Partnering for Care
in HIV Prevention Trials:
A How-To Manual

By Kathleen M. MacQueen and Mike May
Family Health International

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Family Health International

National Institute of Allergy and Infectious Diseases

HIV Prevention Trials Network

USAID FROM THE AMERICAN PEOPLE

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About this Manual

This manual describes strategies for meeting the health care needs of participants in clinical trials related to HIV/AIDS. The information presented here comes from the knowledge gained from several studies: the Partnering for Care project, which was a collaboration between the HIV Prevention Trials Network (HPTN) and Family Health International (FHI), with funding from the U.S. National Institutes of Health; HIV prevention trials funded by the U.S. Agency for International Development (USAID) and implemented by FHI and others; and a study carried out by the Global Campaign for Microbicides with USAID funding, called *Mapping the Standard of Care at Microbicide Clinical Trial Sites*.

We created this manual to assist a wide range of readers. These include clinical trial developers, implementers, physicians, community partners, and other stakeholders. Health care advocates of all kinds could also benefit from some of the information that follows. In addition, we hope that this manual proves useful to a range of other readers, including public health experts, government leaders in trial communities and countries, and more.

Overall, we hope that this manual serves as a resource to support health care efforts in many ways. Consequently, we include many anecdotes to give readers a sense of on-the-ground experiences that support our conclusions. Also, to give this manual a very practical side, we include a series of how-to steps and checklists to simplify the application of this information.

Although this manual focuses on health care related to HIV/AIDS clinical trials, much of the information presented here also applies to other situations. For example, many of the steps explained here could strengthen health care systems behind clinical trials for various conditions and treatments. Moreover, communities — or even wider geographic regions — could apply many of the steps described here to build a more effective system of health care in general.

If you have suggestions for improving any of the following information, we would welcome them. Please direct your comments to:

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Executive Summary

Ensuring the effective care and treatment of people who are HIV positive is a critically important counterpart to the search for methods to prevent the spread of the virus. Many clinical trials of new HIV-prevention methods, such as vaccines and microbicides, are underway or planned in several parts of the world. The men, women, and children in these trials often face multiple health threats, not simply from HIV, but also from poverty, hunger, and other challenges that can drive poor health. Here, we describe a system for building bridges between the participants in these trials and the health care they need.

The Partnering for Care Project — undertaken by the HIV Prevention Trials Network (HPTN) and Family Health International (FHI), with funding from the U.S. National Institutes of Health — examined strategies at more than two dozen international clinical trial sites and described the challenges faced and successes achieved when addressing the health care needs of trial participants.

Based on the results of the Partnering for Care project, we developed seven steps to building bridges between the research context and local health care systems for participants in HIV clinical trials. (See box titled "Seven Steps to Effective Partnering for Care.") Several features in this series of steps encourage interactions between clinical trial developers, local communities, host countries, and clinical trial participants, and other groups. Also, this system of steps could be used by communities and organizations to develop care for any people living with HIV/AIDS, as well as those with other health problems.

Seven Steps to **Effective Partnering for Care**

Step 1: **Build a public health attitude among research leaders and staff**

Viewing research as a component of public health encourages research teams to find problem-solving opportunities.

Step 2: **Assess the local community's values, attitudes, and priorities**

A successful health care strategy requires understanding of and respect for local community perspectives.

Step 3: **Assess the assets and constraints of the public health system**

The larger, surrounding system of public health must be assessed and considered in developing a care strategy.

Step 4: **Engage the community**

The local community provides essential support for a trial, such as practical guidance for recruiting participants and for solving health care challenges.

Step 5: **Determine the extent of care to provide**

Sponsors and principal investigators must determine what form of care will be provided, over what duration, and whether it will be provided by clinical trial staff or through partnerships.

Step 6: **Build relationships with nearby resources**

Trial sites with nearby resources tend to build bonds that lead to better health care for the participants.

Step 7: **Develop a referral system**

These steps require a system that creates and follows a referral from start to finish, and documents the process.

Chapter 1:

The Power in Partnering

1

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The Power in Partnering

1

There are many ways that HIV/AIDS touches and connects all of us. Those infected with HIV experience direct consequences. Other people feel the impact through people they know — such as a family member, friend, neighbor, or coworker — or in their work as health care providers, outreach workers, or counselors. Even at a distance, we are connected through empathy generated by the global reach of this devastating pandemic. Moreover, this virus proves difficult to overcome. It can disguise or remodel itself, which presents researchers with a camouflaged or moving target. Though effective treatments now exist, it has been challenging to develop them, and a cure seems unlikely, at least for now. Given the rapid spread and complexity of HIV/AIDS, no person, community, nation, or organization should stand alone against this virus. To treat current patients and reduce the extent of future infections, public health workers must build a variety of partnerships around the globe.

As of December 2007, according to the United Nations Joint Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO), HIV afflicted an estimated 33.2 million people around the world, with some estimates reaching as high as 36.1 million. Moreover, the level of HIV infection in 2007 marked a new high. In that year alone, 2.5 million people acquired the virus and another 2.1 million people — roughly one-third of a million of them under the age of 15 — died from it.

Examining the HIV/AIDS numbers on a daily basis emphasizes the acute public health emergency created by this disease. "Every day, over 6800 persons become infected with HIV, and over 5700 persons die from AIDS, mostly because of inadequate access to HIV prevention and treatment services," reports the 2007 AIDS Epidemic Update. Although countries and communities around the world all address HIV/AIDS, some areas are affected more than others. In sub-Saharan Africa, for example, AIDS is the leading cause of death.

The broad impact of HIV and the difficulty in controlling or eliminating it as a health threat stimulate an ongoing series of HIV prevention and treatment clinical trials. Some of these trials test new pharmaceuticals designed to slow the progression of disease in those who are infected. Other trials study ways to prevent the transmission of HIV from an infected mother to a child during birth, or from one sexual partner to another. Some trials also test potential vaginal products to determine whether they can protect women from acquiring HIV during sex; others test the use of antiretrovirals (ARV) by both men and women to prevent acquisition. In fact, the list of interventions being tested covers a range of approaches. The AIDS Vaccine Advocacy Coalition (AVAC) keeps an updated list and description of HIV prevention trials on their Web site (http://www.avac.org/timeline-website/index.htm).

The Trials and Treatments

In addition to being at risk for HIV, people enrolled in these trials often face other health concerns. Some of the most common health issues revolve around reproduction, including other sexually transmitted infections and unintended pregnancies. Likewise, trial participants often live with other diseases, including cervical cancer, malaria, and tuberculosis. Other problems include social harms, such as domestic violence, family planning challenges, and substance abuse. In both developed and developing countries, participants in HIV prevention trials often lack access to proper foods, resulting in hunger and malnutrition.

The breadth of these health issues generates extensive medical and psycho-social needs among the participants. Unfortunately, participants often face long lines and waiting lists when seeking care. Moreover, stock-outs of even the most basic medicines are common.

People living with HIV/AIDS face even greater challenges in securing antiretroviral therapy (ART) — the only treatment that slows HIV. "The day when ART is available to anyone who needs it is a long way away," writes Henry Richardson in the *American Journal of Public Health*. Nevertheless, public health professionals continue to provide ART for an increasing number of people globally. According to *Ethical Considerations in Biomedical HIV Prevention Trials*, in low- and middle-income nations, two million people infected with HIV had access to ART in 2007, and that surpassed 2003's availability of treatment by five times. Nonetheless, "despite this tremendous progress in the roll-out of antiretroviral treatment, global coverage of needs is below 30%," continues this report.

Currently, people acquire HIV faster than medical professionals can secure ART for them. In 2006, for example, six more people acquired HIV for each new person placed on ART. Moreover, ART only slows HIV; it cannot cure it. Besides the fact that people must receive ART for life, antiretrovirals can trigger side effects that range from anemia to nerve damage and beyond, depending on the specific drug and person. Nonetheless, with appropriate medical care, people with HIV can live long, productive lives thanks to ART.

Effective HIV prevention is even more challenging than treatment. Nevertheless, antiretrovirals have been proven effective for reducing the risk of transmission from infected mothers to their infants, and male circumcision has been demonstrated to provide a level of protection against infection for heterosexual men. However, despite numerous trials of vaccines and microbicides, none has yet been found that is effective. For those currently being evaluated, it is also likely that any that prove effective will, in fact, be only partially effective. Consequently, biotechnology and pharmaceutical companies, public health and nonprofit organizations, and governments around the globe will continue to conduct clinical trials related to HIV prevention for the foreseeable future.

The Partnering for Care Study

As clinical trials continue, participants will also need medical care. The information in this manual was derived from clinical trial sites affiliated with the HIV Prevention Trials Network (HPTN – http://www.hptn.org/). Established in 1999, HPTN brings together more than two dozen international sites. Its current research agenda focuses on ART for prevention, behavioral interventions, control of sexually transmitted infections (STIs), and substance abuse. In the past, projects supported by HPTN also included microbicides and perinatal prevention strategies.

In 2004, HPTN identified a need to assess the care provided to trial participants at the participating sites. Specifically, HPTN was interested in studying both HIV-related care and the treatment of other medical needs. In addition, the network envisioned a study that would consider both care provided directly by the clinical trial sites and indirect care from referrals to other medical facilities. This overall vision emerged as the Partnering for Care project, with the goal of describing both the challenges faced and successes achieved by HPTN research sites when addressing the health care needs of trial participants. The Partnering for Care project was undertaken by HPTN in collaboration with Family Health International (FHI – http://www.fhi.org), with funding from the U.S. National Institutes of Health (NIH – http://www.nih.gov). The information in this manual also reflects experience gained from the conduct of HIV prevention trials funded by the U.S. Agency for International Development (USAID – http://www.usaid.gov) and implemented by FHI and others. In addition, this manual benefits from a study, *Mapping the Standard of Care at Microbicide Clinical Trial Sites*, carried out by the Global Campaign for Microbicides (GCM – http://www.global-campaign.org) with USAID funding.

FHI grew out of contraceptive research at the University of North Carolina at Chapel Hill in 1971. As an independent nonprofit organization, FHI pursues an international public health mission: "to improve lives worldwide through research, education, and services in family health." Moreover, FHI forges a wide range of partnerships with community groups, governmental and nongovernmental organizations, research institutions, and the private sector.

Among other goals, FHI helps to prevent the spread of HIV/AIDS. In 1987, FHI took charge of USAID's first five-year, HIV/AIDS prevention program in developing countries. Now, FHI has managed more HIV/AIDS programs than any other group in the world. These programs — operating in more than 60 countries — address a range of objectives, including monitoring and evaluating programs, preventing mother-to-child HIV transmission, and promoting prevention and care.

For HIV/AIDS programs connected with HPTN and FHI, USAID makes a strong partner. This federal government agency — created in 1961 — supports a range of policy objectives, including global health. From 1987 through January 2006, USAID launched HIV/AIDS prevention programs in 32 countries. Moreover, USAID has trained 40,000 people to support HIV/AIDS programs around the world.

All three of these organizations — FHI, HPTN, and USAID — realize that clinical trial participants need care that continues after the research stops. For example, *Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials* from UNAIDS/AVAC (AIDS Vaccine Advocacy Coalition) notes, "... trial participants have the right to access medical care for trial-related injuries and harm, and to the experimental product under investigation should it prove effective. In the specific context of biomedical HIV-prevention trials, participants who acquire HIV infection during the conduct of the trial have the right to access a comprehensive package of care, including eventual antiretroviral treatment, which is negotiated before trial conduct and defined in terms of components and timeframe."

As shown in the results of the Partnering for Care project, serving the ongoing needs of trial participants depends on developing a plan for care that includes specific features. For example, sustainability and continuity of care are best ensured if participants can be linked to appropriate health care in their local communities. Moreover, successful linkage requires establishing partnerships with local clinics and organizations, verifying that needed care is available, and ensuring that those who are referred actually receive appropriate care.

Take Seven Steps

This manual focuses on issues revealed in the Partnering for Care project. An effective health plan for participants in HIV/AIDS clinical trials depends on building bridges between the research context and local health care systems. To see how those goals can be achieved, the Partnering for Care project studied systems at various sites from multiple clinical trials. Such breadth of knowledge provides readers with possible approaches for handling the variety of challenges that might arise under different circumstances. For example, if a trial site lacks nearby medical resources, what might encourage or facilitate the trial staff to provide more care? Similarly, if leaders of a clinical trial develop partnerships to refer participants to other facilities, how can trial staff track the referrals?

We address these questions and others through a how-to approach. Using the results from the Partnering for Care project and related studies, this manual describes a seven-step approach to improving the care for participants in need during HIV trials, and for developing long-term solutions for post-trial care. (See box titled "Seven Steps to Effective Partnering for Care.") Each of the steps will be described in detail in later sections.

Seven Steps to Effective Partnering for Care

Step 1:

Build a public health attitude among research leaders and staff

When the most difficult challenges arise for meeting participant health care needs, success largely depends on the attitude of the research team, especially those who provide leadership. When research is viewed as a component of public health, research teams see problem-solving opportunities rather than obstacles.

Step 2:

Assess the local community's values, attitudes, and priorities

The best intentions can go astray if they are not grounded in an understanding of and respect for local community perspectives.

Step 3:

Assess the assets and constraints of the public health system

Any health care related to a clinical trial operates within a larger system of public health, including at the local, state, and national government levels, and that system must be assessed and considered in developing care strategies.

Step 4:

Engage the community

The effectiveness of any clinical trial or system of health care depends on getting local communities involved. This leads to many benefits, including support of a trial, helping to recruit participants, more effective health care during and after the trial, and a solid, long-term relationship between the health care system and communities for ongoing programs of care and future trials.

Step 5:

Determine the extent of care to provide

Early in the creation of a system, sponsors and principal investigators must determine what care will be provided and over what duration. In addition, it should be determined what care will be direct — provided by clinical trial staff — and what will be indirect — provided through partnerships with other medical facilities.

Step 6:

Build relationships with nearby resources

The strength of interaction with local resources — such as clinics, hospitals, and pharmacies — correlates with proximity. Trial sites with nearby resources tend to build better bonds that lead to better health care for the participants.

Step 7:

Develop a referral system

Simply building partnerships does not ensure effective indirect care. That requires a referral system — a process that creates and follows a referral from start to finish, and documents the process.

We understand that some experts might recommend a different order to these steps. Nonetheless, we based this order on a particular rationale. Specifically, Step 1 creates a mindset that will be receptive to what is learned in Steps 2 and 3. In combination, the first three steps provide a strong foundation for engaging the community as a partner in the research endeavor, which is Step 4. With a public health attitude, knowledge about the local health system and community, and informed input from the community, the research team is well positioned to make determinations about the extent of care to provide directly and by referral, which is Step 5. In many situations, however, the decisions made in Step 5 will be very tightly constrained by sponsors, research networks, research timelines, and funding. There needs to be recognition that such situations increase the potential for problems down the line, as those constraints might work against the ability of the research team to develop a plan that meets local standards for what is fair and equitable. Steps 6 and 7 logically follow from Step 5.

Even Bigger Steps

While these steps can guide a process for developing better health care for participants during and after a clinical trial, this approach can also yield other benefits. For example, this seven-step approach should foster a productive relationship between clinical trial developers, local communities, and host countries. The interactive nature of these steps makes community leaders and government officials interact with clinical trial leaders as partners in the overall process. That partnership encourages future interactions on additional clinical trials. Moreover, the interaction with communities and other organizations can also spark additional programs, such as educational or public outreach programs, that enhance HIV/AIDS prevention among community members.

This seven-step model also goes beyond health care in clinical trials. Communities and organizations could follow these steps to develop care for any people living with HIV/AIDS, as well as those with other health problems, from medical care to psychological and social assistance.

In the end, a wide range of partnerships between researchers and care providers can support the public health effort against HIV/AIDS. The global impact of this disease and the need for complex forms of treatment, as well as the value of behavioral steps to prevention, demand that experts with many skills — from analytical and clinical, to epidemiological and psychological — work together. The power of partnering makes up one of the key intentions behind the information provided here.

Chapter 2:

Methods Behind the How-To Steps

2

Chapter 2:
Methods Behind the How-To Steps

2

To develop a system of steps toward improved health care for participants in HIV/AIDS clinical trials, we worked from findings in the Partnering for Care project, as well as experience gained from HIV prevention trials funded by USAID and the Bill & Melinda Gates Foundation and carried out by FHI and others. The complete results from the Partnering for Care project are available in *Partnering for Care in the HIV Prevention Trials Network. Part I: Overall Findings*, by Kathleen M. MacQueen, Kerry McLoughlin, Patty Alleman, Holly McClain Burke, and Natasha Mack, and *Partnering for Care in the HIV Prevention Trials Network. Part II: Case Studies*, edited by MacQueen and McLoughlin. Here, we provide an overview of the Partnering for Care project and GCM's *Mapping the Standard of Care at Microbicide Clinical Trial Sites*.

In the summer of 2004, the Partnering for Care project started with a survey. Using e-mail, MacQueen and her colleagues contacted the principal investigators and study coordinators at all 33 of the HPTN sites. This survey simply asked — "yes" or "no" — if the sites had developed any partnerships to provide care for participants in clinical trials.

In June 2005, the leaders of the Partnering for Care project sent a second survey. Only those who had responded to the first survey received the second one. In addition, the second survey only went to staff at sites with an active or pending HPTN protocol between May 2004 and May 2005. For the second survey, those who responded "no" to the first survey were asked to describe health care referral options, regulatory requirements, and any other

policies related to care for trial participants. Principal investigators and study coordinators who responded "yes" to the first survey also received a second survey, which included the questions about health care referral options, as well as a request to describe their partnerships, among other questions.

By December 2005, the Partnering for Care project collected surveys from 16 sites. Then, the study leaders consulted with a project advisory group to select sites for case studies based on four criteria:

- Unique aspects regarding referral systems, referral follow-up, or capacity building
- Geographic diversity — at least one site from Africa, Asia, Latin America, and the United States
- Adequate detail provided in the survey or from follow-up contacts by e-mail and telephone
- Willingness on the part of the site research team to be a case study

As a result of the two surveys, follow-ups, and case-study criteria, the Partnering for Care project team selected seven HPTN sites for further study (see Appendix 2 for more details on each site):

- Fiocruz, Rio de Janeiro, Brazil
- Makerere University–Johns Hopkins University (MU–JHU) Research House, Kampala, Uganda
- Medical Research Council (MRC), Durban, South Africa
- National AIDS Research Institute (NARI), Pune, India
- University of North Carolina Project (UNC Project), Tidziwe Centre, Lilongwe, Malawi
- University of Pennsylvania, Philadelphia, Pennsylvania, USA
- University of Zimbabwe–University of California, San Francisco (UZ–UCSF) Collaborative Research Programme, Harare, Zimbabwe

With the case study sites selected, project leaders turned to in-depth approaches. From March through May 2006, social science investigators from FHI — working with HPTN staff at the seven case study sites — visited the clinical trial sites, referral treatment sites, and the communities in which the trial participants lived or worked. These visits included observations of the programs and discussions with staff at the trial and referral sites, as well as talking with members of community advisory boards (CABs) where they existed. Each site visit lasted at least five days, and follow-up contacts through e-mails and telephone calls provided additional information.

From the combined information collected, the leaders of the Partnering for Care project assessed how sites develop and maintain health care for clinical trial participants both through trial staff and referrals to partners. In addition, the Partnering for Care project looked for the challenges faced in creating and maintaining effective partnerships.

This manual also relies on findings from GCM's *Mapping the Standard of Care at Microbicide Clinical Trial Sites*, which was conducted in mid-2006. This study examined the care and prevention services provided for women primarily in clinical trials of microbicides used in HIV prevention. Specifically, this GCM study evaluated six microbicide trials and one trial that studied the use of diaphragms for HIV prevention.

The GCM study included three phases. First, researchers studied documents related to the trials, including study protocols, standard operating procedures, policy documents, and staff training manuals. Second, the investigators conducted telephone interviews with study sponsors and staff, including at least one principal investigator, from each site. Last, researchers visited six trial sites in four African countries. The visits included interviews with investigators and staff, observations of clinical facilities, and assessments of local and referral care.

We can combine knowledge from this variety of studies — including the Partnering for Care project, GCM's *Mapping the Standard of Care at Microbicide Clinical Trial Sites*, and others — to assess a wide range of health care strategies during clinical trials designed for treatments that might prevent HIV.

Chapter 3:

Results from the Partnering for Care Project

3

Chapter 3:
Results from the Partnering for Care Project

3

Health care for participants in HIV/AIDS clinical trials comes in two general forms: direct and indirect. Direct health care comes from the clinical trial staff, and indirect care comes through referrals based on partnerships with other health facilities, such as clinics and hospitals. The Partnering for Care project found that most HPTN sites use a combination of direct and indirect care.

Specifically, 13 of the 16 sites that responded to the FHI study use referral sites. Moreover, the HPTN sites arranged referrals with one to seven sites — most of them developed through partnerships with other organizations or facilities. In most cases, HPTN sites created referral systems to provide care that was not available through the trial. Some referral sites also provided technical or laboratory support. In addition, some HPTN sites developed partnerships for help with enrolling participants in studies.

The Partnering for Care project found that the balance between direct and indirect care depends on several — often interacting — factors:

- **Public health system constraints.** All HPTN sites work with participants with a range of health care needs. Moreover, the neediest participants were at sites where local health services struggled with long waiting lists and limitations in the level of care. Such constraints must be considered in developing a program of direct and indirect care.

- **Local community values, attitudes, and priorities.** The way people live their lives, interpret their experiences, and envision their collective future needs to be understood and respected. Cultural, historical, and political factors vary; a strategy that is successful in one context might fail in another.
- **Public health attitude.** Clinical trial leadership and staff must recognize the balance between research and health care challenges, meaning that trials must reach scientific goals while handling treatment needs. In many cases, the latter depends on developing partnerships for referrals.
- **Referral follow-up.** Only by following up on referrals can clinical trial staff evaluate the performance and limitations of a referral system. Referral systems can face a variety of challenges, including transportation needs, costs of referrals to both the program and the participants, pharmaceutical shortages, and so on.
- **Physical proximity.** Referral systems prove more effective when developed with nearby resources. By developing partnerships with nearby facilities or by setting up research sites near appropriate facilities, clinical trial staff can keep better track of referral success or failure and develop stronger partnerships with the referral agencies.
- **Capacity building.** The availability of health care resources depends on the research being conducted by a clinical trial, the capabilities of the organization running the research, and the resources available through the trial and local facilities and agencies. Building more capacity for health care depends on assessing these resources for strengths and weaknesses.
- **People living with HIV/AIDS enrolled in research.** Studies focused on participants who are infected with HIV often contain more in-house health care resources for direct care. On the other hand, studies that focus on healthy, uninfected participants often must rely more heavily on referrals to partners.

- **Community engagement.** To better understand the needs of participants, clinical trial leaders and staff and the local community must interact. Such interactions improve problem-solving and enhance the health care provided to participants and the community overall.
- **Partnership-building.** Many of the above factors depend on partnerships, particularly for referral care. Such partnerships develop through contacts of the clinical trial staff, by interactions with the community, and sometimes through unique circumstances that arise during a study.

Although HIV/AIDS clinical trials face a range of health care concerns encountered by participants, the needs often surpass medical issues. For example, the Partnering for Care project also documented a range of psychological and social challenges. Many of the HPTN sites developed systems that specifically addressed such additional needs. For example, in Kampala, Uganda, the MU–JHU team developed a Psychosocial Support Group that helps to meet a wide range of needs. (See box titled "The MU–JHU Psychosocial Support Group.")

The MU–JHU Psychosocial Support Group

Agnes Ssendege and other members of the MU–JHU team created the Psychosocial Support Group in 2003. Ssendege was a health visitor — part of a team of nurses and midwives that follows up on trial participants throughout a study.

That support group started when Ssendege arranged a meeting between HIV-positive participants in a trial and a visitor to the research site. The encouraging comments from the participants led Ssendege to see the need for a support group, where participants could share concerns and stories. The leaders of the MU–JHU project agreed, and the support group grew from five couples to 200 members in just one year. Eventually, the MU–JHU team made an official, full-time position for Ssendege as psychosocial coordinator. Ssendege — soon known simply as "Mama Agnes" — was called "one of our angels" by a member of the MU–JHU team.

Today, the Psychosocial Support Group provides many benefits beyond health care for trial participants. For example, one program makes small loans available to members to start businesses. Other programs provide grief counseling to families, skills for making and selling crafts, peers who provide counseling, programs for HIV-positive children, and more. In fact, the Psychosocial Support Group proved so effective that members of the MU–JHU team often volunteer their time to the group, including securing funding from the Doris Duke Foundation for a building for the group.

To meet medical needs and psychological support at HPTN sites — and certainly within any group focused on care related to HIV/AIDS — leaders must overcome one ongoing problem: sustainability. Many health needs, and particularly those of people living with HIV, extend well beyond the life of a clinical trial. To keep participants connected with the necessary care and treatment, clinical trial programs must build partnerships with health care in the local communities.

Some clinical trials have already provided extensive health care for participants. The GCM's *Mapping the Standard of Care at Microbicide Clinical Trial Sites* study, for instance, found that the women in those clinical trials — and even those who screened out — received some effective HIV-prevention services. They also received HIV testing, as well as pre- and post-test counseling. Almost all women screened for trial participation also received STI testing and treatment.

To maintain an effective system of health care for participants in an HIV/AIDS clinical trial, leaders must focus on the list of interacting factors: public health system constraints, public health attitude, stigma and discrimination, referral follow-up, community engagement, and so on. Furthermore, these factors must be considered at stages from trial planning through follow-up after a trial's completion.

Chapter 4:

Seven Steps to Improving HIV-Related Care

4

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4

Early planning forms the basis of any effective health care system for participants in an HIV/AIDS clinical trial. For example, *Ethical Considerations in Biomedical HIV Prevention Trials* from UNAIDS/WHO states, "The provision of antiretroviral treatment to trial participants who acquire HIV infection during the trial requires planning for logistics and implementation." In fact, planning makes up the foundation of all levels of health care offered to clinical trial participants. Nonetheless, it is not easy to meet those health care needs without jeopardizing the conduct of trials or detracting from the goal of identifying critically needed new HIV-prevention technologies. In an effort to help trial planners manage these issues, we used results from the Partnering for Care project and others to identify seven steps to developing a system of care.

As planners review these steps, they will see a variety of obstacles that can emerge. Developing an effective and lasting system of care requires an assessment of many factors, from medical and scientific to cultural and demographic. Indeed, by expecting challenges, planners stand a much better chance of success. Only then can they create a health care program that meets as many needs of the participants as possible.

Our seven-step plan follows.

Step 1:
Build a public health attitude among research leaders and staff

The success of a trial-related system of health care revolves around the attitudes of the people running the trial. Developing a public health attitude depends on several factors:

- Recognizing that HIV-prevention research is conducted in a larger context of health care delivery and public health policy
- Knowing that the research team might need to go beyond the minimum level of care necessary to meet scientific goals
- Understanding the limits of what the research team can accomplish in terms of providing health care while still meeting research goals
- Expecting to build partnerships to extend care
- Embracing the value of empowering community members to more effectively access health information and local resources for care
- Appreciating that a key component to sustainable improvements in the health of host-community members is strengthening the capacity of the local health system

In combination, these factors can fuel a better health care program, because they help the research team solve problems that may arise. Often, a "can-do" attitude grows from a stated sense of moral responsibility for the well-being of research participants that, in turn, creates a willingness to invest personally in building relationships, identifying resources, and creating solutions.

For instance, the research team at the MU–JHU project in Kampala, Uganda, wrote grants that sought funding to serve the needs of their participants. The staff also contributed personal time and money and arranged for community volunteers who helped study participants. Such altruism clearly goes beyond what is required of researchers.

Step 2:
Assess the local community's values, attitudes, and priorities

Developing a trial-related system of health care must fit with local cultural norms. According to *Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials* from UNAIDS/AVAC, "Respect for communities includes respect for communal values; protecting and empowering social institutions; and, where applicable, abiding by the decisions of legitimate communal authority." Consequently, a health care program for participants in a clinical trial must consider several factors:

- What are the key public health goals of the study population or local community?
- Is the local community open to working with outside groups?
- How does the local community view HIV/AIDS? For example, are infected people shunned?
- How does the local community view health care in general, and is it open to public health education?
- Are there any forms of treatment that go against local values? For example, is condom use stigmatized because it is associated with HIV or certain sexual behaviors?
- Is the local community involved in other issues — such as economic or political challenges — that could affect health care?
- What belief systems are present in the community, and how do people view the relationship between health and faith, prayer, and spirituality?

These factors can interact in ways that benefit or block trial-related health care. For example, HIV hit Brazil in the early 1980s, when the country also faced political unrest — battling a dictatorship. Still, those people fighting the dictatorship teamed up with nongovernmental organizations and medical professionals to actively battle this disease. As a result, HIV-prevention research in Rio de Janeiro works alongside the communities. As noted in *Partnering for*

Care in the HIV Prevention Trials Network. Part I: Overall Findings, Brazilian AIDS activist Herbert de Souza said, "AIDS has to be viewed as a social issue and not an individual problem." Planners of health care in clinical trials for HIV/AIDS can create even more thorough and effective programs by mirroring that philosophy.

To determine how local community values, attitudes, and priorities might impact health care in a clinical trial, see Appendix 4: Checklist — Local Obstacles and Issues.

Step 3:
Assess assets and constraints of the public-health system

Any trial-related system operates within a larger system of public health, and that must be assessed and considered in developing a trial-related program of health care. In particular, clinical trial planners must remember that a study takes place under a range of assets and constraints: local community issues, as well as larger economic, political, and social situations. This range of assets and constraints must be considered. For example, if a trial takes place in an area that often lacks crucial pharmaceuticals, simply referring participants for care for common ailments such as malaria will be inadequate. Guidelines for assessing assets and constraints are outlined in the box titled "Assessing Assets and Constraints from the Public Health System"; to apply these guidelines to the planning of health care for participants in a clinical trial, see Appendix 5: Checklist — Public Health System Constraints.

Assessing Assets and Constraints from the Public Health System

The following are guidelines that planners can use, adapted from the results of the Partnering for Care project:

- **Consider the common medical needs in the area, such as other infectious diseases. How are these needs likely to affect trial participants? How are they likely to affect trial implementation?**
- **Examine the available local care, such as clinics and pharmaceutical availability and cost. How can these be used to provide health care to trial participants? Will the trial staff need to provide additional time and materials to offset insufficient local resources? Is the cost of key pharmaceuticals prohibitive for the public sector?**
- **Consider the implications of marshaling local resources for participant care or of injecting new resources into the host community. Will doing so create or exacerbate inequalities between trial participants and nonparticipants?**
- **Do the local services limit the types of care offered at specific locations? Will this require trial participants to visit multiple locations for health care?**
- **Consider treatments that are likely to be needed by a participant's family members, including a spouse or children. Which conditions will the trial address, and how? How will providing these added treatments affect the trial financially and logistically?**

- **Consider economic constraints, such as lack of health insurance, even in developed countries. Will this prevent trial participants from receiving some forms of health care? Are free services available when needed?**

- **Study any ongoing changes in government programs related to care that might affect participants. Could these changes affect the ways participants seek health care? Will these changes affect the local resources that provide health care?**

- **Note other funding opportunities that could improve care. Could such opportunities reduce the financial responsibilities of the clinical trial? Could other financial resources improve the quality of health care for trial participants? Are there funds that researchers can access to improve care both within the trial and the larger community?**

Step 4:
Engage the community

Many of the steps listed here involve local communities in some way. Consequently, effective health care related to an HIV/AIDS clinical trial must involve the local community (see Appendix 6: Checklist — Engaging the Community). Engaging the community can produce community support of the trial which, in turn, helps to provide participants with more effective health care both during and after the trial. As well, a solid, long-term relationship with the community is important for ongoing programs of care and future trials. As *Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials* notes, "Effective *community* engagement during the entire life-cycle of a biomedical HIV prevention trial, and beyond, through genuine, transparent, meaningful participatory processes enhances both the quality and outcome of research." However, to make that engagement as strong as possible, the planners should involve communities before the trial begins.

Clinical trial planners and leaders can engage communities in a variety of ways: the following points are adapted from information in *Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials*.

- Budget community involvement and education into a trial's plan
- Begin involving communities early in the protocol development process
- Share goals of a study with communities through written plans or public meetings
- Make someone on the research team responsible for community interactions
- Develop a CAB or other formal means of collaboration, with regularly scheduled meetings and a range of members, such as:
  - Government representatives
  - Community members of various ages and sexes, particularly people who share the characteristics of the study population
  - People living with AIDS

- Local religious leaders
- Traditional healers
- Members of the local media
- NGO/CBO representatives
- Health officials

- Regularly review the researcher–community relationship through meetings between trial leaders and staff and the communities where the trial takes place

In the Partnering for Care project, researchers documented several examples of interactions that improved relations between community members and clinical trial planners and staff. In Philadelphia, for instance, a CAB made educational videos about research on an HIV vaccine. Such information, education, and communication strategies can be developed to foster not only dissemination and sensitization about research, but to ensure that researchers are informed about and engaged with communities in a substantive way.

For example, the NARI project in Pune, India, focuses considerable energy and resources on involving the local community. There, the HPTN principal investigator and community program supervisor give 30 percent of their time to activities related to community involvement. Moreover, the clinical staff contribute about 20 percent of their time to community activities. This project includes 15 full-time staff members who run a community outreach office that was designed specifically to build and nurture the project's interaction with the local community.

As another example, GCM's *Mapping the Standard of Care at Microbicide Clinical Trial Sites* found that STI care could improve through more work with local communities. The trials described in the GCM mapping study took place in areas with relatively high rates of STIs and limited public-sector services to diagnose and treat them, especially in women. Consequently, most of the trials provided STI testing and treatment for all women screened for trial participation, as well as treatment or referral for their sexual partners, as a service to the

community. Since STIs were secondary endpoints for all but one of the trials described, regular STI testing and treatment was done primarily for research purposes, but the decision to test and treat women at a first screening visit gave them free STI care, even when they proved ineligible to participate in the trial. The *Mapping* study concluded that trial staff could contribute in a sustainable way by training local providers in syndromic management of STIs and encouraging use of effective, single-dose treatments.

Step 5:
Determine the extent of care to provide, and the balance between direct versus indirect care

In *Ethical Considerations in Biomedical HIV Prevention Trials*, UNAIDS/WHO notes that a health care package for participants in HIV/AIDS clinical trials can involve many features:

- Counseling
- Preventive methods
- Treatment for other sexually transmitted infections
- Prevention of mother-to-child transmission
- Prevention and treatment of tuberculosis
- Prevention and treatment of opportunistic infections
- Nutrition
- Palliative care, including pain control and spiritual care
- Referral to social and community support
- Family planning
- Reproductive health care for pregnancy and childbirth
- Home-based care
- ART
- Legal assistance
- Services for orphans and vulnerable children (OVC)

A clinical trial team might not be able to provide this entire list. In fact, there is no consensus on the precise list of care that should be provided. For example, Henry Richardson writes in the *American Journal of Public Health* that when dealing with infected patients in a developing country, the "researchers might provide any of the following levels of care: 1) recommend treatment and provide a referral; 2) provide only palliative care for opportunistic infections;

3) provide palliative care and try to arrange funds to pay for ART; 4) provide palliative care and provide or pay for ART; or 5) provide palliative care, ART, and monitoring." But for how long should researchers provide care? Planners of a clinical trial should decide ahead of time what services to provide for participants and for what period of time, such as to the end of the trial or longer. The potential for the emergence of drug-resistant HIV strains when ART is stopped — with implications for both individual and community well-being — underscores the importance of thinking about the long term.

To an extent, the offered treatment depends on the skills and resources of the clinical trial staff. So, during planning, the in-house capabilities must be considered to assess the potential for direct care. Each site must decide how far down the list of health care needs the research team can go without depleting the time, resources, and energy needed to do the research (see Appendix 7: Checklist — Care and Treatment Package).

In some cases, the nature of a trial will not include staff who can offer basic health care to participants. For example, at the HIV Prevention Research Unit at the University of Pennsylvania Center for Addiction Studies, the staff runs behavioral studies. Consequently, most health issues among trial participants get resolved through indirect care, or referrals. Because referrals are so important, considerable effort has gone into developing a comprehensive list of agencies and organizations that provide needed services. Personal contact between center staff and key service providers is also emphasized.

Direct and indirect care offer both pros and cons. Direct care, for example, provides many benefits: Participants can get health care without going to clinics with long wait times; it can reduce strain on local health care facilities; and it can build goodwill between leaders of a clinical trial and the local community. On the other hand, direct care also creates some trouble spots, such as taking away time and resources from the trial itself, as already mentioned. Moreover, there is also a risk that research sites that provide substantial health care directly to participants will draw staff away from already stressed health care facilities, thus inadvertently undermining local capacity. Finally, depending on the degree of direct care provided, it might create

perceptions of undue inducement for people to join a trial. As a result, it becomes especially important to clarify the difference between standard of care and the research intervention during the consent process, as therapeutic misconception is common in many resource-limited settings.

With indirect care, obstacles might be more apparent, such as requiring participants to arrange care at other facilities, find transportation, and so on. Nonetheless, indirect care can also provide advantages, such as building relationships between clinical trial teams and local professionals and leaders. This type of care can also enhance sustainability of care for participants after the research has ended.

Different clinical trials might also encourage different forms of care. For example, GCM's report on *Mapping the Standard of Care at Microbicide Clinical Trial Sites* encourages cervical screening, in part because HIV-positive women run a higher risk of cervical cancer. There is also increasing support for providing women in microbicide trials with contraception to improve overall care, as well as to enhance research designs. Investigators in the GCM study also found that direct provision of contraception increased the time that participants spent on the study product. This increased the power of the study to show a difference between separate arms of the trial, because pregnant women could not use the product.

In some cases, trial leaders must consider health care for people who fail to qualify for a trial. For example, at the UZ–UCSF project in Harare, Zimbabwe, a clinical trial could not enroll HIV-positive people. Nonetheless, the local CAB wanted the trial leaders to provide care for people identified as HIV-positive during the screening process. As a result, the trial leaders developed a system of care for those people, which included both direct and indirect features. Those who screened ineligible for the study because they are HIV-infected received two additional counseling sessions at the research site and referral to services as needed, including general, opportunistic-infection, and social-welfare referrals. The partners of the potential participants who screened ineligible are also offered HIV testing.

Step 6:
Build relationships with nearby resources

The strength of interaction with local resources — clinics, hospitals, pharmacies, and so on — correlates with proximity. Trial sites with nearby resources tend to build better bonds that lead to better health care for the participants. For example, the Fiocruz site in Rio de Janeiro works with three government health care sites: two in the city and one in a very poor section outside the city. These three clinic locations provide patients with immediate access to some of the highest quality care in Rio. This collection of sites also gives participants a choice on where to seek health care.

Working with nearby partners provides several health care benefits:

- Improved ability to handle referral challenges
- Participants have easier access to further care, perhaps even within walking distance or near where they live or work
- Easier follow-up on referrals — for example, through meetings with referral staff

Working with nearby partners, though, can also create challenges:

- The proximity can make research staff feel compelled to escort participants to referral sites, which takes time and might violate a participant's privacy and confidentiality.
- Research staff can also be expected to provide more resources or staff time to referral sites than is possible.

In balance, however, nearby partners provide long-term benefits. For example, these relationships contribute to capacity building. "In the coming years, there will be increasing demands on clinical sites so that national governments, sponsors, and researchers should think about how to sustain site capacity and retain research staff expertise," according to *Ethical Considerations in Biomedical HIV Prevention Trials*. "Given the long time frames of biomedical HIV prevention

research, special attention to communication and transparency is needed in order to build and maintain trust with participating communities, and to sustain site capacity even after the end of a trial." Nearby partnerships can trigger such benefits, especially sustainability.

Likewise, GCM's *Mapping the Standard of Care at Microbicide Clinical Trial Sites* examined how care continued after the study. It also found that study sites that set up stand-alone clinical facilities to provide care cannot continue it when the study is over. Even if those sites were utilized for new research, they only provide care related to screening or participation for that trial. However, sites that provided care for participants through partnering and capacity building of established public health facilities and were co-located with them (e.g., within or next door) enabled screened-out women, families, etc., to continue to access the same level of care as those participating in the trial. One site set up a parallel, mobile system of care for participants, but it is questionable whether this system will be sustainable when the trial is over.

In building partnerships, clinical trial planners and leaders must know what they can provide. This can include:

- Funding
- Infrastructure, such as clinic repairs or providing laboratory equipment
- Staff time — including medical screening done as part of the research protocol, which reduces strain on nearby staff
- Supplies
- Training

For example, the UNC project in Malawi mandates that all medical staff contribute one day a week in local clinics and hospitals. In addition, this project provided laboratory use, medical and office supplies, pharmaceuticals, and other resources for the Kamuzu Central Hospital.

On the other hand, clinical trial planners and leaders must know what they expect from partners. This can include:

- Additional medical treatment
- Further testing
- Psychological or social benefits for participants

The partnerships can also go beyond medical facilities. Local organizations can help with community interactions. For example, at the UNC Project in Malawi, the community-based group, National Association of People Living with HIV/AIDS in Malawi (NAPHAM), refers participants to the clinical trials. This group is active in the CAB and conducts educational dramas about specific research studies in marketplaces, in collaboration with community education staff. Such connections provide even broader capacity building.

To build such partnerships, clinical trial leaders can use several approaches:

- Make contacts through acquaintances in the local community
- Connect with community members, perhaps through hiring a community liaison officer who can build strong local contacts and has effective networking skills, and who can visit referral sites on a regular basis
- Develop a formal partnering process, such as sending a member of the clinical trial staff to make a presentation to a potential partner identified by the community liaison officer
- Put agreements in writing, such as a "Memorandum of Understanding" or other locally relevant documents that outline what each will contribute to the partnership and how research participants will benefit

The sites studied by the Partnering for Care project used various partnership-building techniques. Projects in Durban and Hlabisa, for instance, used the community–liaison–officer approach. In Pune, a community programs supervisor works with the clinical trial's principal investigator to build and sustain partnerships. The key, really, comes from developing a partnership-building plan and continuing to work at it.

Step 7:
Develop a referral system

Many of the steps above mention indirect care through referrals, often with partners. Nonetheless, simply building partnerships does not ensure effective indirect care (see box titled "Trials with Tenofovir"). Getting the most effective indirect care requires a referral system — a process that creates and follows a referral from start to finish, and documents the process (see Appendix 8: Checklist — Creating a Referral System). Such a system works best if it includes several features:

- A formal referral procedure, such as providing a participant with paperwork that outlines the intention of the referral
- Mechanisms that get participants to the referral site
- A follow-up procedure

At the UNC project in Malawi, staff members found that participants or their family often failed to obtain indirect care simply because they did not go to the referral site. The reasons for not going were often related to lack of transportation. Sometimes they also resulted from a decision to go home first, especially if the participant was concerned about a long wait at the referral clinic, with the result that efforts made to facilitate the referral were undone. To bypass that problem, a nurse on the clinical trial staff was available to escort the participant to the referral site, providing transportation if needed, and thus ensuring that the participant could receive needed care in an expedited way. Thus, this solution addressed the realities of the local health care system, as well as participant concerns about time away from family and household responsibilities.

However, to track the effectiveness of a referral, clinical trial staff must follow up on it. All 13 sites studied in the Partnering for Care project used some type of follow-up procedure. For instance, many sites performed this follow-up through discussions with the participant on the next visit in the clinical trial. Likewise, if a study placed staff members at a referral site for some exchange of

services, this also allowed referral follow-up. Even if a participant screened out of a trial, some studies tried to follow up on any related referrals, either by contacting the screened-out participant or the referral site to see if participants were accessing care. However, in many places, referral sites may not provide any information on their clients so as not to violate their privacy and confidentiality. Follow-up of screened-out participants can also require considerable staff time, especially in areas where 25 percent (or more) of participants might be screened ineligible due to HIV infection or other health reasons.

Referral follow-up also exposes potential problems:

- Costs to participants at the referral site
- Drug stock-outs at the referral site
- Incomplete referral treatment
- Long waits for care at referral sites
- Transportation issues
- Understaffing at the referral site

However, by discovering such obstacles to referral treatment, the clinical trial staff could implement solutions, such as:

- Provide funding to participants to cover referral costs. Typically, covering these costs has a minimal impact on site resources, but it removes a major obstacle for participants. Covering such costs can also be accomplished via a financial contract between the trial and a local provider or organization if direct reimbursement to participants is problematic.
- Stock needed pharmaceuticals at the study or referral site
- Provide medical documentation to reduce strain on the referral-site staff, improve participant treatment, and reduce wait times
- Provide transportation to the referral site
- If a referral site is understaffed, the clinical trial team might be able to provide some staff hours

Two sites employed referral slips as part of a follow-up system. A participant received a slip that documented the needed treatment, and then the trial staff could see if the slips ended up at the referral site, indicating that the participant completed the referral. Although this seems like a good system, it provided mixed results at best. In some cases, a referral slip helped trial participants move ahead in treatment lines, which was helpful. However, in terms of tracking the success of referrals, the slips occasionally got lost at the referral site. This highlights one of the issues for follow-up of referrals: They should not add an additional administrative burden to an already over-burdened referral site.

In the end, a referral follow-up system depends on energy from the trial staff. Someone from the trial staff must make regular visits to the referral site to observe the complete process. Only then can follow-up problems be identified and repaired.

For an overview of the resources that can be used with these seven steps, see Appendix 9: Checklist — Resources to Implement. This checklist provides suggestions of approaches and likely timeframes.

Through these seven steps, clinical trial planners, leaders, and staff can develop an effective health care system for participants in an HIV/AIDS study. The ensuing results will benefit the participants and create lasting relationships between trial staff, community leaders, and partners.

4

Trials with Tenofovir

Between June 2004 and March 2006, FHI staff and others ran a Phase II clinical trial to determine whether tenofovir — an antiretroviral drug that has been used to treat HIV infection — could be used to prevent infection as well. The FHI trial was conducted in Cameroon, Ghana, and Nigeria, with funding from the Bill & Melinda Gates Foundation. As published in *PloS Clinical Trials*, too few HIV infections occurred during the trial to indicate whether tenofovir is protective, but this trial did show that short-term use of tenofovir is safe and acceptable for HIV-negative women at high risk of becoming infected. However, beyond the clinical results, this trial revealed some of the challenges in developing an effective referral system.

Before the trial started, FHI collaborated with host-country social scientists to conduct formative research at all sites. This research included assessments of the care and treatment available at each site for people living with HIV and AIDS. The clinical research teams at each site used this information to develop referral procedures for participants who tested HIV positive during screening, or during the trial itself. Here, we will focus on Cameroon, where the trial enrolled 400 women.

The Cameroon formative research team visited facilities and organizations that could potentially provide health care and services for the trial participants. In addition, researchers interviewed people living with HIV/AIDS and health care experts treating them to learn more about the resources available. Based on this information, the formative research team prepared a report, which was shared with the clinical research team. The latter then developed a referral system for women identified as seropositive. As planned, this system

would depend on a clinic that was implementing a new program for ART. Moreover, this clinic's chief medical officer was the main physician for the trial in Cameroon.

To facilitate referrals for all health care needs of trial participants, FHI added financial support for each trial site to hire a health counselor or referral manager. This position was designed to help trial participants obtain referral care, including women who tested HIV positive at screening and those who became HIV positive during this trial. The health counselor would also handle other obligations, including accompanying any seropositive woman to the referral service to help her register, developing relations with referral care providers, maintaining a database of referral options, and other administrative duties.

Despite these efforts, FHI staff found that Cameroon's referral system was having problems. About the same time, Act Up-Paris raised concerns about the ability of seroconverters to access HIV care and treatment, including ART. Ultimately, the difficulties with the referrals seemed to stem from poor communication and lack of an explicit agreement with the ART program at the local clinic prior to the beginning of the trial and referral of participants for care. As controversies about the trial mounted, tensions also increased with regard to referrals from the trial to the ART program.

In February 2005, Cameroon's Ministry of Public Health suspended this trial's ability to provide the study product (tenofovir or placebo) to participants. The Ministry's subsequent review of study procedures resulted in a number of recommendations, all of which were addressed. However, permission to restart the trial was never given, and FHI closed the Cameroon trial in September 2005.

Still, a meeting of various stakeholders spawned a plan for long-term care and treatment for the 10 women in Cameroon who seroconverted during the trial. This included funding for 10 years of pre-ART care and five years of ART care. The Ministry decided that a government hospital should provide this care and treatment. Consequently, FHI negotiated the 15-year contracts and deposited funds (provided by the Gates Foundation) to provide care for the women who became infected while enrolled in the tenofovir study in Douala, Cameroon.

Despite these efforts, it continues to prove extremely difficult to link the 10 women from the trial with the care and services that had been negotiated on their behalf. FHI staff have communicated repeatedly with contacts at the government hospital, but have not yet received any response. Efforts to work with a local community organization to facilitate the relationship between the seroconverting women and the hospital were initially successful, but then fell apart when a key person left the organization.

Based on this experience and other work, FHI now requires that referral procedures for seroconverters be formalized and standardized for the HIV prevention trials that it implements. Considerations when establishing such procedures should include: formal agreements with referral sites, designated funding to support the referrals, staff that manage referrals, and documentation that ensures that the procedures create the intended outcomes.

Chapter 5:

Incorporating Ethics

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5

In organizing the health care treatment of participants in clinical trials aimed at preventing HIV/AIDS, trial planners and staff must consider various ethical obligations. The preceding chapters touch on some of these obligations, particularly through examples, such as keeping in mind constraints created by cultural norms. Of particular note, the practices described here are closely aligned with principles of justice and fairness. They both seek to meet the needs of the participants and to minimize creating new disparities in health care access based on research participation. Wherever possible, they attempt to raise standards for the community as a whole. This chapter outlines further ethical issues and how to assess them.

Much of the ethical challenge lies around ancillary care, or care that is provided even when it is not part of the study. As noted by participants in the *2006 Georgetown University Workshop on the Ancillary-Care Obligations of Medical Researchers Working in Developing Countries*, "[w]hichever arguments supporting researchers' ancillary-care obligations are accepted, it is clear that these obligations extend to diseases and conditions unrelated to what is under study. The implications of justice are not restricted to the target disease alone; neither are the implications of due concern for welfare, rescue, or what is effectively entrusted to researchers by consenting to participate in certain procedures." The participants outlined four guidance points ("The Four Ps") that should be considered in ethical discussions of ancillary care obligations: positive duty, planning, partnership, and practical provision. (See box titled "The Four Ps.")

The Four Ps: Guidance Points on Ancillary Care Obligations

The participants in the *2006 Georgetown University Workshop on the Ancillary-Care Obligations of Medical Researchers Working in Developing Countries* identified the following points as basic to ethical guidance on ancillary-care obligations.

Positive duty: Researchers and research sponsors, especially those working in developing countries, have some positive moral obligation to provide some ancillary care to their study participants (or to see to it that their participants receive such care).

Planning: Researchers and research sponsors, especially those working in developing countries, should develop plans, both in general and for each protocol, for meeting the ancillary care obligations that may be expected to arise. They should also take account of the unpredictable nature of ancillary care needs and plan accordingly.

Partnership: These ancillary care plans should be developed in dialogue and partnership with the host community, in ways that maintain respectful interaction; avoid displacing or disrupting local health care structures; and represent the population of potential study participants, community advisory boards, and the local medical community.

Practical provisions: Where they have foreseeable ancillary care obligations, researchers and research sponsors should take definite practical steps toward meeting these obligations. This might mean hiring a physician with certain competencies as part of the local study team, setting aside a certain line item or percentage of the budget, or forming partnerships with those who can provide drugs or with development agencies that can aid in improving the local infrastructure.

Unfortunately, the qualitative nature of these factors means that no simple formula answers the question: Should the trial staff provide a specific form of ancillary care in a particular circumstance? Like many of the topics discussed in this chapter, trial leadership must weigh various factors — sometimes, on a case-by-case basis — to determine when ancillary care will or will not be provided. The qualitative nature of the decision also underscores the importance of community engagement and participation, as described in the UNAIDS/AVAC document on *Good Participatory Practices in Biomedical HIV Prevention Trials*.

The health care package for trial participants should also include discussions of potential benefits and risks. Every clinical trial carries some medical risk, and an HIV prevention trial can generate additional risks, including:

- Anxiety
- Depression
- Potential public discrimination or stigma
- Stress on the participant and possibly the family

Where possible, counseling and care should be available for participants who experience side effects. In addition, clinical trial staff should counsel participants on methods of reducing risk during and after the trial.

Given some of the potential risks — particularly public discrimination or stigma — participants should also be assured that all information and data will remain confidential. For example, in *Guidelines on Protecting the Confidentiality and Security of HIV Information: Proceedings from a Workshop*, UNAIDS writes, "*Confidentiality* relates to the right of individuals to protection of their data during storage, transfer, and use, in order to prevent unauthorized disclosure of that information to third parties." Any trial plan should include a written confidentiality policy that describes how information and data will be collected, stored, transferred, and released. Typically, a confidentiality and security officer oversees such tasks, but the entire trial staff must also be aware of the procedures and know how to implement them. Otherwise, the collection of

information on testing and treatment cannot be kept secure, which could cause damage in the lives of participants.

Confidentiality needs to be explicitly considered when developing a referral plan, especially for HIV-positive research participants. In fact, participant concerns about confidentiality can be a significant barrier to effective referrals for those newly discovered to be infected.

Additional challenges emerge when prevention trials are implemented across multiple sites in multiple countries. The UNAIDS/AVAC document, *Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials*, notes that local ministries of health, ethics committees, and regulatory bodies might have divergent requirements. Trial sponsors, in turn, might try to establish uniform standards for participating research sites. At one site, for instance, the sponsor's requirements might provide a minimal baseline, while at another site, the sponsor requirements might fall below the baseline required by local research governance. Negotiating such differences and arriving at solutions that are feasible and equitable will likely remain a challenge for some time to come. The Seven Steps outline a strategy for navigating these ethical challenges.

Appendices

Appendix 1:
Abbreviations Used in this Manual

1

AIDS: acquired immunodeficiency syndrome

ART: antiretroviral therapy

ARV: antiretroviral

AVAC: AIDS Vaccine Advocacy Coalition

CAB: community advisory board

GCM: Global Campaign for Microbicides

FHI: Family Health International

HIV: human immunodeficiency virus

HIVNET: HIV Network for Prevention Trials

HPTN: HIV Prevention Trials Network

HVTN: HIV Vaccine Trials Network

MRC: Medical Research Council, Durban, South Africa

MTCT: mother-to-child transmission

MU–JHU: Makerere University–Johns Hopkins University

NARI: National AIDS Research Institute, Pune, India

NIH: U.S. National Institutes of Health

PEPFAR: U.S. President's Emergency Plan for AIDS Relief

STI: sexually transmitted infection

UNAIDS: Joint United Nations Programme on HIV/AIDS

UNC: University of North Carolina

USAID: U.S. Agency for International Development

UZ-UCSF: University of Zimbabwe–University of California, San Francisco

WHO: World Health Organization

Appendix 2:
Site Descriptions

2

This appendix provides an overview of each of the seven sites participating in the case studies for the Partnering for Care project. For more details, see *Partnering for Care in the HIV Prevention Trials Network. Part II: Case Studies.*

Fiocruz, Rio de Janeiro, Brazil

The Brazilian government plays a fundamental role in health care through its universal health system. This includes treating HIV/AIDS in Rio de Janeiro. For example, in 2006, more than 80 percent of Brazilians who needed ART received it, according to UNAIDS. In addition, the government provides ART for free.

The Brazilian government also sponsors Rio's HPTN clinical trial site. It participated in two HPTN trials that studied serodiscordant couples, as well as many clinical studies directed by other organizations. This site consists of an on-site clinic at Fiocruz, called the Evandro Chagas Clinical Research Institute, and two off-site locations at hospitals: Nova Iguacu General Hospital (Nova Iguacu) and Servidores do Estado Hospital (Servidores). Fiocruz and Servidores lie inside Rio, and Nova Iguacu lies about an hour (by bus) outside the city. Nova Iguacu includes extremely poor areas, and this hospital's emergency room receives an average of 1,500 visits per day.

The Evandro Chagas Clinical Research Institute in Fiocruz manages this three-location site. All data and laboratory management come from Fiocruz.

Makerere University–Johns Hopkins University (MU–JHU) Research House, Kampala, Uganda

Kampala is Uganda's capital and is home to more than one million people. In 2005, according to UNAIDS, HIV infected nearly 7 percent of the adults in the country. Of those who needed ART, about 50 percent received it. ART is freely available from several sources, including government hospitals and various treatment centers with public and private support.

This HPTN site has been active for 20 years. This university-based site has participated in various clinical trials, including those for preventing mother-to-child transmission of HIV, tests of an HIV vaccine, and other research. It provides services from the study's clinic and Mulago Hospital, which is at the same location as the HPTN site. The staff at this site spends about 30 percent of its time providing care.

This HPTN site has also participated in various treatment programs, including the MTCT Plus Program, which is funded by Columbia University. MTCT Plus provides care, treatment, and ARVs for families with an HIV-positive member.

Medical Research Council (MRC), Durban, South Africa

Durban is the second-largest city in South Africa and home to more than three million people. In 2005, nearly 20 percent of the people ages 15–49 were infected with HIV. Although government hospitals and the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) provide ART for free in South Africa, fewer than 20 percent of the people who need ART get it. In part, that low treatment rate could come from the small fee required to access the care at government hospitals and local clinics.

The MRC site in Durban started in 1969. This government-sponsored site focuses on research and has run various clinical trials, including studies of HIV prevention in women and serodiscordant couples. These studies included tests of microbicides.

The MRC also works with RK Khan Hospital, which is about 20 minutes outside of Durban. MRC and RK Khan Hospital have worked together on several clinical trials.

National AIDS Research Institute (NARI), Pune, India

Pune lies east of Mumbai (Bombay) in India's western state of Maharashtra, and was home to more than four million people in 2001. According to UNAIDS, less than 1 percent of the Indian population was HIV positive in 2005. Although the National AIDS Control Organization provides ART free of cost at governmental hospitals in six high-prevalence states, including Maharashtra, only 10 percent of the people who need ART get it.

The government-sponsored NARI study site was established in 1992, and it includes one on-site clinic and laboratory, and six off-site clinics around the city. Four of those sites are at hospitals, and one is at the National Institute of Virology. The other clinic is in Pune's red-light district.

The NARI site focuses on both care and research programs. For example, NARI has participated in several HPTN trials, primarily ones for serodiscordant couples.

University of North Carolina Project (UNC Project), Tidziwe Centre, Lilongwe, Malawi

Lilongwe is Malawi's capital and is home to more than half a million people, according to the 2003 census. In 2005, the HIV prevalence for adults ages 15–49 was just over 14 percent. This country provides free health care.

In 1999, the University of North Carolina and Kamuzu Central Hospital collaborated to form the UNC Project, which is located at the Tidziwe Center. This two-story building provides 20,000 square feet — including a conference room, exam rooms, a laboratory, a lecture hall, a library with online access, and a pharmacy — on the Kamuzu Central Hospital grounds. The laboratory can run a range of tests, including HIV testing, serum and cell separation and storage, and HIV viral-load testing.

The UNC Project has run several HPTN clinical trials, including tests of microbicides to prevent HIV infection and studies of ART. This site also works on non-HPTN studies, such as the Breastfeeding Antiretroviral and Nutrition study.

University of Pennsylvania, Philadelphia, Pennsylvania, USA

According to the 2000 census, more than 1.5 million people live in Philadelphia. The HIV prevalence rate in the United States was 0.6 percent in 2005. ART is available through many sources, including hospitals and various treatment centers with public and private funding. Several programs — including the Ryan White CARE Act and the Pennsylvania Drug Assistance Program — assist HIV-positive patients with the cost of care and treatment. Patients can also seek free care at health care centers run by the city of Philadelphia.

In 1989, the HIV Prevention Research Unit at the University of Pennsylvania Center for Addiction Studies started as an HIV Network for Prevention Trials (HIVNET) site, and now it is an HPTN and HIV Vaccine Trials Network (HVTN) site. This site focuses on HIV risk related to drug use and sexual practices.

The University of Pennsylvania site has participated in several HPTN clinical trials. These include trials on populations that include women at risk for HIV, intravenous drug users and members of their sex and drug networks, and serodiscordant couples.

University of Zimbabwe–University of California, San Francisco (UZ–UCSF) Collaborative Research Programme, Harare, Zimbabwe

Harare is the capital of Zimbabwe and home to more than 1.5 million residents, nearly 3 million in the overall metropolitan area. The HIV prevalence rate in Zimbabwe was just over 20 percent in 2005. Of those who need ART, only about 7 percent receive it. Zimbabwe is not a PEPFAR country, and it receives no Global Funds.

This university-based site — a collaboration between the University of Zimbabwe and the University of California, San Francisco — focuses on research. It includes one on-site clinic and works with other off-site clinics. Given the limited access to ART in Zimbabwe, the HPTN site often tries to make referrals for treatment for participants who screen out as HIV-positive during recruiting for a trial.

The UZ–UCSF site has participated in many HPTN clinical trials. These include various study populations, including high-risk but HIV-negative participants, men who have sex with men, women at risk for HIV, serodiscordant couples, and pregnant HIV-positive women.

Appendix 3: References

3

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Appendix 4:
Checklist — Local Obstacles and Issues

4

In creating a health care system for participants in a clinical trial for HIV prevention, planners — as well as trial sponsors, funders, and others — should understand local cultural norms. To assess these norms, planners can consider the topics listed in the checklist below. In addition, this checklist encourages clinical trial planners to evaluate specific obstacles and issues, as well as seek ways to overcome or resolve such constraints.

Checklist Guidelines

Public Health Goals: For the study population or local community, list the key public health goals, how these goals could affect the clinical trial, and possible approaches to getting the most from the trial in conjunction with the local population goals.

Views on HIV/AIDS: List the most common points of view in the local population regarding HIV/AIDS (e.g., fear, discrimination, etc.), potential impacts on the trial (e.g., causing potential participants to fear association with an HIV/AIDS study) or the participants (e.g., being shunned by other community members for participating), and possible solutions to related obstacles.

Health Care Views: List the most common perspectives on health care in general among community members (e.g., Are they inclined more toward traditional remedies or modern medicine? Are they open to public health education?), how this could affect the trial (e.g., influencing local opinions about the value of a given trial), and what tools might be used to work with local health care views.

Treatment Concerns: List any treatments or forms of health care (e.g., contraception) that are unacceptable, restricted, or stigmatized locally, potential impacts (e.g., participants not practicing "safe" sex), and how trial leaders or staff might handle such obstacles.

Social Constraints: List any local economic or political issues that could affect the trial or its participants, the possible impacts (e.g., a reduction in local health care facilities), and how trial planners or sponsors could resolve these issues.

Checklist — Local Obstacles and Issues

Public Health Goals	Top Goals	Potential Impacts on the Trial	Possible Solutions
Views on HIV/AIDS	Common Viewpoints	Potential Impacts	Possible Solutions
Health Care Views	Key Perspectives	Top Impacts	Possible Solutions
Treatment Concerns	Treatments	Potential Impacts	Possible Solutions
Social Constraints	Top Constraints	Top Impacts	Possible Solutions

Appendix 5:
Checklist — Public Health System Constraints

5

The health care that can be provided with any clinical trial depends on a range of constraints in the surrounding system of public health. To assess challenges and opportunities related to a specific clinical trial in a particular location, consider the items listed below. In addition, fill in the blanks to provide a framework in which to develop a trial's health care system.

Checklist Guidelines

Basic Needs: List basic needs that may be lacking in the trial's area (e.g., nutrition, housing, clean water), the likely impact of these basic needs on the participants and the trial, and potential partnerships or other ways to improve these conditions.

Common Medical Needs: List the most common medical diseases or conditions in the trial area, the top likely impacts of these medical needs on the participants and the trial itself, and potential solutions to any negative impacts.

Local Medical Resources: List the available facilities (e.g., clinics, pharmacies, etc.), the impacts that these facilities could generate for trial participants or the services that trial staff might need to cover, and how to resolve any related problems.

Local Service Limitations: List the key shortcomings in local health care services (e.g., limited available testing or treatments, particularly at specific sites), how these shortcomings will affect trial participants (e.g., traveling for some health care or not receiving it), and ways to improve these situations.

Likely Treatments Needed: List the top treatments that trial participants (and family members) will probably need, how this could affect the participants or the trial (e.g., requiring extra funding), and how to provide these treatments.

Economic Constraints: Note the top economic constraints (e.g., lack of health insurance) faced by trial participants, the crucial impacts on participants (e.g., not receiving some needed care), and what efforts could improve this situation.

Political Constraints: Determine any government changes that might affect health care for trial participants (e.g., dissolution of health care programs), the potential impact on the participants, and possible solutions.

Funding Opportunities: List potential sources (e.g., nonprofit health care organizations, government bodies, PEPFAR, Global Fund, etc.) of additional funding for health care for trial participants, what funds or resources to request, and how to approach these sources.

Checklist — Public Health System Constraints

Medical Issues			
Basic Medical Need	Top Needs	Top Impacts on the Trial	Possible Solutions
Common Medical Needs	Top Diseases/ Conditions	Top Impacts	Possible Solutions
Local Medical Resources	Available Facilities	Top Impacts	Possible Solutions
Local Service Limitations	Key Shortcomings	Top Impacts	Possible Solutions
Likely Treatments Needed	Top Treatments	Top Impacts	Possible Solutions

continued on next page

Checklist — Public Health System Constraints, *continued from previous page*

Socioeconomic Issues			
Economic Constraints	Top Constraints	Top Impacts	Possible Solutions
Political Constraints	Key Issues	Top Impacts	Possible Solutions
Funding Opportunities	Possible Resources	Possible Funds	Steps for Contact

Appendix 6:
Checklist — Engaging the Community

6

The success of any clinical trial for an HIV prevention strategy depends on a strong working relationship with the local community. This relationship can attract participants to the trial, reveal possible referral partnerships, and improve the long-term health care of trial participants and others in the community.

The steps outlined in the checklist below can help trial planners to incorporate community involvement from the start.

Checklist Guidelines

Target Population: List the eligibility criteria for the research project(s) to be implemented in the community and the numbers of men, women, and children (minors) to be enrolled.

Community Involvement Plans: List the goals of engaging the community (e.g., desired interactions), how a trial hopes to reach those goals, and the expected benefits (e.g., enrolling participants, increasing referral partnerships).

Community Involvement Funding: List items related to community involvement (e.g., developing a community advisory council), provide a budget for each item, and note the intended source of the funding.

Community Involvement Staff: Name the position — usually one person who works as a liaison between a clinical trial and the local community — and list expected duties or obligations.

Community Advisory Board (CAB): List the desired categories of members (e.g., diverse community members, local government leaders), note contacts who might put clinical trial leaders in touch with members in each category, and list the actual members of the council as they are added. For guidance on establishing community advisory mechanisms such as a CAB, see the UNAIDS/AVAC document *Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials*.

Review: Note the frequencies and forms of reviews between the clinical trial leaders and the local community (e.g., monthly meetings with the community advisory board or biannual "town meetings").

Checklist — Engaging the Community

Target Population	Eligibility Criteria		Enrollment Targets
			Men Women Children (Minors)
Community Involvement Plans	Goals	Techniques	Desired Outcome
Community Involvement Funding	Item	Funding	Source
Community Involvement Staff	Position	Obligations	
Community Advisory Board	Desired Members	Contacts for Members	Actual Members
Review	Frequency	Form	

Appendix 7:
Checklist — Care and Treatment Package

7

In the planning stage of a clinical trial for the prevention of HIV, leaders should develop a health care package for participants. Using this form, planners can create a checklist of treatments to provide, as well as specific details related to the treatment.

Checklist Guidelines

Treatment: List each treatment that will be provided as part of a clinical trial's health care package.

Recipients: Who will receive the treatment? Is it only for trial participants? Will it be available to others (e.g., those who screen out or family members of participants)?

Source: Who will provide this treatment? Will it come from trial staff (i.e., direct treatment) or from a referral group (i.e., indirect treatment)?

Duration: Determine how long a treatment will be provided. Will it only be available during the clinical trial? Will the treatment or care also be available for a prescribed period after the trial?

Funding: Note how the care and treatment will be funded. Will the clinical trial include a budget item for this care and treatment? Will the trial planners arrange with another group to fund this health care?

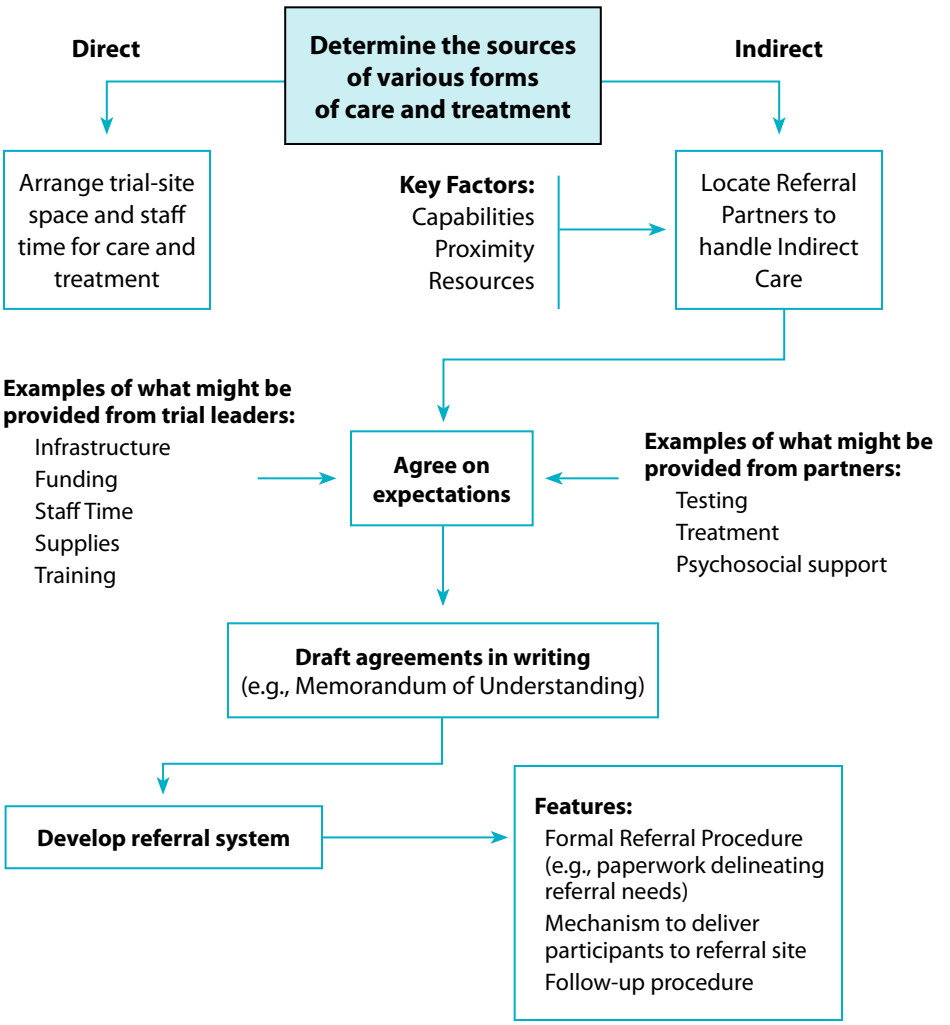
Checklist — Care and Treatment Package

Treatment	Recipients	Source	Duration	Funding

Appendix 8:
Checklist — Creating a Referral System

8

To develop a referral system, use the following checklist for general guidance.



Appendix 9:
Checklist — Resources to Implement

9

The following is a list of the kinds of resources that are likely to be needed to implement the seven steps.

Step	Resource Mechanism	Who	Timeframe
1: Build a public health attitude among research leaders and staff	Formal and informal communication; trainings; incentives	Principal investigator as primary lead with active involvement of other staff	Ongoing
2: Assess the local community's values, attitudes, and priorities	Community assessment or formative research prior to trial implementation	Social scientist plus additional team members as needed	3 months (excluding any required approvals)
3: Assess the assets and constraints of the public health system	Community assessment or formative research prior to trial implementation	Public health evaluator, community health evaluator, or social scientist with community/public health experience plus additional team members as needed	4–6 weeks (excluding any required approvals)

continued on next page

Checklist — Resources to Implement, *continued from previous page*

Step	Resource Mechanism	Who	Timeframe
4: Engage the community	Community advisory board or other formally constituted group plus information-sharing events (such as meetings, newsletters, or radio spots) as appropriate	Community liaison officer and principal investigator plus other staff as needed	Ongoing
5: Determine the extent of care to provide	Systematic review of protocol combined with results of previous steps	Principal investigator, clinical research staff, community advisory board with input from research governance bodies	2–4 weeks
6: Build relationships with nearby resources	Formal meetings with leadership at clinics, hospitals, service organizations, etc.; information-sharing; resource-sharing; and volunteering	Principal investigator, study coordinator, community liaison officer plus other staff as appropriate	Ongoing
7: Develop a referral system	Memoranda of agreement or understanding with referral organizations; monitoring of effectiveness	Health counselor(s), principal investigator, plus other staff as appropriate	Ongoing

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