] out the follow-up plan and schedule together"* (Respondent 1) so that it was manageable and women from migrant populations could be accommodated.

The importance of formative research in the community and of knowing and understanding the demographics and geography of the community was noted as a means of facilitating the location of participants' addresses for follow-up. One respondent noted that if participants fail to arrive at the study site for follow-up visits, research staff 'go to the participant', *"depending on participant consent we do home visits"* (Respondent 11).

Ensuring that participants provide reliable contact details and are willing to work with study staff to ensure ongoing contact, was noted to depend on the establishment of a relationship based on trust between investigator and participant: *"Women need to have a relationship with study staff before they trust them with personal information and are willing to allow for follow-ups by providing them with accurate and reliable contact details"* (Respondent 11). This respondent (Respondent 11) also noted that while establishing the depth of relationship required for women to trust research staff may be *"a challenge for timelines"*, it is critical to ensuring retention and valid study outcomes. Furthermore, steps taken to overcome stigma and discrimination through community outreach activities should also enhance the likelihood of women providing investigators with reliable contact information, as they may not be so afraid of the consequences of their participation in the study being revealed.

Another suggestion to enhance retention was the establishment, with participants' and others' consent, of referral networks among women's friends and fellow participants to improve the ability to maintain contact with participants who may be 'mobile' and otherwise difficult to trace.

1.2.4 *Trial requirements*

a. Eligibility criteria

One of the primary obstacles to women's participation in HIV prevention trials was their

reported failure to satisfy eligibility criteria. Even when rates of recruitment for women surpass that of men, a failure to meet eligibility criteria means that fewer women enrol in trials (Respondent 5). These trials may require that women use contraceptives, not be pregnant or breastfeeding and avoid becoming pregnant for the duration of the trial. Given that in many cultures, a woman's value is intricately related to childbearing (Ashburn et al., 2008), contraceptive requirements may deter participants. Women may also be concerned that the vaccine (or other HIV prevention product) may affect their chances of having children in the future (UNAIDS, 2007).

Respondents noted that even when many women are recruited for trials, most of these women are not subsequently enrolled as they do not meet eligibility criteria. In some circumstances the women do not meet the sexual activity inclusion criteria engage. However, for the most part, barriers relate to reproductive criteria: "*Women were as willing as men to be enrolled but could not fulfil some of the inclusion criteria such as being on long-acting user independent contraceptives or not being pregnant or not breastfeeding*" (Respondent 5). To reach the required study populations, HIV prevention trials must enrol women who are sexually active and of reproductive age (Raymond et al., 2007). However, many want to have children:

> "*The challenges met when recruiting women in intervention studies are essentially related to their reproductive health. Some are reluctant to take contraception, to delay reproduction, others are either pregnant or breastfeeding. In our country the government recommends breastfeeding children till the age of two and many women continue thereafter. The young age of eligible volunteers (mean age of our study participants is around 28 years) mean that they are at the peak of their reproductive age and this [is] associated with the traditional desire for large families [which] means that some will be reluctant to delay having children or afraid of possible effects of intervention or contraceptive on their reproductive life*" (Respondent 5).

> *"Women were not willing to commit that as part of the protocol they will not fall pregnant. Many who were not taking contraception or used only condoms were not willing to switch to more reliable forms of contraception (e.g. injectables)"* (Respondent 2).

Some women were naïve about contraceptive use and concerned about its effects on fertility and would not enrol. Therefore, while some participants viewed contraception as a benefit of trial participation, others were reluctant to use contraception due to fear of side effects and stigma (Raymond et al., 2007):

> *"For most HIV prevention studies it is a requirement that women are using stable*

contraception for the duration of the study or until after a specified time period after enrolment. Women do experience difficulty in attending family planning clinics due to time and work commitments. Some also need the husband/partner's approval and do not always have a say in when to use and when not to use contraception."
(Respondent 9)

Many respondents noted that pregnancies also have a major impact on retention rates and are a major reason for why most women do not complete trials: *"Pregnancy during the trial resulting in discontinuation of vaccination is another challenge"* (Respondent 3).

Eligibility criteria: Best Practices/ Strategies for overcoming challenges

Most respondents reported facilitating access to contraception and family planning services as a strategy for ensuring that women meet the eligibility criteria of the study. In response to concerns that access to family planning services and to reliable forms of contraception may be a barrier, several respondents reported that sites either provide these services on-site or through agreements with off-site service providers:

"We have been providing on-site family planning with continuous family planning counselling. During counselling, our nurses put emphasis on long-term user independent family planning techniques" (Respondent 5).

"We have made arrangements with an off-site family planning provider to ensure easy access to contraceptive methods for those who might find access to contraception a barrier to participation" (Respondent 3).

Because most trial ethics approvals and eligibility criterion require it, respondents reported that sites did not enrol women who were pregnant or planned to become pregnant during the duration of the trial. Pregnancy was also noted as a reason for the withdrawal of women from the trial. Furthermore, it is suggested that women should receive ongoing counselling to emphasise the need to avoid becoming pregnant while they are part of the trial (cf. Kapoor, 2004). Respondents noted the importance of recommending reliable, long-term methods of contraception. The literature also emphasises the need for partner and community education regarding contraception and the importance of avoiding pregnancy during a trial. These efforts could be achieved through the education and community engagement campaigns reported by respondents as successful strategies for enhancing women's participation; and also through engagement and counselling of partners.

Respondents also noted the importance of recognising and addressing participant concerns about contraceptive use: *"They sometimes complain of adverse events related to*

contraception and one has either to change the method or reassure the volunteers" (Respondent 5).

It was also noted that providing support to breastfeeding women was a successful strategy for encouraging female enrolment: *"For eligible women breastfeeding children older than two years and willing to enrol in the vaccine trial, we have provided nutritional supplements for the children"* (Respondent 5).

b. <u>Duration of the trial</u>

Large-scale endpoint driven efficacy (phase III) trials may take as long as five years to complete, depending on incidence rates. Some respondents reported that women were dissuaded by the long term commitment required for participation in large scale efficacy trials: *"Others have said they become 'tired' of study procedures and the study is too long"* (Respondent 2) and *"Some women have a problem with the duration of the trial and the time required from them when participating in the trial"* (Respondent 10).

<u>*Duration of the trial*: Best Practices/ Strategies for overcoming challenges</u>
In addition to facilitating women's participation in trials and maintaining ongoing interest and engagement through strategies of accommodating their work and personal schedules; ongoing communication and community education; providing support and incentives like health care benefits; and encouraging partner support and involvement, several respondents noted the importance of acknowledging the participants' contributions to the study in order to overcome feelings of 'fatigue' or dissatisfaction with the trial duration:

> *"We found that recognizing and appreciating the participants' participation is invaluable. We do this by providing a certificate of participation that is laminated and signed by the director. We also offer small token gifts at various points in the trial. We obtain IRB approval to buy gifts that are not valued more than e.g. R10, 00"* (Respondent 2).

> *"Retention parties – annually we have get-togethers to encourage women who had enrolled early to acknowledge their participation. For those recently enrolled it provides an opportunity to continue with participation"* (Respondent 10).

Some of the respondents reported that *"celebrating events like World AIDS day and Women's day; [holding] end of year functions … for participants and their children"* (Respondent 10) and marking *"special days like Valentines day with gifts of chocolates"* (Respondent 11); were useful strategies in the retention of women participants and for engaging with the community.

Respondents also suggested *"acknowledging birthdays and other special days"* (Respondent 11) as strategies for enhancing the retention of female participants.

1.2.5 *Other challenges*

Several respondents also noted that sometimes women withdrew from studies voluntarily but did not provide reasons for their withdrawal. This is a challenge to retention.

> *"There are a number of challenges described in literature which could potentially prevent women from enrolling but we have not been able to definitely establish these reasons. Many eligible participants do not just turn up for enrolment and sever communication with the site. A study to look at some of these challenges particularly targeting those that have been found eligible but decline enrolment would provide important information"* (Respondent 3)

1.3 General Recruitment and Retention Strategies

In addition to the strategies described in response to challenges surrounding women's participation, respondents also noted more general strategies for the recruitment and retention of women in HIV prevention research:

> *"We designed some materials that specifically target females though these are distributed at information seminars. We have a brochure that talks about Women and HIV that describes the rationale for womens participation in vaccine trials. We also designed a poster with a female face. The poster features a popular female musician advocating for participation in vaccine trials."* (Respondent 3)

Respondents reported success using community-based education and awareness drives. Several respondents also noted using the popular media, like local newspapers and radio stations as a means of raising awareness about the study and of encouraging women to participate:

> *"We used articles in the local newspapers and also a slot on the local radio station to recruit women"* (Respondent 4)

> *"We used broadcasts on the local radio station to encourage women to participate. We generally used midday shows to target women as this is the time when they are likely to be at home, to have completed their chores and to be able to listen to the radio. In these shows we talk about the study and the vaccine but also about general health*

issues. We try to package the study in terms of general health" (Respondent 11).

Another respondent, however, noted that the use of local media was one of their least effect strategies for recruiting women into studies: "*The one strategy that did not seem to be effective in recruitment of women for studies is media advertising. We did not get many enquiries from women after media campaigns"* (Respondent 9).

Several respondents reported that recruitment of women for HIV prevention research via health service providers was not an effective strategy: *"Asking service providers e.g. doctors and nurses to refer patients has low yields"* (Respondent 2) and *"giving education sessions at service providers- e.g. clinics where there was lack of space and too much movement. And in most cases they are not interested in what you are saying because they are there to be provided a service they require"* (Respondent 4). Furthermore *"giving education sessions at some of the faith based organization - where sexual issues are taboo"* (Respondent 4) was also ineffective.

"A short recruitment process for example a one time contact to provide information about the study followed by informed consent and screening" (Respondent 3) was also noted to be ineffective.

2. LIMITATIONS

This exploratory study aimed to canvass the views of a key stakeholder group (trial staff dealing with the recruitment, enrolment and retention of women) on enrolment outcomes and practices by gender. While we intentionally targeted trial sites in Southern Africa, response rates from other countries, were notably poor. Therefore this study has limited generalizability to trial sites across Southern Africa. Nevertheless, given the general correspondence between our findings and the literature, it is possible to argue that the challenges and best practices identified by our sample may be relevant to the general context of HIV prevention trials in Africa, and other developing countries.

3. CONCLUSION

This study canvassed the views of HIV prevention trial site staff, dealing with recruitment, enrolment and retention, challenges and best practices associated with the inclusion of women in clinical trials. Respondents identified women's childcare and family responsibilities, their economic dependence on men, socio-cultural barriers to autonomous decision-making and participation, distrust of and myths about research, stigma around HIV and failure to meet eligibility criteria is key obstacles to the successful inclusion of women in clinical research. Trial

sites adopted various strategies to overcome these challenges including specific strategies like the provision of on-site child-care, financial compensation for trial participation, and the provision of family-planning services on-site. They also identified involving male partners and intensive community engagement efforts as critical strategies to address the macro-level obstacles like stigma and distrust of research, and to facilitate informed decision-making. Generally the obstacles identified by respondents, as well as the steps taken to overcome these obstacles (See Appendix 2 for a table of best practices), correspond with those identified in the literature. Our sample consisted of respondents from various HIV prevention fields, including HIV vaccines, microbicides and herpes suppression. Women-only HIV prevention trials, such as microbicide and cervical barrier trials were strategically sampled to provide important insights into useful mechanisms for including and retaining women in trials. In fact, Wassenaar and Barsdorf (2007, p. 47) recommended "closer cooperation and resource sharing between HIV vaccine and microbicide initiatives to promote best recruitment, consent, risk-reduction and retention practices in women". There has been increased acknowledgement in the value of convergence among various fields of HIV prevention. Indeed, as demonstrated by the results, important lessons can be learnt regarding the inclusion of women by partnering with other women initiatives such as microbicide prevention studies, who exclusively enrol women.

Only a few HIV vaccine trial sites reported better recruitment, enrolment and retention outcomes for women compared to men, and those that did indicate favourable outcomes for women noted that women present unique challenges in terms of their inclusion in trials.

There is a strong scientific, social and ethical imperative to enrol women. Women are at heightened vulnerability for HIV infection biologically and due to their social position. Therefore, they need to enroll in trials so that they can benefit from successful products. However, their inclusion in HIV vaccine trials has been largely inadequate and even when women are enrolled in sufficient numbers there are several obstacles to their retention in trials. To date, research exploring the challenges to the recruitment, enrolment and retention of women has been largely conceptual rather than empirical. This study provides important empirical data on challenges and best practices from the perspective of site staff at vaccine and microbicide trials. However, while trial site staff have important contributions to make in terms of women's participation in trials, future research should include potential and enrolled female participants and host communities to provide more detail and perhaps a different perspective on the barriers and enablers of their participation.

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Appendix 1: Email Questionnaire

Email Survey: Enrolment practices and outcomes by gender for HIV vaccine trials in developing countries

We are conducting a study that exploring recruitment and retention strategies at sites. Thank you for agreeing to participate in this study.

Please be aware that:

- Your participation is completely voluntary.
- All information will be confidential and your personal and institutional identity will be strictly protected.
- Only the research team will see your answers.
- By completing this questionnaire you are confirming your consent to participate

Demographic information:

Name (optional)	
Institution	
Highest qualification	
Position	
What are your primary duties/role in organisation?	
What HIV prevention technology is the focus of your research?	

1. **Recruitment and retention outcomes by gender**

    a) Please comment on the recruitment rates of men compared to women based on your experience in HIV prevention trials.

_____
_____
_____
_____

    b) Please comment on the enrolment rates of men compared to women based on your experience in HIV prevention trials.

_____
_____
_____
_____

    c) Please comment on the retention rates of men compared to women based on your experience in HIV prevention trials.

_____
_____
_____

2. Do you have a different strategy for recruiting men and women? If yes, please describe how they are different.

_____
_____
_____
_____

3. Please describe some of the challenges you have encountered when recruiting women into studies.

_____

_____
_____
_____

4. Please describe any strategies you have used to overcome the challenges you faced.

_____
_____
_____
_____

5. Please describe the strategies which you have found most effective in recruiting women.

_____
_____
_____
_____

6. Please describe the strategies that you have found not so useful in recruiting women.

_____
_____
_____
_____

7. What are the challenges that women face that prevent them from enrolling in trials?

_____
_____
_____
_____

8. Do you have a different strategy for retaining men and women in trials? If yes, please describe how they are different.

_____
_____
_____
_____

9. What are some of the challenges you face in retaining women in trials?

_____
_____
_____
_____
_____

10. What are the challenges that women face that prevent them from completing trials?

_____
_____
_____
_____

11. Comment specifically on the roles of the following in recruitment and retention of women in HIV prevention trials?

11.1. Financial incentives

_____
_____
_____
_____

11.2. Access to healthcare benefits

_____
_____
_____
_____

11.3. Community engagement activities

_____
_____
_____
_____

11.4. Other

_____
_____
_____
_____

12. Have you published any reports on this or related topics? If so, please provide the references.

_____
_____
_____
_____

13. Are you aware of published studies on this or related topics? If so, please provide refs?

_____
_____
_____
_____

14. Would you like to receive a copy of the report or materials generated by this study? Yes or No?

_____
___

15. Would you be willing to participate in a follow-up interview? Yes or No? If yes, please provide contact details.

_____
___

Thank you for your participation!

Appendix 2: Table of Best Practices

Best Practices for enhancing women's enrolment and retention in HIV prevention trials
Care responsibilities
Provide supervised, on-site childcare facilities to enable women to attend study visits more easily. Ensure a family friendly waiting and care area at each site.
Economic barriers
Employment commitments
1. Run clinic hours to accommodate women who work, e.g. Saturday and after hour's clinics. 2. Provide transport services between places of work and study sites to minimise time away from work. 3. Consider performing only absolutely necessary procedures at study visits when women are under time pressure.
Economic Dependence
Provide financial support to women, that is, reimbursement of expenses and consider payment for time and inconvenience
Socio-cultural barriers
Informed & autonomous consent
1. Educate and provide information to community and potential participants about: a. HIV generally b. Research c. Research Ethics d. The specific trial - This information should be available both in English (or the official language of the study) and the local languages 2. The informed consent process should be structured in order to empower participants to be fully aware of their rights, and the risks and benefits of trial participation (cf. IAVI, 2004; Kapoor, 2005). a. Participants should be informed of the ethical and regulatory bodies overseeing the study as well as the partners involved in the study. b. The right to autonomous, informed and voluntary participation as well as the right to withdraw must be emphasised. 3. To overcome some of the challenges posed by the need for partner consent for women's participation in HIV prevention trials, and the potential for partner objections to negatively affect retention: a. Partners should be included in the education, recruitment, enrolment and retention processes b. Couples-counselling and VCT is a potential entry point into educating partners around the research. This strategy has been argued to "facilitate couple communication and mutual support" and to create a 'safe' environment for disclosure of HIV status and trial participation and therefore to mitigate negative partner reactions (IAVI, 2004; Kapoor, 2004; 2005). c. Women should be encouraged to disclose participation to their partners. Sites can facilitate this by encouraging women to bring their partners to the site for further discussions. 4. Peer influences on women's decisions to participate in research are an important consideration. Peer-influence and support could form part of a successful information dissemination, recruitment and retention strategy:

a. Provide enrolled women with information about the trial and encourage them to act as a point of referral for other potential participants and to share their experiences with other interested women.
b. Informed consent could take the form of both an individual and group process:
    - Be aware of the fact that in some contexts women may be more comfortable discussing sensitive issues in a group situation, while in others this may raise concerns about privacy and confidentiality and one-on-one sessions may be better.
    - Women should be given the option to decide whether they prefer individual or group informed consent discussions.

5. Overall, it is important to ensure that the informed consent protocol is flexible and responsive to the demands of the situation.

Distrust & myths about the research

1. Developing trust and understanding between the study population and the investigators is critical in overcoming fears and misinformation related to trial participation. Investigators must be aware of any rumours or misunderstandings and should address these as they arise.
    a. Best practices and strategies for meaningful community engagement are outlined in UNAIDS-AVAC (2007) *Good participatory practice guidelines for biomedical HIV prevention trials.*
    b. Community participation and engagement is critical in the development of trusting investigator-community relationships.
    c. Community engagement activities and the establishment of community representative structures will alert investigators to rumours and concerns in the community and will assist in addressing these.

2. Suspicions about clinical research, for example that investigators are purposefully concealing information relevant to participation decisions, may arise because confidentiality procedures may be perceived to indicate secret or shameful experimentation – keeping information hidden may be seen to imply that the research is ethically questionable and in contravention of the cultural norms (cf. Essack et al, 2009 in press).
    a. Investigators should be transparent about trial procedures and information.
    b. Investigators should ensure that communities understand the importance of maintaining individual confidentiality.
    c. A means of achieving this transparency and ensuring understanding is meaningful community engagement.

3. Suspicions about research may be heightened in the face of negative media reporting on research. In order to overcome the potential impact of these negative messages on recruitment and retention in other similar trials, investigators must recognise and respond to emerging issues in the research context (UNAIDS-AVAC, 2007).
    a. Ongoing community engagement is critical to address potential negative influences.
    b. Investigators should anticipate emerging issues and should use these as tools for building research literacy in communities.
4. *UNAIDS-AVAC (2007)* lists 'building research literacy' as one of the core principles for ensuring meaningful community participation in research and for overcoming conflicts, confusion and mistrust and misconceptions of research.
    a. Investigators should build research literacy by providing structured education around research methods, design, terminology and ethics to potential participants and communities.
    b. Educating women about HIV and clinical trials is a strategy for overcoming low recruitment as a result of a lack of interest due to poor understanding of research.

5. A successful strategy for overcoming concerns about the safety of the product is the

provision of information about the product.
    a. Include clear descriptions of what is known about it on the basis of literature and experience and what is still unknown about it.
    b. Provide clear information about the possibility of vaccine-induced seropositivity.

Stigma and the fear of testing positive for HIV

1. Ensuring confidentiality about trial participation and of the results of HIV-tests goes some way to avoiding potential HIV/AIDS-related stigma and social harms (IAVI, 2004; Kapoor, 2004; 2005).
    a. Group information sessions should be supplemented with private, one-on-one opportunities for participants and potential participants to:
        - raise questions and concerns; and
        - to make autonomous and voluntary, informed decisions about research participation.

2. Research sites should be established in neutral locations and their link to HIV/AIDS or STIs should not be emphasised (cf. IAVI, 2004; Kapoor, 2005).
    a. A strategy would be to package women's recruitment and participation in HIV prevention trials in terms of general health.
3. Research teams should adopt a sensitive, compassionate and supportive stance when communicating HIV-status to participants and should support and facilitate disclosure of results or trial participation to others, where the participant so desires (IAVI, 2004; Kapoor, 2004).
    a. Encourage women to know their status and inform them of the treatment, care and support options available to them.
    b. Encourage women to disclose their HIV status and trial participation to partners.
    c. Encourage couple-counselling and VCT.

4. The establishment of high quality and women-friendly health provision is recommended in order to offset and overcome potential social harms related to stigma and discrimination (IAVI, 2004; Kapoor, 2004).
    a. Women should have regular access to healthcare and advice, either provided at the clinic or via facilitated referrals to other sites.
    b. Sites should also facilitate access to care and treatment for HIV/AIDS and related conditions – this could either be through making arrangements to provide ART when it is required or through establishing facilitated referral networks.
    c. If possible make provision for healthcare to participants' families.

5. Addressing misconceptions and gender-stereotypes which lead to AIDS-related stigma and discrimination involves community education and engagement.

Relocation & Migration & Loss to follow-up

1. Site staff should work out the follow-up schedule with participants to ensure that it is manageable and that they are accommodated.
    a. Where a woman indicates that she wishes to withdraw from the study, research staff should work with the participant to identify the barriers and facilitate continued participation if necessary. Where this is not possible the decision to withdraw should be respected.

2. Investigators should engage in formative research in the community to facilitate being able to locate addresses.

3. Ensuring that participants provide reliable contact details and are willing to work with study staff to ensure ongoing contact, depends on the establishment of a relationship based on trust between investigator and participant.

a. Investigators should invest time and effort into developing these relationships with participants.
b. Steps taken to overcome stigma and discrimination should also enhance the likelihood of women providing investigators with reliable contact information, as they may not be so afraid of the consequences should their participation in the study be revealed.
c. Research teams should encourage the establishment of referral and support networks among participants to improve the ability of investigators to maintain contact with participants who may be 'mobile' and otherwise difficult to trace.
d. Research teams should ask participants to provide the contact details of a trusted friend or relative, or should ask them to nominate a fellow participant who can be contacted in the event that contact cannot be established with the participant herself.

Trial Requirements

Eligibility criteria

1. Facilitating access to contraception and family planning services is a useful strategy for ensuring that women meet the eligibility criteria of the study.
    a. Sites should either provide these services on-site to overcome difficulties in attending family-planning clinics.
    b. Where sites cannot directly provide contraception and family-planning services, access to these should be made possible through agreements with off-site services providers.

2. It is good medical practice to avoid medications during pregnancy unless they are proven safe (cf. Kapoor, 2004).
    a. Sites should not enrol women who are pregnant or plan to become pregnant during the duration of the trial.
    b. Women should receive ongoing counselling to emphasise the need to avoid becoming pregnant while they are part of the trial (cf. Kapoor, 2004).
    c. Reliable, long-term methods of contraception should be recommended and, where possible, provided.
    d. Women's partners and the community will need to be informed and educated about contraception and the importance of avoiding pregnancy during a trial.

3. Research teams need to monitor women's reactions to and experience of various forms of contraception. This involves recognising and responding to concerns and adverse reactions through adapting the method where necessary.

4. Women who are breastfeeding may not meet the eligibility requirements of the trial because safety of test products in breastfeeding may not have been established.
    a. For eligible women who are breastfeeding children older than two years and who are willing to enrol in the trial, the provision of nutritional supplements for the children may be a useful strategy for encouraging female participation.

Duration of the trial

1. In addition to facilitating women's participation in trials and maintaining ongoing interest and engagement through strategies of accommodating their work and personal schedules; ongoing communication and community education; providing support and incentives like healthcare benefits; and encouraging partner support and involvement; it is important to acknowledge the participants' contributions to the study in order to overcome feelings of 'fatigue' or dissatisfaction with the trial duration. Some useful strategies include:
    a. Providing a certificate of participation.
    b. Offering tokens of appreciation (which have been ethically approved) at various points in the trial.
    c. Holding 'retention' parties annually to acknowledge women's participation.
    d. Celebrating events like World AIDS day and Women's day to encourage

participation and community support.

e. Acknowledging special days like Valentine's Day and life events like birthdays through text messages or token gifts like chocolates.