



PROTOCOL

Non-inferiority of short-term catheterization following fistula repair surgery

Sponsors:	United States Agency for International Development Ronald Reagan Building Washington, DC 20523-1000	EngenderHealth 440 Ninth Avenue New York, NY 10001-1620, USA
	World Health Organization Avenue Appia 20 1211 Geneva 27 Switzerland	
Funded By:	The United States Agency for International Development	
Principal Investigator:	Mark A. Barone, DVM, MS, EngenderHealth, NY, USA	
Co-Investigators:	Ahmet Metin Gulmezoglu, MD World Health Organization +41 79 516 892 gulmezoglum@who.int	Joseph Ruminjo, MD EngenderHealth/Fistula Care Project +1 (212) 561-8458 jruminjo@engenderhealth.org
	Steve Arrowsmith, MD Fistula Consulting LLC + 1-505-979-1995 sda@fistulaconsulting.com	
USA Contact Information:	Mark Barone, DVM, MS + 1 (212) 561-8084 mbarone@engenderhealth.org	
Switzerland Contact Information:	Ahmet Metin Gulmezoglu, MD +41 79 516 892 gulmezoglum@who.int	
Study Coordinator	Mariana Widmer, MSc +41 22 791 43 23 widmerm@who.int	
Sites & Local Investigators:	Dolorès Nembunzu, Diplôme en Santé Publique et Promotion de la Santé, Diplôme de Médecine Tropicale, Docteur en Médecine Hôpital Saint Joseph de Kinshasa Kinshasa, Democratic Republic of Congo + 243 99 991 9812 donembunzu@yahoo.fr	Mulu Muleta, MD, MS, PhD Gondar University Hospital Fistula Unit Gondar, Ethiopia +251 911 225 042 m.muleta@yahoo.com

Sites and Local Investigators (Continued)	<p>Thierno Hamidou Barry, Docteur en Médecine L'Hôpital Préfectoral de Kissidougou, Guinea + 224 67 58 76 24 + 224 64 48 54 16 thiernoamidou2@yahoo.fr</p>	<p>Weston Khisa Wakasiaka, MBChB, MMED (OBS & GYNAE) Kenyatta National Hospital Nairobi, Kenya + 254 721 24 23 47 westonkhisa@yahoo.com</p>
	<p>Lucien Djangnikpo, CES, Docteur en Médecine Maternité centrale de Zinder Zinder, Niger + 227 20 510 729 djangnikpo@yahoo.fr</p>	<p>Ileogben Sunday-Adeoye, MD, MS National Obstetric Fistula Centre Abakaliki Ebonyi State, Nigeria +234 803 797 1503 juladeoye@yahoo.com</p>
	<p>Alyona Lewis, MD Aberdeen Women's Centre Freetown, Sierra Leone + 232 76 60 32 86 alyonalewis@rocketmail.com</p>	<p>Robert Olupot, MBChB, MMED (Surgery) Kagando Hospital Kasese District, Uganda + 256 772 604425 + 256 712 604425 olupotr@yahoo.com</p>

Project Summary

Background. A vaginal fistula is a devastating condition, affecting an estimated 2 million girls and women across Africa and Asia. There are numerous challenges associated with providing fistula repair services in developing countries, including a dearth of available and motivated surgeons with specialized skills, operating rooms, equipment, and funding from local or international donors to support both surgeries and post-operative care. Finding ways of providing services in a more efficient and cost-effective manner, without compromising surgical outcomes and the overall health of the patient, is paramount. Shortening the duration of urethral catheterization following fistula repair surgery would increase treatment capacity (by freeing available bed space and increasing availability of nursing staff), lower costs of services, and potentially lower risk of healthcare-associated infections among fistula patients. There is a lack of empirical evidence supporting any particular length of time for urethral catheterization following fistula repair surgery.

Objective. The primary study objective is to examine whether short-term (7 day) urethral catheterization is not inferior to longer-term (14 day) urethral catheterization in terms of incidence of fistula repair breakdown, among women with simple fistula presenting at study sites for fistula repair service.

Methods. This facility-based, multi-center randomized controlled trial (RCT) will test the non-inferiority of short-term (7 day) urethral catheterization compared to longer-term (14 day) urethral catheterization in terms of predicting fistula repair breakdown. The primary outcome is fistula repair breakdown three months following fistula repair surgery as assessed by a urinary dye test. Secondary outcomes will include repair breakdown one week following catheter removal, intermittent catheterization due to urinary retention and the occurrence of septic or febrile episodes, prolonged hospitalization (defined as a stay at the facility beyond one week following initial catheter removal related to an adverse event), catheter blockage, and self-reported residual incontinence. This study will be conducted among 507 women with simple fistula presenting at 8 study sites for fistula repair surgery over the course of 16-18 months at each site.

Management. The trial will be managed by EngenderHealth in New York, USA and the Special Programme of Research, Development and Research Training in Reproductive Health (HRP) at the World Health Organization (WHO) in Geneva, Switzerland.

Expected outcomes. If no major safety issues are identified, the data from this trial may facilitate adoption of short-term urethral catheterization following repair of simple fistula in sub-Saharan Africa and Asia. The results of this study will be disseminated in at least one international conference attended by fistula surgeons, several regional/local dissemination meetings and at least one publication in a peer-reviewed journal.

Description of project

3.1 Rationale and objectives of the study

3.1.1 Rationale

A vaginal fistula is a devastating condition, affecting an estimated 2 million girls and women across Africa and Asia. The primary cause of a vaginal fistula is prolonged obstructed labor: the fetus's head compresses the soft tissues of the bladder, vagina and rectum against the woman's pelvis, cutting off blood supply to the tissue, causing the tissue to die and slough away. The result is an abnormal opening between the vagina and bladder, or between the vagina and rectum, or both, and either urinary and/or fecal incontinence.

Approximately 80-95% of vaginal fistula can be closed surgically;¹ however, the provision of fistula repair services in developing countries is not without challenges. Specialized training and skills are necessary, especially to handle more complex cases, and this limits the availability of services. Women with fistula are predominantly poor and from rural areas, and often cannot pay for surgery or transport to a service site. Thus, fistula repair services must be provided free of charge. Fistula services are few and far between in Africa and Asia: the availability of services depends not only on the availability and motivation of surgeons with specialized skills, but also the availability of operating rooms, equipment, and funding from local or international donors to support both surgeries and lengthy post-operative care. In most contexts, the need for repair services exceeds the available human and infrastructural capacity. Moreover, the prolonged bladder catheterization that is frequently employed after surgery translates into a need for longer hospitalization, more intensive nursing care, increased costs, and thus decreased capacity for treating other patients. In light of these challenges, finding ways of providing services in a more efficient and cost-effective manner, without compromising surgical outcomes and the overall health of the patient, is paramount.

Duration of bladder catheterization has direct cost-effectiveness and health implications (particularly lowered risk of healthcare-associated infections). Publications about fistula surgery often state that bladder drainage through catheterization should continue between 10 and 14 days post-operatively.^{2, 3} However, in both fistula repair⁴ and other types of gynecological surgery,⁵ the duration of bladder drainage via indwelling urinary catheter is primarily based on custom rather than empirical research, and the duration of drainage varies substantially. For instance, a recent survey of 40 fistula surgeons conducted by Arrowsmith and colleagues⁶ found that catheterization durations following fistula repair surgery ranged from 5 to 21 days; 13% surgeons reported catheterizing women for 8 days or less following surgical repair of simple fistula. Preliminary analysis of a prospective observational study examining predictors of repair outcomes recently completed by Fistula Care/USAID* also found a wide distribution in post-repair duration of urethral catheterization among over 1,400 women from 11 sites in 5 countries. The distribution of duration of bladder catheterization seen was: 0-10 days: <1%; 11-14 days: 32%, 15-21days: 34%; and >21 days: 34%. A wide range has also been found for duration of catheterization following colovesical fistula repair: a retrospective review of data at

* Determinants of Post-Operative Outcomes in Fistula Repair Surgery. This multi center study was carried out at 11 sites in 5 countries between 2007 and 2010. A total of 1450 women were enrolled. Analysis is underway and findings are expected by mid 2011.

Massachusetts General Hospital conducted by de Moya and colleagues found that duration of catheterization following colovesical fistula repair secondary to diverticulitis ranged from 3-42 days.⁷ While colovesical fistula repairs differ considerably from vaginal fistula repairs (the former are abdominal surgeries undertaken primarily in response to complications of diverticulitis), these findings nonetheless indicate that not only is shorter-term catheterization currently being implemented for different types of bladder surgery, but that it may be a feasible alternative to longer term catheterization following the repair of simple fistula.

Short-term urethral catheterization may in fact pose no additional risk to patients, in terms of repair prognosis. For non-contaminated wound healing in general, the critical period involving granulation and neovascularization peaks at 5 days, inflammation is over in 1 week,⁸ and matrix deposition and cell proliferation continue until at least 30 days. Tensile strength increases rapidly during the first 5 days, although final tensile strength is not reached until over 100 days. No basic physiologic studies on the dynamics of wound healing in the bladder after fistula repair have been published to date and it is possible that the wound healing process following fistula repair may be more prolonged than noted above given the contaminated and chronic nature of most vaginal fistula.

One purpose of post-repair urethral catheterization is to provide an opportunity for adequate tensile strength to develop so that bladder distension does not disrupt the healing wound. The presumption behind prolonged catheterization is that the bladder heals better “at rest” (i.e. when it is not filling and emptying); however, there is little evidence to support this. A recent study by Boruch and colleagues (2010) evaluating the effects of long-term catheterization on extracellular matrix (ECM) biological scaffold remodeling following partial cystectomy in canines, found that early bladder filling (i.e. shorter duration of catheterization) mediated a constructive remodeling response.⁹ While biologic scaffolds composed of ECM are a cutting edge innovation not feasible for fistula repair in developing countries, the results of this study nonetheless indicate that removing the catheter early and allowing the bladder to begin filling and emptying, may be beneficial, rather than harmful, to bladder healing.

While evidence supporting long-term over short-term urethral catheterization is lacking, it is clear that longer duration of bladder catheterization has important implications in terms of both cost and healthcare-associated infections. For instance, Nardos and colleagues calculated the cost implications of urethral catheterization duration at the Addis Ababa Fistula Hospital, where approximately 1200 fistula repairs are performed annually. They reported that assuming no compromise in patient outcomes, a four day reduction in postoperative hospitalization due to early bladder catheter removal (10 vs. 14 days) would allow the number of patients who could receive surgical care to be increased by 20%.⁸ Longer duration of urethral catheterization may also increase risk of UTI. For instance, a recent Cochrane review of urinary catheterization following urogenital surgery in adults examined seven trials which compared shorter postoperative duration of catheter use to longer duration; these trials suggested that shorter-term catheterization was associated with fewer UTIs.¹⁰ In sum, short-term urethral catheterization has the potential to reduce hospital stays for women, thus freeing bed space, reducing costs per patient, and allowing for a greater number of patients to receive clinical care. It may also have implications for the probability of infection, and possibly sepsis, following surgery. Given the potential benefits of short-term urethral catheterization, and the fact that it is currently being

practiced by some fistula surgeons, empirical evidence is needed to determine the non-inferiority of short-term urethral catheterization compared to longer-term urethral catheterization.

3.1.2 Objectives

The primary study objective is to examine whether short-term (7 day) urethral catheterization is not worse by more than a minimal relevant difference to longer-term (14 day) urethral catheterization in terms of incidence of fistula repair breakdown among women with simple fistula presenting at study sites for fistula repair service.

3.2 Previous similar studies

There is a dearth of evidence supporting the benefit of either short-term or long-term catheterization following vaginal fistula repair surgery, or indeed, any type of gynecological surgery, with duration of catheterization informed by convention rather than empirical evidence. Only one study has been published on duration of bladder catheterization following obstetric fistula surgery to-date. Nardos et al.⁸ conducted a retrospective study of 212 obstetric fistula patients at Bahir Dar Hospital in Ethiopia, comparing patients catheterized for 3 different durations of time: 10 days (group 1), 12 days (group 2), and 14 days (group 3). The authors found no difference in the proportion of repair breakdown between the three groups, leading them to suggest that urethral catheterization for 10 days may be sufficient for management of less complicated fistula (and certain types of more complicated fistula). However, the conclusions that can be drawn from this study are limited, as the duration of urethral catheterization was influenced by the severity of the fistula (e.g. the relationship between breakdown and duration of catheterization may be confounded by severity of the fistula), and outcome was not assessed for all women, but rather only those who returned to the clinic with urinary complaints. The study was likely underpowered to detect differences that may have existed between the three catheterization duration groups.

Several studies have been conducted examining early catheter removal after other types of gynecologic and urogenital surgery. de Moya and colleagues conducted a retrospective analysis comparing 32 patients undergoing colovesical fistula repair in whom urethral catheters were removed 7 or fewer days (n=6) after surgery to those in whom urethral catheters were removed more than 7 days after surgery (n=26); the range of catheterization durations was 3 to 42 days.⁷ These authors found that patients with early catheter removal were no more likely to have significant complications (including UTI) compared with patients in whom the catheter was removed later. While no bladder leaks occurred in any patients, the results of this study must be interpreted with caution, given its observational nature and small sample size.

There is a mounting trend for decreasing the duration of urethral catheterization following surgery for a variety of pelvic disorders, such as vaginal prolapse^{11, 12} and hysterectomy.¹³ More research on the non-inferiority of short-term urethral catheterization relative to longer-term urethral catheterization following fistula repair in particular is warranted.

3.3 Design and methodology

3.3.1 General outline

The proposed study is a non-inferiority randomized controlled trial (RCT) comparing the new proposed short-term (7 day) urethral catheterization to longer-term (14 day) urethral catheterization in terms of predicting fistula repair breakdown, measured 3 months following fistula repair surgery. This study will be conducted among 507 women with simple fistula presenting at study sites for fistula repair surgery.

The objectives of this study can be uniquely met through this study design. First, as mentioned above, currently only a minority of surgeons practice short-term urethral catheterization on a routine basis; it would thus be difficult to obtain an adequate sample size for a retrospective record review or prospective cohort study. Moreover, the benefit of RCTs is that the process of randomization ensures that the control and intervention groups in the study are, on average, similar with respect to all potential factors that might confound the association between the intervention and the outcome. Women will be randomized to either shorter or longer-term urethral catheterization arms following surgery and just prior to catheter removal in the short-term catheterization arm (i.e. at 7 days). Random allocation, stratified by site, will ensure that within and across sites, women randomized to either intervention will on average be similar with regard to demographic and fistula characteristics and pre-, intra- and early post-operative procedures received. In contrast, in an observational study, the relationship between duration of urethral catheterization and fistula closure may be confounded by other factors. For instance, a provider's assessment of fistula complexity might influence the duration of catheterization chosen, and may also predict the outcome of the surgery. Finally, assessing outcome three months following fistula repair will ensure that any association between short-term urethral catheterization and fistula repair breakdown following hospital discharge that might exist would be captured.

The primary study endpoint is fistula repair breakdown as determined at a follow-up visit three months following the surgery. Repair breakdown will be assessed through administration of a dye test.

Detailed information about patient demographics, fistula characteristics, co-morbidities, pre-intra- and post-operative procedures conducted, and complications experienced will be collected from all study participants on standardized case report forms. Study procedures are discussed in more detail in sections 3.3.2-3.8 below.

3.3.2 Study outcomes

The primary study endpoint is fistula repair breakdown anytime after day 7 after urethral catheter removal up to three months following surgery. Repair breakdown will be assessed using a dye test; a urinary catheter will be inserted into the bladder, saline colored with dye will be introduced into the bladder via the catheter, and the suture line will be checked for leaks.

Repair breakdown is a possible complication of any fistula repair surgery and would result in the woman leaking urine again. Some women with a repair breakdown may heal spontaneously or may heal after long term (several weeks) urethral catheterization. Other women would require a second fistula repair surgery. In any case, it is likely that a repair breakdown would increase the length of a woman's hospital stay. Only women with simple fistula will be included in the study and they would have a positive prognosis for a second repair should the first one fail. As part of the normal pre-operative counseling women are routinely told of the risk of post-operative repair breakdown, the consequences and the potential treatment options.

Secondary outcomes will include the following: repair breakdown one week following indwelling urethral catheter removal, the need for intermittent catheterization to manage urinary retention, the occurrence of septic or febrile episodes, prolonged hospitalization, catheter blockage and self-reported residual incontinence. Prolonged hospitalization will be defined as a stay at the facility beyond one week following initial catheter removal.

3.3.3 Study intervention

The study intervention will entail removal of the urethral catheter at 7 days after surgery in the intervention arm and 14 days after surgery in the control arm. While 7 and 14 days are the target days for urethral catheter removal in the two groups, should it be necessary to remove the catheter either one day later or one day earlier (e.g. holiday, surgeon unavailable) in either group (i.e. 6-8 days or 13-15 days) these women will still be considered as compliant with the group assignment. Each patient will receive the same type of catheter and with the exception of the timing of catheter removal, all other procedures related to the removal of the catheter will remain the same across both study arms.

No drugs or new devices will be examined as part of this study.

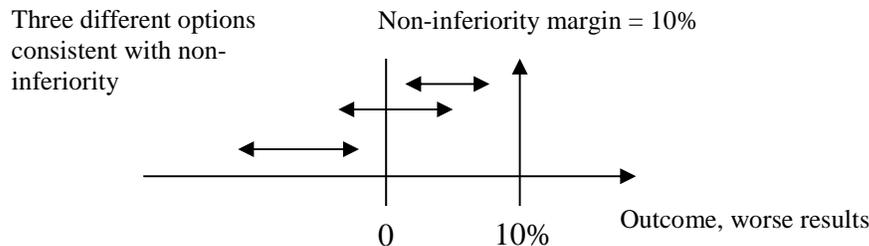
3.3.4 Sample size and statistical power

The research question of interest is whether short-term catheterization is not worse by more than a minimal relevant difference than longer-term catheterization in terms of achieving fistula closure. This question lends itself to a non-inferiority design, whereby the goal is to show that an experimental treatment is not worse by more than a minimal relevant difference than the standard treatment. The sample size formula for this design is $([Z_{1-\alpha} + Z_{1-\beta}]^2) * [P_S(1 - P_S) + P_E(1 - P_E)] / (P_S - P_E - \Delta)^2$ where $Z_{1-\alpha}$ is the critical value for the Type 1 error rate, $Z_{1-\beta}$ is the critical value for the power, P_S is the probability of success in the standard treatment group, P_E is the probability of success in the experimental group, and Δ is the equivalence limit or non-inferiority margin.

The choice of a non-inferiority margin, i.e. the smallest clinical difference that is acceptable between the two treatments, is based on a combination of clinical judgment and statistical reasoning. One technique that is used to define the clinical difference is to look at the effect of the gold standard (i.e. what is currently accepted as the desirable duration of catheterization) compared to placebo (i.e. no catheterization) in past trials, and to preserve a certain proportion of the benefit seen with the gold standard. In general, Δ should be smaller than the clinically relevant effect chosen to investigate the superiority of the standard treatment against placebo in previous trials. In the case of catheterization post-fistula repair, there are no data from prior

trials. Thus, we have relied on our own and outside experts' clinical judgment to determine that a margin of inferiority of 10% is an irrelevant small difference.

In other words, if the two-sided 95% confidence interval (95% CI) for the difference in fistula repair breakdown rates ("7-day" minus "14-day") lies fully to the left of the 10% non-inferiority margin, we will have proved non-inferiority of the "7-day" procedure at the level of significance $\alpha=0.025$; superiority (as a bonus) will be demonstrated at the level of significance $\alpha=0.05$ if the two-sided 95% CI lies fully to the left of 0.



Preliminary analyses were conducted using data from Fistula Care's prospective cohort study examining fistula repair outcomes in order to determine the probability of successful closure in women with simple fistula catheterized for longer periods of time (i.e. the equivalent of the "standard" treatment group in the study outlined here). Among the women with simple repairs in the prospective study for whom follow-up data were available (n=145), 87% had a fistula closed at follow up. Thus, we believe that it is reasonable to expect the failure rate (e.g. proportion of fistula that are not closed) to be between 10 to 15%.

Assuming 13% failure rate in the control group, non-inferiority will be demonstrated within the margin of 10% at a one-sided significance level of 0.025 and a power of 80% (calculated when failure rates in both arms are the same), with a sample size of 177 per arm (354 women in total). Adjusting by 20% for loss to follow-up and 10% for protocol violations and withdrawals, this would result in a total sample size of 507 women.

3.3.5 Study sites

We have identified 8 sites to participate in the study. Given a sample size of 507 women, and assuming 32% of all reported repairs are 'simple' repairs,* we will need a combined caseload of approximately 1,584 women at the chosen study sites to complete the study in a timely manner. The following selection criteria were used to select the sites:

- Ongoing routine fistula services at the site
- Sufficient fistula case load to recruit adequate numbers of participants. As discussed, we will only be including simple fistula and we estimate that this is about 32% of the all fistulas seen at a given site. In order to meet the sample size in reasonable period of time, we estimate we need 8 study sites, with a minimum case load of approximately 150 fistula repairs/year (all cases).

* As part of the observational study currently being conducted by Fistula Care, surgeons are asked to give a subjective assessment of the difficulty of each fistula repair (simple, intermediate and complex). According to this assessment, our preliminary analysis shows that 31.8% of women have been classified as having a simple fistula.

- Agreement to adhere to the study protocol in terms of the procedures outlined and also completion of the study forms.
- Availability of clinical staff for implementation, including a surgeon interested and motivated to serve as the site investigator, commitment of other surgeons that do fistula repairs at the site, and willingness of nursing staff to support the study protocol.
- Support from the facility administration for conduct of the study; e.g. assurances from the administration that the surgeon(s) would have adequate time for the duties required to conduct the study.
- Agreement to have an EngenderHealth research assistant based at the site to participate in the conduct of the study and to oversee the study activities at the site. This person will need a place for a desk, cabinets to store participant folders, supplies, etc, a private area for the informed consent process and conducting interviews, etc.
- Prior research experience
- Internet connectivity to facilitate communication

Fistula Care contacted 15 facilities in sub Sahara Africa, to ask about their interest in participating in the study. These sites completed a short questionnaire about current practices and caseload which we used in the selection process. We have identified eight sites in eight countries—DR Congo, Ethiopia, Guinea, Kenya, Niger, Nigeria, Sierra Leone and Uganda. Six of these sites are currently supported by Fistula Care and two of the sites are supported by WAHA International. Selection of Fistula Care supported sites is a strong consideration in terms of costs, as funds are set aside through other project mechanisms to support repair surgery.

The study sites all receive financial support from donors for fistula services, including pre-and post-operative care and the repair surgery itself. The RCT budget, however, does include some funds to support surgeries and follow-up care if supplemental funding is necessary at a few of the facilities. All of the study sites provide services free-of-charge to women with fistula. This includes cases where the fistula requires more than one surgery to complete the repair. Should shorter-term urethral catheterization cause increased wound breakdown in any of the study participants, the costs of any necessary clinical care (including additional fistula repair surgery) would be covered by the study sites.

The sites and local co-investigator are listed in the table below. Details of each facility follow.

Country	Facility Name	Co-investigator
DR Congo	Hôpital Saint Joseph	Dr. Dolorès Nembunzu
Ethiopia	Gondar University Hospital	Dr. Mulu Muleta
Guinea	L'Hôpital Préfectoral de Kissidougou	Dr. Thierno Hamidou Barry
Kenya	Kenyatta National Hospital	Dr. Weston Khisa Wakasiaka
Niger	Maternité central de Zinder	Dr. Lucien Djangnikpo
Nigeria	National Obstetric Fistula Centre Abakaliki	Dr. Ileogben Sunday-Adeoye
Sierra Leone	Aberdeen Women's Centre	Dr. Alyona Lewis
Uganda	Kagando Hospital	Dr. Robert Olupot

Hôpital Saint Joseph**Kinshasa, Democratic Republic of Congo**

This private, 300-bed urban hospital is part of a network of over 80 health facilities managed by the Kinshasa Archdiocese. The Hospital serves a significant portion of Kinshasa's population, and most patients are from middle and low-income brackets. A network of community leaders may refer patients from rural areas to the hospital or other clinics in the Archdiocese network. The Department of Obstetrics and Gynecology provides treatment to fistula patients. Ten beds and one operating theatre are routinely reserved for fistula services, and during "campaigns" 24 beds are available for fistula clients. The women who attend the hospital for fistula repairs are generally quite poor.

Gondar University Hospital**Gondar, Ethiopia**

This 200-bed public teaching hospital serves a mostly rural and poor population of four million from the surrounding region. Fistula clients receive services in the Department of Gynecology and Obstetrics; they are generally of low socio-economic status and travel far distances for care. The fistula unit has two operating rooms and 65 beds.

L'Hôpital Préfectoral de Kissidougou**Kissidougou, Guinea**

Fistula services are routinely available at this site in Southern Guinea. The patients who attend the hospital are from both rural and urban areas and diverse socio-economic backgrounds. Fistula clients here are generally poor, young women from rural areas. The 119-bed hospital has 16 beds available for patients with fistula. One operating theatre is used for all surgeries relating to maternal health and one surgeon, two surgeon assistants, four midwives, and seven nurses make up the fistula care unit staff. Routine fistula repair surgeries are available, and during fistula repair "sessions" national and international surgeons also provide services at this hospital.

Kenyatta National Hospital**Nairobi, Kenya**

This 800-bed hospital is the largest referral and teaching hospital in Kenya. The hospital is Ministry of Health Facility and it serves primarily low and middle-income patients. However, most clients seeking fistula treatment are poor. Ten beds are generally reserved for fistula patients; however during campaigns up to 60 beds are used for fistula clients.

Centre de prise en charge des FVV, Maternité central de Zinder**Zinder, Niger**

The Centre de prise en charge des FVV de Zinder (Center for Treatment of VVF of Zinder) is located within a public clinic that provides maternity services. Clients at the center are from urban and rural areas and from a range of socio-economic backgrounds. Most fistula patients (about 98%) come from rural areas and are very poor; treatment is provided to them for free. The facility as a whole contains 70 beds, 20 of which are for fistula clients. Fistula surgery is integrated with other activities and takes place two days per week in one operating theatre.

National Obstetric Fistula Centre Abakaliki**Abakaliki, Ebonyi State, Nigeria**

The National Obstetric Fistula Centre Abakaliki, a unit with the Ebonyi State University Teaching Hospital, was recently moved under the auspices of the Federal Government of Nigeria as the first national fistula hospital with mandate for treatment, training, rehabilitation, prevention and research. It is a stand alone fistula hospital containing 90 beds, a conference hall,

laboratory, pharmacy, records unit, and surgical unit. The surgical unit has one operating theatre, but several operating tables to allow three surgeries to be ongoing at the same time. The clients in the catchment area are highly indigent and have challenges providing for themselves. Services provided to these clients are free.

Aberdeen Women’s Centre

Freetown, Sierra Leone

The Aberdeen Women’s Centre is a non-governmental hospital with 46 beds, a fistula surgical centre, a maternity unit, and an outpatient pediatric clinic. Two wards, with a total of 25 beds, are available for fistula clients, and one operating theatre is regularly used for fistula surgery. Patients at the clinic are from a range of socio-economic backgrounds. While most patients who attend the clinic for pediatric and maternal care come from Freetown, most clients seeking fistula care are from rural areas and lack formal education. Some fistula patients come from neighboring countries. Many work as farmers or are engaged in small businesses.

Kagando Hospital

Kasese District, Uganda

Kagando Hospital is a private, 300-bed non-profit mission hospital which serves clients from rural, impoverished areas. Fistula treatment is one of many services available at this site, and the ward for fistula patients has 80 beds. Women who attend for fistula treatment are generally poor and lack formal education. The hospital has one theatre space for fistula surgeries that is currently undergoing extension. Kagando Hospital was a study site for the recently completed EngenderHealth/USAID study *Determinants of post-operative outcomes in fistula repair surgery: A prospective facility-based study*.

3.3.6 Research Study Participants

507 participants will be recruited from those women scheduled to undergo vaginal fistula repair surgery at study sites. The pool of potential study participants will include women with fistula who present at study sites for fistula repair surgery, however, women will not be asked if they are potentially interested in participating in the study until after the surgeon has determined that the woman is a suitable candidate for fistula repair surgery (i.e. her leakage is due to a fistula, she has no contraindications for surgery in general or to repair a fistula, etc).

3.3.6a Inclusion/Exclusion Criteria

All women who are part of the study sample (i.e. those women randomized) must meet the following inclusion criteria:

- Have a “simple” fistula, as determined at the end of fistula repair surgery (irrespective of the number of prior repair attempts and the cause of the fistula, with the exceptions noted under the exclusion criteria below)
- Have a closed fistula at completion of surgery
- Have a closed fistula 7 days after surgery (i.e. at the time of randomization)
- Understand study procedures and requirements
- Agree to return to the facility for one follow-up visit three months after the date of surgery
- Provide informed consent to participate in the study or in the case of non-emancipated minors, both consent to the study and receive proxy consent to participate in the study
- Have no contraindications precluding their participation.

Women will be excluded if there is one of the following conditions:

- Have a fistula that is determined to be “not simple” (i.e. intermediate or complex)
- Have a fistula that is radiation-induced, associated with cancer or due to lymphogranuloma venereum (These cases will be excluded because the healing process is very different from fistula resulting from other causes. We expect there to be few cases of these fistulas at the study sites)
- Have a fistula that is not closed immediately after surgery or 7 days after surgery (i.e. at the time of randomization)

No age restrictions will be placed on study participation. It is possible that at some study sites young women/girls who are minors will present for fistula repair, with or without a guardian. A person will be determined to be a "minor" in accordance with the legal age of adulthood in the country in which the research is being conducted, and in accordance with local legal definitions of an “emancipated minor” (e.g. a minor who is married or has children). Proxy consent for non-emancipated minors will be sought in accordance with host country legislation and, where appropriate, will be obtained from a relevant legal authority (i.e. parent, guardian or others with parental responsibility). Proxy consent will not substitute for the minor’s own consent, but will supplement it. Proxy consent will not be required for "emancipated minors."

Given the limited number of empirical studies examining the relationship between duration of catheterization and fistula repair outcomes, and the possibility that the effect of catheterization duration on repair outcomes differs across strata of fistula complexity, this study will be restricted to those women considered to have a “simple” fistula. We define “simple” as those fistulas that require less technical skill to repair surgically, which in turn means that prognosis for closure after repair, is high and likelihood of complications is low. This is the safest, most conservative approach for the first RCT to examine duration of catheterization.

Surgeons will decide, at the end of surgery, if they would consider a woman’s fistula to be “simple” or “not simple” using their own criteria, clinical judgment and experience. We have chosen this approach—as opposed to outlining a set of parameters to define “simple” because:

- Currently at least 25 systems for classifying fistula are being used by surgeons worldwide,¹⁴ with no single, accepted standardized system and consequently, no common definition of what constitutes a “simple” fistula.
- The classification systems were developed to help aid in making treatment decisions and/or for prognostic purposes. None of them were designed to categorize fistula in terms of simplicity (i.e. either simple vs. not simple, or as simple, intermediate, complex) and thus we cannot use any of the existing classification systems for the purposes of this study.
- Determination of ‘simple’ is before randomization and so any differences in ways that fistula are classified would, on average, be equally distributed between the two study arms (i.e. a subjective approach to classifying fistula would not affect the study’s internal validity).
- It would be most representative of actual clinical practice where there are many different ways fistula are defined and classified. Using a narrow definition of simple could limit the generalizability of the results. Assuming short-term catheterization is found to be non-inferior to longer term catheterization, surgeons may tend to use short-term catheterization only when fistula meet the specific characteristics used in the inclusion criteria for this study.

- Detailed information on clinical characteristics of the fistula will be collected at the time of the surgery for all women consenting to participate in the study and thus it will be possible to retroactively classify fistula using a variety of classification systems.

To determine the degree of variability in what different surgeons call “simple” we tested inter-rater reliability of classification of “simple” fistula among 17 fistula surgeons at a consultative meeting in December 2010.* Participating surgeons were asked to review a set of 30 drawings depicting size, location, degree of scarring, and other important clinical findings, and to classify the fistula as “simple” or “not simple”. During development of the drawings we had classified each as simple, intermediate or complex based on the expert opinion of a highly experience fistula surgeon. The distribution of drawings among these three categories reflected the distribution of fistulas by complexity as subjectively reported by surgeons in Fistula Care’s prospective observational study mentioned under section 3.1.1.

We calculated a multi-rater kappa statistic to assess the amount of agreement expected above chance alone.* The kappa value obtained was .55, indicating a moderate/good level of agreement. While we had expected to see even better inter-rater reliability from this exercise, there was some variation in how the surgeons classified the drawings; however, it is notable that the majority of the disagreement fell into the fistula drawings that we had a-priori termed ‘intermediate’. In addition, we acknowledge that there is likely variation in perspective between surgeons based on their experience (more experienced surgeons might tend to say more of the fistula they see are simple compared to less experienced surgeons) and whether “simple” fistula are those considered to be easier to close or those that are likely to have a better prognosis. Nonetheless, the potential for women with complex fistula to be included in the study is unlikely given that the misclassifications based on our categorization of the drawings were only in the intermediate range (i.e. no one classified as simple a fistula that we had defined as complex). Overall, the results of this exercise make us confident that surgeons’ subjective classifications of what is and is not a simple fistula are not too divergent.

Additionally, preliminary data from the Fistula Care prospective observational study (N = 1214) show that there is good agreement between surgeons as to what qualifies as a “simple” fistula. In that study we asked surgeons to classify each fistula as simple, intermediate or complex, using their own criteria—the same approach we are proposing for this RCT. Fistula classified as simple were significantly more likely than fistula not classified as simple (i.e. either intermediate or complex) to have the following parameters: no or mild scarring, clean edges, no necrotic tissue present, mid-vaginal or trigonal location, < 2 cm, intact bladder neck and urethra, and ureters draining into the bladder. The subjective approach to defining “simple” actually has an objective profile based on these results. Moreover, these individual characteristics have been shown in our studies and others to be associated with favorable repair prognosis and thus our

* The Fistula Care Project, in collaboration with WHO and USAID held a two day consultative meeting in Dakar Senegal, December 10-11, 2010 with fistula surgeons from sites that have expressed interest in potentially participating in the RCT and other stakeholders. A total of 17 surgeons from nine countries attended. The purpose of the consultation was to review the draft protocol for the RCT and to receive input and feedback from fistula surgeons.

* This statistical procedure assesses the amount of agreement between different raters. It is considered to be a more robust measure than simple percent agreement since it takes into account the agreement occurring by chance. A Kappa value of .4 is conventionally interpreted as "fair", .6 as "good" and .75 as "excellent."

approach should not present any safety issues for women participating in the study. Women classified as simple, intermediate and complex in the Fistula Care study had a closure rate at 3 months of 92%, 83% and 67%, respectively. There is no reason to believe that a subjective definition of ‘simple’ is more likely to be associated with higher AE rates, or to otherwise compromise the safety of study participants, compared to a more objective definition.

An alternative approach would be to have a list of fistula characteristics that would define which women would be eligible to participate in the study. To help us evaluate this option, we gave fistula surgeons attending the meeting mentioned above a list of 11 clinical parameters for describing fistula. We asked them to rank order the list in terms of how important each parameter would be for defining a fistula as simple to determine if there was consensus on a manageable number of parameters.* The top five criteria on which there was consensus were

1. Good Access
2. Minimal scarring
3. Smaller size (although, not pinpoint)
4. Mid-vaginal position
5. No urethral involvement

Even using a list of ‘objective’ criteria as above, it is clear that there would be subjective judgments involved (e.g. what is good access and minimal scarring). It may be impractical or financially prohibitive to conduct the study if we use a list of criteria like those above, because few women may meet strict inclusion criteria, requiring a large number of sites and/or a prolonged recruitment period. For instance, based on data from Fistula Care’s prospective observational study, only 11% of women meet the criteria of minimal scarring, small size (0.5-2 cm) and mid-vaginal position.

3.3.7 Study procedures

All participants at all sites will be required to stay at the facility for at least 7 days after catheter removal (i.e. day 14 post- surgery for the ‘7 day group’ and day 21 post-surgery for ‘14 day group’). Currently, only three of the sites keep women for a week or more after catheter removal. Following discharge, study participant will make one follow-up visit to the facility at 3 months from the time of surgery.

Use of dye testing and assessment of urinary retention vary among the sites. Most of the study sites conduct a dye test to assess for fistula closure at the end of surgery (two do not), and some, but not all, routinely use dye tests to assess fistula closure at the time of planned urethral catheter removal. Use of a dye test one week following catheter removal, as mandated by our study protocol, is not routine care at most of the study sites. Some of the sites routinely conduct a dye test to assess fistula closure at one or more of the follow-up visits, other do not, but may conduct a dye test if clinically indicated.

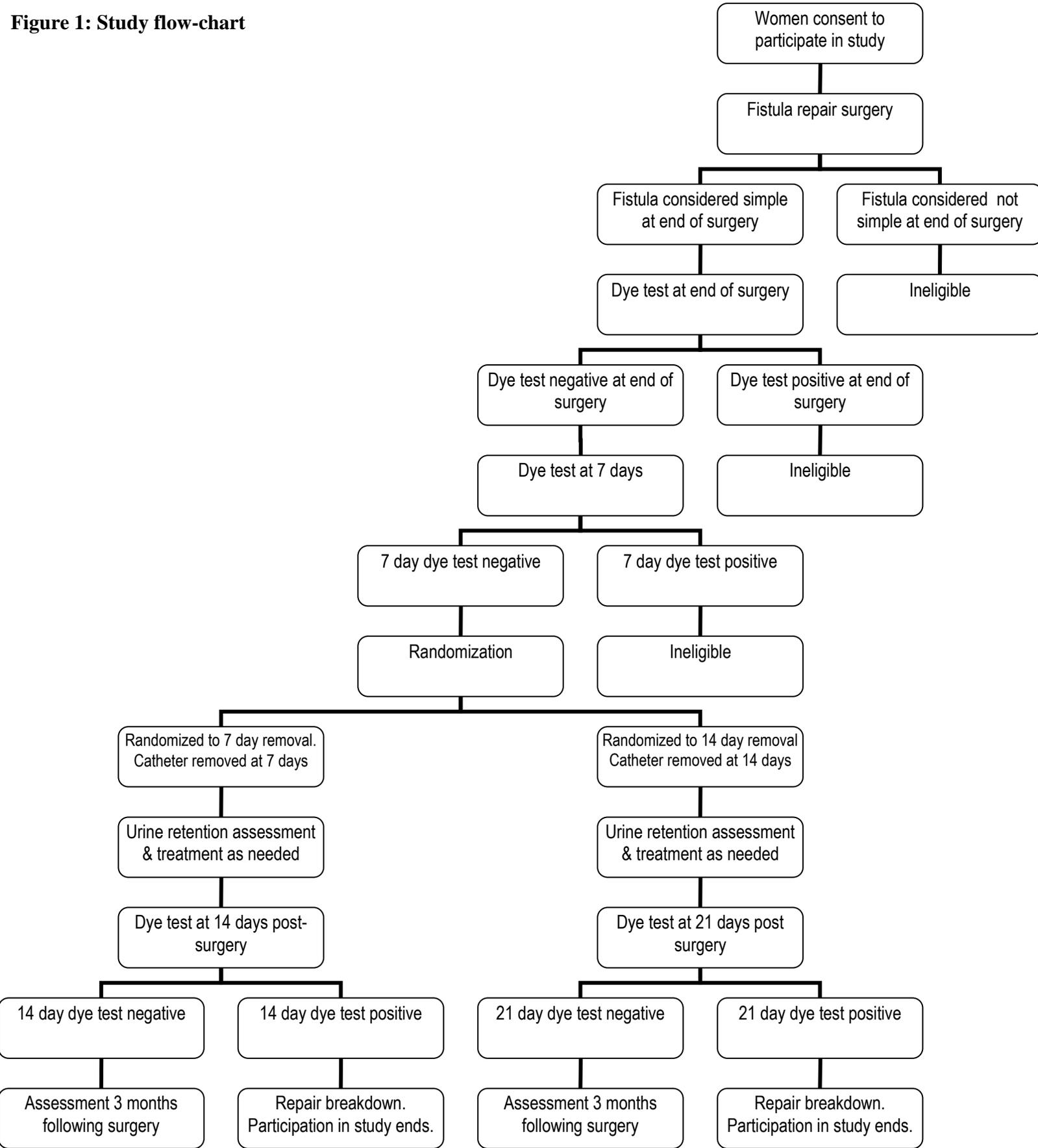
* Size; Mild/moderate/severe; Location (juxta-urethral, mid-vaginal, juxta-cervical); Location (Midline, Lateral); Location (Distance from external urethral orifice); Vaginal Rugae Preserved (yes/no) ; Urethral involvement yes/no; Access (good, impaired, difficult); Duration of fistula (months/years); Co-morbidities: (yes/no; specific: diabetes, AIDS); Iatrogenic (Yes/no)

Some of the study sites assess urinary retention either routinely or when deemed clinically appropriate for fistula repair clients by passing a urethral catheter and emptying the bladder after the women has voided. Urine retention will be assessed at 1, 3 and 7 days following catheter removal for all study participants. Women found to have urine retention will be treated by intermittent catheterization, the same treatment that would be used for similar cases identified during routine clinical at the study sites.

All of the study sites have agreed to implement the procedures outlined in this protocol, including those that are a departure from their current clinical practice. The informed consent process and forms will make it clear to potential study participants that some of the study procedures (e.g. assessment of urinary retention and some of the dye tests) may not be routine at the site or may be conducted at times different from the routine care the facility provides.

Study procedures are described in more detail below, and are depicted in **Figure 1**.

Figure 1: Study flow-chart



3.3.7.a. Participant screening

Women scheduled to undergo vaginal fistula repair surgery will be informed about the study and asked if they are interested in participating. Once a woman has expressed an interest in the study, study staff will explain the study in detail, including: (a) the study requirements, (b) their potential role in the study, (c) conventional catheterization procedures and experimental procedures to be used as part of the study, and (d) the study procedures. Each woman will be asked to sign the informed consent form to document her voluntary decision to participate in the study, and her willingness to return for a follow-up visit three months following the surgery.

Each woman signing the informed consent form will be assigned a unique Screening ID number. Each screening ID will have 3 digits. Screening of women in the study population will continue from when a participant gives her informed consent through the surgery, since it is during the repair surgery itself that the most accurate and reliable information about the fistula, and whether or not it is simple, can be obtained. Thus, it will be at the end of surgery that the surgeon determines if a woman meets the eligibility criteria of having a simple fistula. In addition, the fistula must be closed at the end of surgery, since bladder catheterization following a failed repair serves a different purpose than catheterization following a repair where the fistula was successfully closed. Thus, women whose fistula are not closed at the end of surgery will be considered ineligible to participate.

For all women who have consented to participate, data will be collected at two time points: prior to surgery and at the time of surgery. Prior to surgery, detailed demographic information will be collected (age, marital status, parity, and rural vs. urban residence, and education status), causative delivery, duration of the fistula, previous attempts at repairing the fistula, pre-operative care, including patient co-morbidities and the specifics of pre-operative care provided for these co-morbidities, if any, as well as any other pre-operative procedures. At the time of surgery, a detailed clinical examination will be conducted to assess the characteristics of the fistula, and to allow the surgeon to determine if he/she would consider the fistula “simple” or not. For all participants, detailed information will be recorded on the anatomical and clinical characteristics of the fistula(s), including the presence of scarring, location and type of the fistula and length and width of the fistula. Data will be gathered using standardized case report forms developed for the study. Women with fistula that are deemed to be moderate or complex following surgery will not be eligible for inclusion in the study. These women will continue to receive care at the study sites according to standard practice based on clinical indications and the fistula surgeon(s) clinical judgment.

Details of the surgical procedure will be collected for women who remain eligible for inclusion in the study at the completion of surgery. Procedures and surgical techniques will not be standardized, but the details will be recorded on standardized case report forms developed for the study. Data will be gathered on administration of antibiotics (type administered, dose, and duration of administration), the type of anesthesia, surgical route, and the technique used to close the fistula. Information on who performed the surgery and the circumstances under which the repair was carried out (e.g. camp, training event, routine service), as well as the status of the fistula repair and any intra-operative complications experienced, will also be recorded. While participants are convalescing in the post-operative recovery ward, and prior to catheter removal, details of any post-operative care provided (e.g. administration of antibiotics for prophylaxis or

treatment, and duration of bed rest / timing of ambulation) will also be recorded on standardized case report forms developed for the study, but the post-operative care itself will not be standardized (i.e. site can use whatever procedures they usually do or feel are appropriate).

It is not practical to standardize pre-operative, intra-operative and early post-operative care, nor the surgical procedures for repairing the fistula. Our recently published survey of current practice indicates many variations in fistula repair surgery.⁶ We would be unable to get agreement from surgeons as to what specific surgical techniques to use, and even within simple fistula, there is enough variability that surgeons need to be able to make the decision on the exact surgical technique to use on a case by case basis. It is difficult to standardize fistula repair surgery in the way that one could, for example, standardize relatively straightforward procedures, like elective cesarean section or vasectomy. Since the pre-operative, intra-operative and early post-operative care, as well as the repair surgery, is before randomization, any variability should be evenly distributed between the two arms.

In summary, for all participants consenting to participate in the study, the following procedures will be conducted:

- Administer informed consent
- Collect information on socio-demographics and other biographical information
- Collect data on comorbidities and pre-operative care provided
- Collect data on characteristics of the fistula
- Fistula repair surgery and dye test at completion of surgery

For women who are determined eligible for the study at the completion of surgery, the following additional procedures will be conducted:

- Collect data on the details of the surgical procedures
- Collect data on post-operative care provided

3.3.7.b. Participant randomization

On day 7 prior to conduct of the dye test women will be consented again to ensure they understand the study objectives and potential risks of the intervention, and confirm their continued interest in participating in the study. Women who wish to no longer participate in the study will receive continued post-operative care at the study sites according to the site's standard practices and based on clinical indications and the fistula surgeon's clinical judgment.

Women who reaffirm their consent to participate will be assigned to treatment groups (i.e. randomized) on the 7th day after repair surgery in order to ensure that women are, on average, equally distributed between the two arms with regards to socio-demographic factors, fistula characteristics, and pre-, intra- and early post-operative procedures. A dye test will be conducted at 7 days for all patients with simple fistula that were closed at surgery. Patients with a positive dye-test indicating a failed repair will not be eligible for randomization, but would receive continued care at the study site according to standard procedures and the surgeon's clinical judgment. Participants to be randomized must have a closed fistula at the time of randomization.

Outcomes of the dye-test at 7 days will be recorded for all participants, regardless of whether or not they are randomized.

Patients with a negative dye-test at 7 days following repair surgery, indicating their fistula is closed, will be asked to confirm their interest. Those women who remain interested in participating in the study will be randomized to either the 7-day or 14-day catheterization arm.

Randomization will be done using permuted blocks within site to ensure similarity of comparison groups with regard to potential confounding factors that might influence repair outcomes within a particular study site. Randomization will be automated through a computer program, to avoid bias introduced by clinical staff who have a preference for one or the other catheter removal time. Specifically, the random allocation sequence will be generated at WHO Headquarters using statistical software. Randomization will be stratified by site. Sealed opaque envelopes will be generated at WHO-HQ with the blocked random allocations per site. Allocation will use a 1:1 ratio.

Once a participant has been randomized, she will be assigned a unique ID number which will subsequently be written on all her CRFs and logs. Each Participant ID number will have 3 digits and a check letter, and each participating site will be assigned a unique range of Participant IDs.

In summary, the following procedures will be conducted at the time of randomization:

- Dye test
- Assign the woman a participant number
- Record outcome at 7 days

3.3.7.c. In-patient study procedures following randomization

Those women who are randomized to the day 7 removal group will have their urethral catheter removed on the day of randomization. Those randomized to the 14 day removal group will wait an additional 7 days before having their urethral catheters removed.

Women in both groups will have a dye test conducted 7 days after catheter removal (i.e. 14 and 21 after surgery in the short-term and long term catheterization group, respectively). Patients who have a positive dye-test at that time will be considered to have had a repair breakdown and their participation in the study will end. Those with a negative dye-test will be asked to return 3 months following the date of the surgery for a final dye test.

Ideally to minimize a potential source of bias, dye tests should be done by a fistula surgeon who did not conduct the repair surgery, as well as by someone who is blinded to the woman's random assignment. Unfortunately, neither of these is practical at the study sites and this will be a limitation of the study. Staffing at most of the potential study sites is limited and there are unlikely to be sufficient numbers of fistula surgeons to make independent assessments feasible. Moreover, most fistula surgeons would be uncomfortable with others doing dye tests on their patients, and this could affect the clinical care women participating in the study receive. Some attending surgeons may want to repeat dye tests, subjecting study participants to additional vaginal exams and dye tests. Decisions about further care of study participants, particularly those

with failed dye tests, will be based on the dye test results and surgeon needs to see the result him/herself in order to decide on an appropriate course of action.

Women who have a positive dye test at any of the points described above (whether they are excluded from participation in the study or are classified as repair breakdowns and thus their participation in the study is completed) would be treated clinically in whatever manner the site/surgeon sees fit. For example, if the surgeon wants to leave the catheter in for an additional time period or do another surgical repair, that would be their prerogative.

Urine retention will be assessed at 1, 3 and 7 days following catheter removal for all participants. Specifically, post-void residual urine volumes will be assessed, by passing a urethral catheter and emptying the bladder after the women has voided, and recorded on the 1st, 3rd and 7th days following urethral catheter removal (i.e. at 8, 10 and 14 days for the short-term catheterization group, and 15, 17 and 21 days for the long-term catheterization group). In the event of excess urine retention, defined as residual amount of urine in the bladder greater than 50% of the voided volume, intermittent urethral catheterization will be implemented, whereby a nurse will pass a urethral catheter a minimum of three times a day to drain the bladder. Intermittent catheterization will cease once the residual volume is less than 50% of the voided volume for 2 consecutive determinations. In a Cochrane Review of available clinical evidence it was found that, when compared to indwelling urethral catheterization, the practice of intermittent catheterization is associated with reduced rates of urinary symptoms and bacteriuria and increased rate of return to normal bladder function.¹⁵

Once women are randomized, sites will be asked to standardize procedures including use of antibiotics and anti-helminthics, bed rest vs. ambulation, catheter management (e.g. fixation, clearing blockages), instructions given to clients about sexual activity, perineal and vaginal hygiene, and type and timing of bladder training and pelvic floor exercises and, as noted above, use of intermittent catheterization for urine retention. Specific guidelines to ensure standardization of these procedures are in Appendix F. Information on these procedures will be recorded on standardized case report forms developed for the study for all participants who are randomized.

At the time of discharge from the facility, women will be asked to provide the address where they expect to be living over the next 3 months and if possible, either a mobile or fixed telephone number. In addition, participants will be asked to provide the name of someone with access to a phone who would be expected to know the participant's whereabouts after she is discharged from the hospital. The follow-up visit will be scheduled, and the participant's number, surgery date and scheduled return date will be noted in a Follow-Up Log.

In summary, the following procedures will be conducted following patient surgery and through discharge:

- Catheter removal on day 7 or 14, depending on random assignment
- Dye test at 14 days in the 7 day removal group
- Dye test at 21 days in the 14 day removal group
- Record details of post-operative care
- Record urinary retention levels and perform intermittent catheterization if indicated

- Record outcome at 14 days and 21 days
- Record contact information
- Schedule follow-up visit and record follow-up visit information in Follow-Up Log

3.3.7.d Three month follow-up visit

Research Assistants will consult the Follow-Up Log (see “Scheduling of Follow-Up Visit” above) weekly to see if there are participants scheduled to return for their 3-month post-surgery visit the following week, and will contact women by phone call and/or SMS, or by contacting alternative contacts provided, several days before the scheduled visit as a reminder. All reasonable efforts will be made to locate women who do not return for follow-up visits, including mobile phone/SMS follow-up, communicating with alternate contacts provided by the study participants at enrollment, and home visits if possible and necessary.

An interview and dye test will be conducted at the follow-up visit. The purpose of the interview will be to assess whether the participant has engaged in any behaviors following discharge from the facility which might contribute to risk of repair breakdown (e.g. sexual activity, insertion of objects into the vagina) or protect against repair breakdown. A dye test will be administered, and women with a fistula that is no longer closed at the time of the follow-up visit, as determined through a positive dye test, will be classified as having a “repair breakdown.” Study participants will be asked about the presence of residual incontinence, and any adverse events (AEs) experienced following discharge will be recorded in the Adverse Event Form as described below. Participants will be asked to recall the details of an AEs event to the best of their ability.

Participants who fail to return for their scheduled follow-up visit and who are not successfully contacted will be considered lost-to-follow-up.

Participants will be provided compensation for transportation to and from the clinic at the end of each follow-up visit, and given a small gift (e.g. cloth or blanket) as a token of appreciation for returning for the three-month follow up visit. We believe that this approach has been helpful in the high follow-up rate we have seen in the prospective observational study that Fistula Care recently completed.*

In summary, the following procedures will be conducted at patient follow-up:

- Survey of behaviors / activities following discharge administered
- Dye test administered
- AE recorded, if applicable
- Participant compensated for time and travel

3.3.7.e Determination of participant eligibility and discontinuation of randomized participants

Prior to randomization, women may be determined ineligible for randomization for a number of reasons (e.g. fistula is determined to be intermediate or complex during surgery, fistula is not closed based on dye test results at the end of surgery, fistula is not closed based on the results of

* Nearly 1,500 women were enrolled in the study and asked to return for a 3 month follow-up visit. Follow-up rates among ranged from 73-100% at the 11 sites, with a mean of 95.9%.

a dye test at 7 days after surgery before catheter removal). The study sample will comprise women who are randomized on day 7 following surgery. If, after randomization, it is necessary to remove someone from the study (e.g. she withdraws consent, medical/safety reasons) she will be considered discontinued. Any participant who is discontinued following randomization will be noted as such, and reasons for discontinuation will be recorded on a case report form.

3.3.7.f Adverse event reporting

Adverse events (AEs) will be assessed at any time they occur during the period of the study, i.e. from when a woman signs an informed consent form until she is either determined ineligible, completes the study, or is discontinued early. All adverse events, whether thought to be related to the study procedure or not, will be recorded. Examples of related AEs that may be seen include repair breakdown (the primary study outcome), catheter blockage or loss, wound infection (e.g. abdominal incision, episiotomy site, etc), hemorrhage, urinary tract infections, and death. Adverse events will be classified based on severity, seriousness and relatedness. Adverse event grading and attribution will be as follows:

Each sign or symptom reported will be graded on a 3-point scale of severity:

- *Mild*: awareness of event, but easily tolerated
- *Moderate*: discomfort enough to cause interference with usual activity
- *Severe*: inability to carry out usual activity

The attending clinician will determine whether or not the adverse event is considered serious. The following require classification as serious:

- Fatal or life-threatening;
- Resulted in significant/persistent disability;
- Resulted in hospitalization or prolongation of hospitalization;
- Jeopardized participant and required medical/surgical intervention to prevent serious outcome; and/or,
- Any other event that the investigator considers serious.

An adverse event classified as severe is not necessarily a serious adverse event, but serious adverse events would generally be classified as severe.

A study clinician will evaluate each adverse event for its relatedness to the procedure under investigation. For the purpose of this study, the length of urethral catheterization is considered to be the study procedure by which the relatedness of an adverse event will be evaluated. The following criteria will be used for determining the relationship of adverse events to the study procedure:

- *Not Related*: This category applies to those adverse events that, after careful medical consideration, are clearly explained by a cause other than the catheterization time (disease, environment, accidents, etc.).
- *Possibly Related*: This category applies to those adverse events that, after careful medical consideration, might be explained by the catheterization time, but could equally or more likely be explained by other causes.

- *Probably Related*: This category applies to those adverse events that, after careful medical consideration, are felt most likely explained by the catheterization time, but could possibly be explained by other causes.
- *Definitely Related*: This category applies to a complication that is clearly related to the time of catheterization.

All adverse events will be recorded in an Adverse Event form, which will collect information on the nature of the event, the relatedness of the event to the intervention, timing of the event, treatment for the event, and date of resolution.

3.3.7.g Serious Adverse Events

The site investigator or his/her designee must report all serious adverse events to WHO and EngenderHealth *within 24 hours* of becoming aware of an outcome that classifies an AE as an SAE. The Site Investigator or his/her designee should complete a SAE Report Form and fax or email it to:

Dr. Mark Barone at EngenderHealth
mbarone@engenderhealth.org
Fax: +212-561-8067

Dr. Mariana Widmer at WHO
widmerm@who.int
Fax: +41227914171

All SAEs resulting in prolongation of hospitalization or death will be reported to the IRBs within 10 days of when notification is received by WHO and EngenderHealth of the event for hospitalization and within 24 hours of any research participant's death, unless otherwise required by the specific IRB.

3.3.8 Laboratory and other investigations

No routine laboratory tests will be conducted as part of this study. Individual study participants may have laboratory tests done at the discretion of the study clinician as part of her clinical care should that be deemed necessary.

Fistula closure will be assessed through dye test and pelvic exam at completion of surgery, before catheter removal, one week after catheter removal, and at the 3 month follow-up visit. A urethral catheter will be inserted into the bladder, saline colored with dye will be introduced into the bladder via the catheter, and the suture line will be checked to assess leakage. The presence of dye at the suture line indicates that the fistula is not closed. Administration of a dye test via urethral catheter is a low-risk procedure, with only mild discomfort associated with insertion of the catheter experienced by the patient and limited risk of AEs.

To assess for urinary retention, each woman will be catheterized for residual urine at one, three and seven days after catheter removed. The woman will be asked to void, the voided amount

will be measured, and then a urethral catheter will be immediately passed and the amount of urine remaining in the bladder will be measured. If the residual amount of urine in the bladder is greater than 50% of the amount of urine voided, the woman will be placed on a regimen of “intermittent urethral catheterization,” whereby a nurse will pass a urethral catheter a minimum of three times a day to drain the bladder. Intermittent urethral catheterization will cease once the residual volume is less than 50% of the voided volume for 2 consecutive determinations.

3.3.9 Data management

Data from all study sites will be centrally collected, managed and processed at WHO headquarters in Geneva.

3.3.9.a Data transfer

Data will be collected on two-ply carbonless Case Report Forms (CRFs). CRFs will be reviewed and signed off on by the site investigators or their designees. During study monitoring visits the study monitor will review CRFs (see 3.3.9.d). When any problems have been addressed and appropriate corrections made, he/she will separate the original and copy of each CRF. Original white copies of the forms will be sent by the study monitor via express courier to the WHO headquarters in Geneva for data entry. The remaining yellow copy will be retained in the participant’s study files at the study site. It is imperative that originals and copies of all CRFs match in every detail. Thus, changes will not be made to the forms after they are separated, unless the change can be documented with a query form attached to the CRF. Before the forms are separated, changes can be made to the form if the changes are initialed and dated by the staff member responsible for making the change. No white-out or other obscuring method may be used to correct errors. Only the study monitor should separate CRFs.

3.3.9.b Data storage

Participant’s folders will be stored in a locked cabinet within each facility. All study documents with the participant’s name should remain at study sites at all times. All study data should be kept at the study site for at least 3 years after completion of the study.

3.3.9.c Data entry

Data entry will be coordinated at WHO headquarters in Geneva. Data will be entered into a Good Clinical Practice (GCP) compliant data management system for clinical trials and data entry screens will be created for each form used in the study. All data will be double-entered to minimized data entry errors. All data will be stored in a GCP compliant server, and data transmission will be encrypted to assure data integrity and patient confidentiality. Access to the data management solution will be password protected and only authorized users will be given access.

3.3.9.d Data quality assurance

Information on CRFs will be checked four times: by the local study staff at the study site when the participant is still present; by the Research Assistant at the site on a daily basis; at monitoring visits; and during data entry at WHO. Study staff will check all forms for completeness before the participants leave the clinic to ensure that any answers to questions missed or left blank can be ascertained. Site visits by study monitors will be made during the first month of the study, and every two months subsequently; the purpose of these visits will be to ensure the quality and

accuracy of data collected on the CRFs, determine that all regulatory requirements surrounding clinical trials are met, and ensure that the study protocol is being followed as written. Study monitors will be responsible for assuring that all forms are properly completed and to the extent possible, that data are accurate. The monitor will do 100% review of the forms to ensure completeness and to resolve inconsistencies.

In addition, at each study monitoring visit, 10% of CRFs will be randomly selected for verification against source documents. Study monitors will match participant forms to patient records for the selected participant, to ensure that patient data are not fabricated. In order to perform this role effectively, study monitors will be given access to primary source documentation that support data entered into the study case record forms, *i.e.* original client records or registers.

A detailed clinical monitoring plan will be developed for the study. The monitoring plan will specify the responsibilities and qualifications of the study monitors, back-up provisions, in-house monitoring procedures, and site monitoring visit procedures. All monitoring visits will be documented and reports written that detail any problems with conduct of the study or quality of the data that need to be addressed.

Finally, at WHO Headquarters, the data management system will check the data for inconsistencies and missing values. Data queries will be sent to the sites on standardized query forms, and requests will be sent (via query forms) to study sites for further clarification. All data changes to the study forms once they are separated will be documented with query forms attached to each page of the client report form. The data management system will maintain a full audit trail of all data edits.

Retraining of the study staff by the Principal Investigator, study monitor or other appropriate EngenderHealth or WHO staff will be undertaken if necessary.

Various authorized individuals may visit the study sites to audit the progress of this study (e.g., EngenderHealth, WHO or USAID staff). All clinical records (if applicable) and the data collection forms for the participants enrolled in this study will be made available for review by these authorized individuals.

The study will be registered at www.clinicaltrials.gov before the start of data collection and study results will be reported according to CONSORT guidelines (see also Appendix D).

3.3.10 Data analysis

A detailed analysis plan that covers both the final analysis and the planned interim analyses will be developed prior to the initiation of the study. The following is a summary of the planned analyses; any deviations to be made from this summary plan will be documented in the detailed analysis plan.

3.3.10.a Analyses of the primary objective

The primary outcome of the trial is repair breakdown at 3 months or earlier in an ITT analysis. The primary analysis will be conducted for the ITT population.

Fistula closure will be categorized dichotomously as a “yes” or “no” variable. For superiority trials, the intent-to-treat population (ITT) is considered the primary analysis population, as it adheres to randomization and tends to best reflect clinical practice. It has been shown that difference between the per protocol (PP) or ITT analysis depends on many factors, including the type of protocol deviation and the method of handling missing data in the ITT population.^{16, 17} In this context the ITT population would include patients for whom protocol is violated (i.e. patients who are randomized to short-term catheterization but are in fact catheterized for longer durations, or patients who are randomized to the long-term catheterization group but are in fact catheterized for only 7 days) and withdrawals. The roles of the ITT population and PP population in non-inferiority studies are not clearly defined.¹⁸

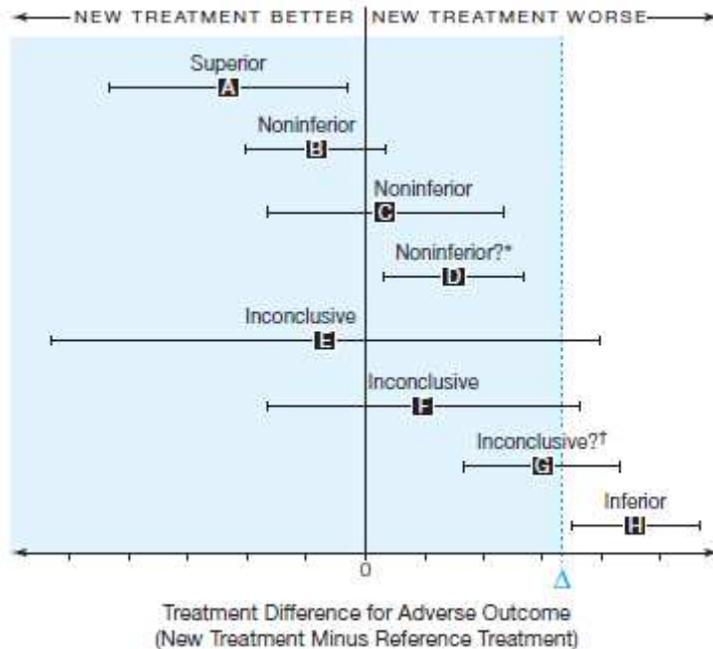
Sample size computations have been performed to ensure sufficient numbers of subjects in the PP population and then increased for the ITT population based on the projected protocol violation and withdrawal rate. Non-inferiority is likely to be more difficult to demonstrate using the PP population, so sample size calculations based on the PP population ensure that the ITT analysis is adequately powered.

We will first conduct a comparison of the demographic and fistula characteristics (e.g. location of the fistula, size of the fistula, duration of the fistula, etc) of the patients across the two treatment groups to ensure comparability at baseline. Frequencies and percentages will be reported, and analyses will be pooled by randomization group.

Unlike a superiority trial, where the treatment effect is the primary parameter of interest, the interpretation of a noninferiority trial’s results depends on the location of the CI for the effect of the experimental treatment relative to the margin of non-inferiority (Δ) and a null effect. A range of possible scenarios are depicted in Figure 2 below, where error bars indicate 2-sided 95% CIs, and the tinted area indicates the zone of inferiority. Thus, primary analyses will be interpreted as follows: if the whole 95% CI lies to the right of the non-inferiority margin of 10% (scenario H), the experimental intervention will be declared "inferior." If the whole 95% CI lies below the non-inferiority margin, the intervention will be considered to be non-inferior to the standard treatment (scenarios B-D); scenario D, where the CI does not contain Δ but the new treatment is significantly worse than the standard is unlikely, because it would require a very large sample size. If the 95% CI includes the non-inferiority margin Δ (scenarios E, F and G) study results will be deemed inconclusive. In scenario E the 95% CI is too wide, reflecting a sample size too small, implying that the trial was unable to recruit the target sample size to obtain sufficient power. Scenario G is inconclusive; however while it is still possible that the true treatment difference is less than Δ , the new treatment is significantly worse than the standard treatment. Finally, in scenario A, since the 95% CI lies completely to the left of zero, the new treatment may be considered superior to the standard treatment.¹⁸

Once non-inferiority is demonstrated, it is acceptable to then test the hypothesis that the new treatment is superior to the active control, with a significance level defined a priori and with an ITT analysis.¹⁹

Figure 2: Interpreting results of non-inferiority trials (Source: Piaggio et al. 2006¹⁸)



3.3.10.b Missing data

Data can be missing for a number of reasons. First, some questions may not be applicable to all women in the study. Secondly, sometimes questions are accidentally skipped. In these cases, where possible (based on other responses), missing values will be assigned values that allow us to include them in the analyses. However, values will never be estimated if the correct value cannot easily be deduced from responses to other questions. Thirdly, as with any prospective study, loss to follow-up will be unavoidable in this study. However, sample size estimates, will account for loss to follow-up. Moreover, we will collect extensive data on the patients through discharge, enabling us to test for both socio-demographic and clinical differences between those women who remain in the study and those who are lost-to-follow-up. Moreover, we will repeat our primary analyses using closure of the fistula at 1 week after catheter removal, rather than follow-up, in order to determine whether the same trends in associations exist when loss-to-follow-up is not a factor. Further, in order to assess the degree to which unequal rates of loss-to-follow-up across facilities affect the results, sub-analyses of the data will be conducted to compare those with high retention to those with high rates of loss to follow up. Sensitivity analyses will also be conducted as appropriate. Study withdrawals will be handled in a similar fashion to participants lost to follow-up. All women will be followed up until 3 months or earlier detection of fistula repair break-down. For those women with no primary outcome variable available we will: 1. check to see if the loss to follow-up is balanced between the two arms and, 2. if the numbers are either unbalanced between groups or unexpectedly high (approx. > 15%) we will conduct simulation analyses in two extreme situations (all missing in group A having the outcome versus none in group B having the outcome and vice versa) to assess the potential impact of loss to follow-up on the interpretation of study results.

It is also possible that study staff will leave items on the data collection forms blank for no particular reason. As is described in section 3.3.9 above, study monitors and data managers will attempt to minimize the extent of this problem by flagging such missing items during the

monitoring and data cleaning processes. Where a woman has missing data for a specific item, she will be removed from the question sample for calculation of percentages or other summary measures. If a woman has missing data for one question, she will still be included in samples for any other questions for which she provided data. Further, data that are missing for retained participants will be assessed to determine whether they are missing at random, and thus can be ignored, or whether any systematic errors exist that may bias study results. Any systematic errors will be evaluated, and sensitivity analyses will be conducted to assess the extent of potential bias.

3.3.11 *Interim data analysis*

This study will include one interim analysis after one-third of the study participants have returned for the three-month follow-up visit; in this way, 44% of women will have been recruited by the time of interim analysis. At the time of the interim analyses, event and recruitment rates will be provided to the Data Safety and Monitoring Board (DSMB) by unmasked treatment group. An independent biostatistician, not otherwise involved with the study, will prepare the unmasked tables for the DSMB.

We will recruit a three member DSMB, including a surgeon with expertise in fistula repair, an epidemiologist, and a statistician. They will meet either in-person or by teleconference (whichever is more convenient) before the study begins and will hold an in-person meeting after one third of the participants have returned for the three-month follow-up visit. The DSMB will follow guidelines and procedures proposed as part of the Damocles Charter.²⁰

The following stopping guidelines are proposed for the DSMB regarding surgical outcomes:

- (1) At the time of the interim analysis, the DSMB may recommend stopping the study or temporarily halting recruitment if there are significantly more repair breakdowns in one catheterization group compared to the other; a difference between the two treatment arms will be considered significant if the p value for the difference is less than 0.001.
- (2) In the event that the interim analysis shows notably more AEs in either study arm, the DSMB may recommend stopping the study or temporarily halting recruitment.
- (3) The DSMB may also recommend stopping the study, temporarily halting recruitment or adjusting study sites if it seems that recruitment is not proceeding at rates that will allow the study to reach its target sample size in a reasonable timeframe.

It should be noted that if there appears to be an unexpectedly high number of repair breakdowns among short-term catheterization cases compared to long-term catheterization cases either as reported by study site staff or the study monitor, or based on the interim analysis, any one of the study IRBs may also temporarily or permanently halt the study at any time.

If the study is stopped temporarily or permanently for any reason, follow-up of women already enrolled will continue as originally scheduled and all women already enrolled will receive continued care, appropriate to their clinical condition and circumstances, in line with each sites standard practice.

3.3.12 Duration of project

A total timeframe of two years will be required for this study, excluding preparatory work (e.g. hiring of staff, tool development and translation); a detailed timetable is shown below.

Table 1: Study timetable

	2011				2012												2013									
Activity	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	
Local Ethical Reviews																										
Training for Study Site Teams and Steering committee meeting (Nairobi)																										
Study initiation																										
Participant recruitment and data collection																										
Monitoring of data collection at study sites by Regional Monitors																										
Submission of Case report forms to WHO by Regional Monitor																										
Data entry and cleaning at WHO																										
EH/WHO staff conduct monitoring visits																										
DSMB Meetings - Pre-trial and interim analysis																										
Study Site Investigators/Steering committee Mid study review meeting (location TBD)																										
Study closure																										
Data analysis																										
Data analysis meeting with study investigators																										
Write manuscript(s) for publication																										
Dissemination activities																										

3.4 Project management

This study will be jointly managed by EngenderHealth, NY and WHO. Study activities and the organization with primary responsible for leading these activities are listed in Table 2, below. In addition, a Steering Committee, comprised of principal investigators of the participating sites, representatives from EngenderHealth NY and the WHO Secretariat, and experts in the field of fistula surgery will provide guidance to those working on the study.

Table 2: Study management

Activity	WHO	Fistula Care
Finalize study protocol	Joint	
Develop, translate and print case report forms	Joint	
Database development	XXX	
Development of study manual	XXX	
Study orientation / training for staff, research assistants & medical monitors	Joint	
Designation of data monitoring committee (DMC) and writing the DMC charter	XXX	
Submit proposal to RP2 and WHO ethics committees	XXX	
Submit proposal to local IRBs		XXX
Organization of interim and final collaborators meetings	XXX	
Site visits to monitor trial progress	Joint	
Data entry, queries & cleaning	XXX	
Data analysis and interpretation	Joint	
Write manuscript(s) for publication	Joint	
Dissemination activities	Joint	

3.5 Links with other projects

This project will complement results from an observational prospective cohort study that is currently being conducted by the Fistula Care project and USAID, which examines individual- and facility-level predictors of fistula repair outcomes. While no sites participating in the ongoing cohort study practice catheterization for durations shorter than 10 days, this study will be able to shed some light on the association between duration of catheterization and fistula repair outcomes among more commonly implemented durations of catheterization.

3.6 Main problems anticipated

The primary obstacle that might interfere with the successful completion of the project within the time and costs proposed will be protocol deviations: for instance, if the personnel involved in the study discontinue clients based on a subjective determination that they are unsuitable for participation in the trial. Protocol deviations will be minimized, however, through intensive and continuous training of study personnel, and close monitoring by both trial investigators and trial

monitors. Any protocol deviations will be immediately investigated, and study personnel will be retrained or replaced as necessary. Although unlikely, it is also possible that we may have difficulty recruiting women for the study either because the numbers of women coming for repairs are insufficient, number of cases of simple fistula at the study sites are fewer than we had projected or large numbers of women decline to participate in the study.

We recognize that follow-up of participants may be a challenge, however we are confident that we can maintain a loss to follow-up of less than 10%. In the current Fistula Care observational prospective study, the follow-up has been excellent at 93%. This is likely due to a number of reasons: surgery is a last resort for women with fistula and they have a large perceived benefit from the follow-up care that they are offered; some women spend weeks at a fistula repair facility (sometimes living there for a time before and/or after the surgery) and during this time develop relationships with the nurses and other staff at the sites, making it more likely they will return for follow-up; and we will cover the cost of return transport for the women to come to the facility for the 3 month follow-up visit, we will provide the women with a small thank you gift (chosen by the site staff, e.g. soaps, fabric, baskets). In addition, we will study staff will contact women by phone call and/or SMS, or by contacting alternative contacts provided, several days before the scheduled visit as a reminder. All reasonable efforts will be made to locate women who do not return for follow-up visits, including mobile phone/SMS follow-up, communicating with alternate contacts provided by the study participants at enrollment, and home visits if possible and necessary.

3.7 Expected outcomes of the study

Given the challenges associated with providing fistula repair services in developing countries, finding ways of providing services in a more cost-effective manner, without compromising surgical outcomes and the overall health of the patient, is critical. To this end, further research on factors predicting successful repair, particularly those factors (such as duration of catheterization) contributing to increased hospital stay and risk of infection, is needed. If no major safety issues are identified, the data from this trial may facilitate adoption of short-term catheterization following repair of simple fistula in various countries in sub-Saharan Africa and Asia. The results of this study will be disseminated in at least one workshop / forum attended by fistula surgeons, regional/local meetings, and at least one publication in a peer-reviewed journal.

3.8 References

1. Wall LL, Arrowsmith SD, Briggs ND, Browning A, Lassey A. The obstetric vesicovaginal fistula in the developing world. *Obstet Gynecol Surv.* 2005; **60**(7 Suppl 1): S3-S51.
2. Lassey AT. Simple fistulas: diagnosis and management in low-resource settings--a descriptive report. *Int J Gynaecol Obstet.* 2007; **99 Suppl 1**: S47-50.
3. Kelly J. Current methods of urinary fistulae repair. 1994; **4**(2): 104-6.
4. Wall LL. Obstetric vesicovaginal fistula as an international public-health problem. *Lancet.* 2006; **368**(9542): 1201-9.
5. Schiotz HA, Tanbo TG. Postoperative voiding, bacteriuria and urinary tract infection with Foley catheterization after gynecological surgery. *Acta Obstet Gynecol Scand.* 2006; **85**(4): 476-81.

6. Arrowsmith S, Ruminjo J, Landry EG. Current practices in treatment of female genital fistula: a cross sectional study. . Accepted for publication by BMC Pregnancy and Childbirth.
7. de Moya MA, Zacharias N, Osbourne A, Butt MU, Alam HB, King DR, et al. Colovesical fistula repair: is early Foley catheter removal safe? *J Surg Res.* 2009; **156**(2): 274-7.
8. Nardos R, Browning A, Member B. Duration of bladder catheterization after surgery for obstetric fistula. *Int J Gynaecol Obstet.* 2008; **103**(1): 30-2.
9. Boruch AV, Nieponice A, Qureshi IR, Gilbert TW, Badylak SF. Constructive remodeling of biologic scaffolds is dependent on early exposure to physiologic bladder filling in a canine partial cystectomy model. *J Surg Res.* 2010; **161**(2): 217-25.
10. Phipps S., Lim Y.N., McClinton S., Barry C., Rane A., J.M.O. Nd. Short term urinary catheter policies following urogenital surgery in adults. *Cochrane Database of Systematic Reviews.* 2006; (2).
11. Kamilya G, Seal SL, Mukherji J, Bhattacharyya SK, Hazra A. A randomized controlled trial comparing short versus long-term catheterization after uncomplicated vaginal prolapse surgery. *J Obstet Gynaecol Res.* 2010; **36**(1): 154-8.
12. Hakvoort RA, Elberink R, Vollebregt A, Ploeg T, Emanuel MH. How long should urinary bladder catheterisation be continued after vaginal prolapse surgery? A randomised controlled trial comparing short term versus long term catheterisation after vaginal prolapse surgery. *BJOG.* 2004; **111**(8): 828-30.
13. Chamberlain DH, Hopkins MP, Roberts JA, McGuire EJ, Morley GW, Wang CC. The effects of early removal of indwelling urinary catheter after radical hysterectomy. *Gynecol Oncol.* 1991; **43**(2): 98-102.
14. Creanga AA, Genadry RR. Obstetric fistulas: a clinical review. *Int J Gynaecol Obstet.* 2007; **99 Suppl 1**: S40-6.
15. Niel-Weise BS, van den Broek PJ. Urinary catheter policies for short-term bladder drainage in adults. *Cochrane Database Syst Rev.* 2005; (3): CD004203.
16. Matilde Sanchez M, Chen X. Choosing the analysis population in non-inferiority studies: per protocol or intent-to-treat. *Stat Med.* 2006; **25**(7): 1169-81.
17. Brittain E, Lin D. A comparison of intent-to-treat and per-protocol results in antibiotic non-inferiority trials. *Stat Med.* 2005; **24**(1): 1-10.
18. Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJ. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. *JAMA.* 2006; **295**(10): 1152-60.
19. Lewis J. The European regulatory experience. *Stat Med.* 2002; **21**: 2931-8.
20. A proposed charter for clinical trial data monitoring committees: helping them to do their job well. *The Lancet.* 2005; **365**(9460): 711-22.

APPENDIX A: Ethical considerations

4.1 Informed decision-making and confidentiality

Informed consent

Informed consent will be obtained from all study participants. Since this is a multi-site study common consent forms will be used for all participating sites. However, the forms will be translated into local languages as required. Translated forms will be back translated into English by an individual not involved in the original translation. The original and back translations will be compared and any discrepancies reviewed and resolved. The document will be signed (or thumb print affixed) by each the subject in order for the subject to be eligible for the study, or, when the subject is illiterate, by the staff member who provides the information, and who ascertains that it was understood and confirms that consent was given freely. The recruitment of illiterate subjects will take place in the presence of a literate witness. Whenever possible, the witness will be selected by the subject and he/she will not be connected with the research team. The witness will also sign the certificate of consent, confirming that the subject has been properly informed and voluntarily consents to participating in the study.

No age restrictions will be placed on study participation. However, it is possible that at some study sites young women/girls who are minors will present for fistula repair, with or without a guardian. A person will be determined to be a "minor" in accordance with the legal age of adulthood in the country in which the research is being conducted, and in accordance with local legal definitions of an "emancipated minor" (e.g. a minor who is married or has children). Proxy consent for non-emancipated minors will be sought in accordance with host country legislation and, where appropriate, will be obtained from a relevant legal authority (i.e. parent, guardian or others with parental responsibility). Proxy consent will not substitute for the minor's own consent, but will supplement it. Proxy consent will not be required for "emancipated minors."

IRB approval

The study protocol will be approved by the WHO Research Programme Review Panel and Ethical Review Committee (ERC), as well as local IRBs in each country in which there is a study site. Recruitment of participants at any given site will not begin until both WHO and local IRB approval has been obtained. The common informed consent form is included at the end of Form 4a, below.

Confidentiality

All interviews and clinical exams will be conducted in private and records will be identified by ID numbers only, to maintain participant confidentiality. Completed forms will be kept in locked filing cabinets at the study site and WHO Headquarters. Data that are transmitted electronically or by mail between study sites, EngenderHealth offices and WHO will not contain any identifying information. While regulatory agencies and study monitors may request access to study records, the identity of subjects will always remain confidential to the fullest extent possible by law.

4.2 Risk-benefit assessment

Benefits

The main advantage for participants in this study is the potential for a shorter duration of hospital stay and potential decreased risk of healthcare-associated infections resulting from shorter duration catheterization. Possible advantages for both local communities and fistula care providers include potential increased hospital capacity for providing fistula repair services, if short-term catheterization is indeed found to be non-inferior to longer-term catheterization. This trial will also build research capacity of providers at study sites. For the international research community, this trial will fill a critical gap in the evidence-base supporting fistula repair techniques and procedures, including the most appropriate duration of catheterization following fistula repair surgery.

Risks

For participants assigned to the experimental group, study risks include the possibility of increased risk of breakdown of repair among the short-term catheterization group. However, should any complications occur appropriate care will be provided, including an additional attempt to close the fistula, if indicated and possible (as per the usual protocol at the study site). AEs and repair breakdowns will be monitored routinely at the site-level, and DSMB review will further help to minimize risks. Other potential risks include those risks associated with fistula surgery, although any patient at the site is susceptible to these risks whether or not she participates in the study.

Participants may withdraw from study participation at any time, for any reason, without loss of benefits or services to which they may be entitled. Site PIs may discontinue a participant at any time if he/she feels it is in the best interest of the participant.

4.3 Additional ethical concerns

Each participant in this study will be compensated for transportation to and from the clinic for the follow-up visit, and will be provided a small gift as compensation for her time; however, since participants are not routinely required to return for a follow-up visit following fistula repair, we do not expect that this would constitute undue influence on a participant's choice to participate in the study. Participants will not receive any monetary reimbursement for unscheduled visits or visits that are scheduled for clinical reasons (to receive test results, medical follow-up or treatment).

APPENDIX B:

Informed consent form and certificate of consent to be used at entry into the study

INFORMED CONSENT FORM

Title of study: Non-inferiority of short-term catheterization following fistula repair surgery

Principal Investigator: Dr. Mark Barone

Site Co-Investigator: *[name of site co-investigator will be inserted here]*

Introduction

Hello, my name is *[say your name]* and I am working with Fistula Care, a project that is strengthening fistula services in *[insert country name]*, and the World Health Organization. We are trying to learn about the best and safest ways to take care of women after they have fistula surgery. Specifically, after a fistula operation, all women have a tube put inside the passage that urine flows out of to drain the urine as the fistula begins to heal. This tube is called a catheter. Doctors who do fistula surgery have different ideas about how many days the catheter should be left in after the operation.

Information about the study

Some doctors think that leaving the catheter in for a long time helps the fistula heal better. Other doctors do not think a long time is necessary and worry that leaving the catheter in for too long can cause other problems like infection in the urine. If it is safe for women to have the catheter for a shorter period of time, we can help more women, since everyone would be able to leave the hospital sooner. We do not know if there is a difference between leaving the catheter in for a longer time or a shorter time and if more repairs might fail with one or the other. The only way to know what is best is to compare two groups of women; one group will have the catheter for two weeks, the other group will have the catheter for one week. Shorter duration of catheterization may be better than longer duration, the same, or worse. We do not know. We believe that even if it was a little worse for some individual women it may be preferable to use shorter catheterization for everyone because then we could treat many more women.

Your part in the study

The first step in doing a study like this is to explain to you, as someone who might help us by being in the study, what we are doing and why we are doing it. Then you are free to choose. We don't force anyone to take part in this study. If you hear about it and you do not want to participate, you don't have to be in the study. We will take care of you like any other woman having a fistula operation here. There is no penalty or punishment for women who decide they don't want to be in the study.

If you agree to be in the study, we will ask you some extra questions so that we know as much about your fistula problem as we can. Other than asking you these extra questions and recording some details about you and your fistula that we don't normally gather, your care will be the same as every woman here would receive from now until a week after your surgery. On the seventh day after your surgery we will repeat this informed consent process to be sure you are interested in continuing in the study. If you agree to continue, a test will be done to make sure that you are healing properly after your operation. If your doctor thinks that you are healing properly, then

you will be selected by chance (like the toss of a coin) either to have your catheter removed immediately or to keep your catheter for another week. A computer will decide which group you are in; neither you nor the doctor can choose the group.

Many of our patients who are in the study will need to come back 3 months after the operation for another examination to make sure that everything is still fine. The doctor will tell you if you need to return for this visit when you leave the facility. You will be given transport money to help you return to the hospital for this visit. If the doctors find a problem at the 3 month visit, they will do their best to help you. If you know that you cannot come back after 3 months, please tell us so that we can excuse you from the study.

If you participate in the study there may be some tests that we do more often than we normally do and others that we do not normally use here. One of these tests is called a dye test and helps us to determine if your fistula is closed. The other helps us to know if too much urine is staying inside your body. Both of these tests involve passing a catheter through the passage that urine flows through when you go to the toilet.

Possible risks and benefits

We want everyone in the study to be safe. First of all, if your fistula is a difficult one to repair, we want your doctor to do anything necessary to take care of you, and so women with difficult fistulas aren't going to be in this study. For those women who are in the study, there may be a small chance that there may be a problem with the fistula surgery. If you have a problem or if your repair fails, we will keep taking care of you at no cost and do our best until we have done everything we can to make you well. If you get sick after the surgery from an infection or another problem, we will do our best to give you all the medical treatment you need. This treatment will be provided for free.

Secondly, we will watch what is happening as we do the study. If a lot of women who have a catheter for only one week have a problem, we will stop doing the study. If a lot of women who have their catheter for two weeks have a problem, we will stop the study. We will always be watching to make sure that the study is as safe as it can be.

If we find that keeping the catheter in for the shorter time works just as well as keeping it in for the longer time, it may help us to improve services for women with fistula all over Africa and Asia.

Confidentiality

We also want to protect your privacy. We will not tell anyone else any specific information about you. EngenderHealth and WHO staff may sometimes look at your hospital or study records, and your study records will be sent to WHO staff in Switzerland who are working on the study. However, you will be identified only by a number on the study records that are sent to WHO. In addition, your name will not be used anywhere in study reports or documents, and will not be recorded anywhere on this questionnaire or your clinical forms. All study documents will be kept in a locked cabinet here at the clinic.

If the volunteer cannot read the form herself, a witness must sign here:

I was present while the benefits, risk and procedures were read to the volunteer. All questions she had were answered and she has agreed to participate in the study.

Signature of witness

Date

I certify that the nature and purpose, the potential benefits, and possible risks associated with participating in this study have been explained to the above individual and that she has voluntarily agreed to participate.

Signature of person obtaining consent

Date

Informed consent form and certificate of consent to be used at 7 days post-repair surgery, prior to conducting the dye test.

INFORMED CONSENT FORM

Title of study: Non-inferiority of short-term catheterization following fistula repair surgery

Principal Investigator: Dr. Mark Barone

Site Co-Investigator: *[name of site co-investigator will be inserted here]*

Introduction

Hello, my name is [say your name]. I want to talk with you about the study that you agreed to participate in before you had your fistula surgery and to see if you are interested in continuing to participate before we proceed to the next step of the study. You may recall that the study is to see if leaving the tube through which your urine is passing in place for a shorter period of time is the same as leaving it in for a longer period of time. Remember that the tube is called a catheter. I want to explain the study to you again.

Information about the study

You may recall that we told you previously that doctors don't know if there is a difference between leaving the catheter in for a longer time or a shorter time, for example if more repairs might fail with one approach or the other. The only way to know what is best is to compare two groups of women; one group will have the catheter for two weeks, the other group will have the catheter for one week. Shorter duration of catheterization may be better than longer duration, the same, or worse. We do not know. We believe that even if it was a little worse for some individual women it may be preferable to use shorter catheterization for everyone because then we could treat many more women.

Your part in the study

As you know, we have already gathered some information about you during our previous discussions and we have recorded some details about the care you have received so far. Remember that we don't force anyone to take part in this study and even though you previously agreed to participate, you do not need to continue to do so. You are free to choose. If you want to stop your participation now, or at any point in the future, you can do so. We will continue to take care of you like any other woman having a fistula operation here. There is no penalty or punishment if you decide you don't want to continue to be in the study.

If you agree to continue, later today we will do a test to make sure that you are healing properly. If your doctor thinks that you are healing properly, then you will be selected by chance (like the toss of a coin) either to have your catheter removed immediately or to keep your catheter for another week. A computer will decide which group you are in; neither you nor the doctor can choose the group.

Many of our patients who are in the study will need to come back 3 months after the operation for another examination to make sure that everything is still fine. The doctor will tell you if you

need to return for this visit when you leave the facility. You will be given transport money to help you return to the hospital for this visit. If the doctors find a problem at the 3 month visit, they will do their best to help you. If you know that you cannot come back after 3 months, please tell us so that we can excuse you from further participation in the study.

If you continue to participate in the study there may be some tests that we do more often than we normally do and others that we do not normally use here. One of these tests is called a dye test and helps us to determine if your fistula is closed. That is the test that you will have later today and then again up to two more times. The other test helps us to know if too much urine is staying inside your body. Both of these tests involve passing a catheter through the passage that urine flows through when you go to the toilet.

Possible risks and benefits

We want everyone in the study to be safe. For those women who are in the study, there may be a small chance that you have a problem or that your repair could fail. If anything like this occurs, we will keep taking care of you at no cost and do our best until we have done everything we can to make you well. If you get sick from an infection or another problem, we will do our best to give you all the medical treatment you need. This treatment will be provided for free.

We are watching what is happening as we do the study. If a lot of women who have a catheter for only one week have a problem, we will stop doing the study. If a lot of women who have their catheter for two weeks have a problem, we will stop the study. We will always be watching to make sure that the study is as safe as it can be.

If we find that keeping the catheter in for the shorter time works just as well as keeping it in for the longer time, it may help us to improve services for women with fistula all over Africa and Asia. If it is safe for women to have the catheter for a shorter period of time, we can help more women, since everyone would be able to leave the hospital sooner.

Confidentiality

We also want to protect your privacy. We will not tell anyone else any specific information about you. EngenderHealth and WHO staff may sometimes look at your hospital or study records and your study records will be sent to WHO staff in Switzerland who are working on the study. However, you will be identified only by a number on the study records that are sent to WHO. In addition, your name will not be used anywhere in study reports or documents, and will not be recorded anywhere on this questionnaire or your clinical forms. All study documents will be kept in a locked cabinet here at the clinic.

We will ask you to provide information about where you live and how we can reach you by telephone. We will call you or send you an SMS to remind you about your 3 month follow-up visit on the number(s) you provide. If you miss your scheduled follow-up visit 3 months after discharge, we will attempt to reach you by phone or may contact you at home to schedule another visit. When these contacts are made you will not be identified as being in this study.

If the volunteer cannot read the form herself, a witness must sign here:

I was present while the benefits, risk and procedures were read to the volunteer. All questions she had were answered and she has agreed to participate in the study.

Signature of witness

Date

I certify that the nature and purpose, the potential benefits, and possible risks associated with participating in this study have been explained to the above individual and that she has voluntarily agreed to participate.

APPENDIX C: Gender issues (Form 4b)

1. *Describe how the research addresses a demonstrated public health need and a need expressed by women and/or men.*

A vaginal fistula is a devastating condition, affecting an estimated 2 million girls and women across Africa and Asia. The provision of fistula repair services in developing countries is fraught with many challenges. Women with fistula are predominantly poor and from rural areas, and cannot pay for surgery or often even for transport to a site offering such services. Thus, fistula repair services must be provided free of charge. Most repairs are conducted within special units (with a distinct operating theatre and wards) of district hospitals or within specialist fistula centers, supported by external donors. The prolonged catheterization that is frequently employed after the surgery translates into a need for longer hospitalization, more intensive nursing care and thus decreased capacity for treating other patients. In most contexts, the need for services exceeds the human and infrastructural capacity for doing repairs. In light of these challenges, finding ways of providing services in a more efficient and cost-effective manner, without compromising surgical outcomes and the overall health of the patient, is paramount. Reducing the duration of bladder catheterization following fistula repair surgery has the potential to reduce hospital stays for women, thus freeing bed space, reducing costs per patient, and allowing for a greater number of patients to receive clinical care. It may also have implications for the probability of infection post-surgery, specifically urinary tract infection.

2. *Explain how the research contributes to identifying and/or reducing inequities between women and men in health and health care.*

Underlying causes of obstetric fistula include factors contributing to obstructed labor, such as malnutrition and early marriage, and factors inhibiting access to timely EmOC when obstructed labor occurs, including poverty, lack of education and low social status of women. Obstetric fistula is thus a clear indication that governments, communities and health systems are failing to provide the services and support that pregnant women need. However, this project is concerned with improving treatment for, rather than prevention of, this condition. Thus, it does not directly contribute to identifying or reducing inequities between women and men in health and health care.

3. *Describe plans for disseminating results and sharing knowledge with the research subjects and wider community.*

The results of this study will be disseminated in at least one workshop / forum attended by fistula surgeons, regional/local meetings, and at least one publication in a peer-reviewed journal. Results will not be disseminated among research participants, since the vast majority will not be returning to the facility after their follow-up visit is complete. Moreover, the intervention being tested is a medical procedure, and is not related to participant behaviors; thus, the community of interest for dissemination of results is the medical community.

4. *Does the nature or topic of the research make it important that the researchers are women rather than men or vice versa? Please explain. What is the sex composition of the research team and what are their duties and responsibilities in the proposed research?*

The nature or topic of the research does not make it important that the researchers are one sex or the other. The local PI, and the individual responsible for completing the CRFs, will be the surgeon responsible for the fistula repairs and pre- and post-operative care at the facility. Fistula surgery requires specialized training, skills and experience and such surgeons are limited in number. They would under non-research circumstances provide the care that study participants would normally receive. Some interview questions will be of a sensitive nature (e.g. whether or not the participant has engaged in sexual activity since the fistula surgery), and thus would be more appropriately asked by a female. All efforts will be made ensure that study interviewers are female.

Appendix D: CONSORT recommendations in the protocol - Checklist for non-inferiority and equivalence trials, Items 1 through 12¹⁸

PAPER SECTION And topic	Item	Descriptor	Reported on Section #
TITLE & ABSTRACT	1	How participants were allocated to interventions (<i>e.g.</i> , "random allocation", "randomized", or "randomly assigned"), <i>specifying that the trial is a non-inferiority or equivalence trial.</i>	Title in cover page; summary
INTRODUCTION Background	2	Scientific background and explanation of rationale, <i>including the rationale for using a non-inferiority or equivalence design.</i>	Section 3.1, 3.2 (also 3.3)
METHODS Participants	3	Eligibility criteria for participants (<i>detailing whether participants in the non-inferiority or equivalence trial are similar to those in any trial(s) that established efficacy of the reference treatment</i>) and the settings and locations where the data were collected.	Sections 3.3.5 and 3.3.6. No trials have established efficacy of the reference treatment.
Interventions	4	Precise details of the interventions intended for each group <i>detailing whether the reference treatment in the non-inferiority or equivalence trial is identical (or very similar) to that in any trial(s) that established efficacy</i> , and how and when they were actually administered.	Section 3.3.7.a No trials have established efficacy of the reference treatment.
Objectives	5	Specific objectives and hypotheses, <i>including the hypothesis concerning non-inferiority or equivalence.</i>	Section 3.1.2
Outcomes	6	Clearly defined primary and secondary outcome measures <i>detailing whether the outcomes in the non-inferiority or equivalence trial are identical (or very similar) to those in any trial(s) that established efficacy of the reference treatment</i> and, when applicable, any methods used to enhance the quality of measurements (<i>e.g.</i> , multiple observations, training of assessors).	Section 3.3.2. No trials have established efficacy of the reference treatment.
Sample size	7	How sample size was determined <i>detailing whether it was calculated using a non-inferiority or equivalence criterion and specifying the margin of equivalence with the rationale for its choice.</i> When applicable, explanation of any interim analyses and stopping rules (<i>and whether related to a non-inferiority or equivalence hypothesis</i>).	Sections 3.3.4 (sample size) and 3.3.11 (interim analysis and stopping rules)
Randomization --	8	Method used to generate the random allocation sequence,	Section

PAPER SECTION And topic	Item	Descriptor	Reported on Section #
Sequence generation		including details of any restrictions (<i>e.g.</i> , blocking, stratification)	3.3.7.b
Randomization -- Allocation concealment	9	Method used to implement the random allocation sequence (<i>e.g.</i> , numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	Section 3.3.7.b
Randomization -- Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.	Section 3.3.7.b
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated.	Section 3.3.10.a
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s), <i>specifying whether a one or two-sided confidence interval approach was used</i> . Methods for additional analyses, such as subgroup analyses and adjusted analyses.	Section 3.3.10.a and b

Appendix E: Dummy tables

Presented below are draft dummy tables for the analysis. These will be finalized upon finalization of the case report forms.

Table 1: Recruitment rates by trial arm in participating sites

	Site X					
7-day removal						
14-day removal						
Total recruitment						

Table 2: Characteristics of women at trial entry

	7-day removal N (%)	14-day removal N (%)
Age		
Parity		
Prior repair		

Table 3: Characteristics of fistula

	7-day removal N (%)	14-day removal N (%)
Characteristic X		
Characteristic X		
Characteristic X		

Table 4: Incidence of repair breakdown by site

	7-day removal N (%)	14-day removal N (%)
Site X		

Table 5: Trial outcome (by patient and fistula characteristics)

	7-day removal N (%)	14-day removal N (%)	RR	95% Confidence Interval
Characteristic X				

Table 6: Trial outcome (by received allocated treatment, categorical outcomes)

	7-day removal N (%)	14-day removal N (%)	RR	95% Confidence Interval
Repair breakdown at 3 month follow-up				
Repair breakdown one week after catheter removal				
Experienced septic or febrile episode				
Experienced prolonged hospitalization				
Experienced catheter blockage				
Any adverse effect				

Table 7: Trial outcome (by intention-to-treat, categorical outcomes)

	7-day removal N (%)	14-day removal N (%)	RR	95% Confidence Interval
Repair breakdown at 3 month follow-up				
Repair breakdown one week after catheter removal				
Experienced septic or febrile episode				
Experienced prolonged hospitalization				
Experienced catheter blockage				
Any adverse effect				

APPENDIX F. Standardized Patient Care Post-Randomization

As noted in section 3.3.7a, sites will not be asked to standardize post-operative care prior to randomization. The most intensive period of care for a patient after fistula repair is the first 48-72 hours. Randomization at 7 days, therefore, occurs at a time in the postoperative period when inputs are relatively few. Study sites will provide standard care from 7 days through discharge for all study participants as follows:

1. All patients will receive daily perineal and vaginal care. Once a day nurses will clean the perineum/vaginal area with betadine or another antiseptic. Putting anything into the vagina is prohibited.
2. No prophylactic antibiotics or anti-helminthic medication will be provided routinely.
3. Patients will receive a regular diet and will have no particular program of increased fluid intake.
4. Patients will no longer be on bed rest during this phase of care; patients will be encouraged to ambulate freely.
5. Patients will be monitored carefully for blockage of the indwelling bladder catheter, and if drainage seems to be impaired, the catheter will be immediately irrigated with sterile saline. If the blockage cannot be cleared, the catheter will be removed and replaced with a new catheter of identical type and size. Each woman's catheter will be kept fixed in place using one piece of tape to secure it against the thigh.
6. Patients with leakage around the catheter from apparent bladder spasm may receive anti-cholinergic medication (oxybutintin, hyoscyamine, or others) if available for symptomatic relief.
7. Nursing staff will monitor patients closely during the week after catheter removal
 - a. If the patient voids spontaneously, she will be straight-catheterized to determine post-void residual urine volume (PVR) on days 1, 3 and 7 after catheter removal.
 - i. If the PVR is more than twice the voided volume, intermittent catheterization will be carried out by the nurses a minimum of 3 times per day to drain the bladder.
 1. Intermittent catheterization will cease once the PVR is less than 50% of the voided volume for 2 consecutive determinations
 2. If PVR remains high (i.e. more than 50% of the voided volume) at 7 days following catheter removal, the patient will be instructed in intermittent self-catheterization. Any woman who is continuing intermittent self-catheterization at discharge will be asked to return for weekly follow-ups until the PVR falls below 50% of the voided volume.
 - b. Patients who are incontinent after catheter removal and have a high PVR will undergo intermittent catheterization as described above. As with all other study participants, patients with incontinence after catheter removal will have a dye test 7 days after catheter removal.
 - i. If this is positive, the patient will be considered a repair break-down, her participation in the study will end at that time, and the attending surgeon will decide on further treatment based on the patient's clinical situation and the usual practices at the study site.

- ii. If this dye test is negative, the patient will be considered to have post-operative incontinence and will be treated according to the preference of the provider in consultation with the patient.
8. There will be no bladder training
9. Women will receive instructions for how to do pelvic floor exercises just prior to discharge.
10. All participants will be instructed not to have sexual intercourse (or to insert anything in the vagina) until after they return for the 3 month follow-up visit.