

**Consultation to Review Manufacturing, Clinical and  
Regulatory Requirements for Male Circumcision  
Devices to Support Programme Expansion in High HIV  
Incidence Settings in Africa**

11-12 March 2009, Nairobi, Kenya

Meeting Report

World Health Organization, Geneva

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**World Health  
Organization**

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(RHR)**



## Executive Summary

Male circumcision has been shown to reduce the risk of HIV infection in men and recommended by WHO and UNAIDS as an additional HIV prevention intervention. Countries with generalized HIV epidemics and low prevalence of circumcision have been working to develop male circumcision policies and implementation plans. Male circumcision devices have been successfully and safely used in babies and young men, particularly in the Asian region. They have the potential to reduce the operation time, might be used by providers with less training than surgeons, reduce the incidence of complications, and decrease wound healing time. However, little information is available on the acceptability, safety, practicality and effectiveness of circumcision devices in adults and young men in African countries.

While there is considerable pressure to move rapidly to clinical testing of devices, the right sequence of steps and information necessary before moving to the next phase of evaluation had not been mapped out. A consultation of regulators from African and developed countries, surgeons, programme managers, product developers and sponsors was convened to review a draft framework that discussed the regulatory and clinical testing requirements for advancing male circumcision devices through testing to introduction in programmes. The objective was to reach a consensus on appropriate clinical evaluation pathways, balancing the requirements of safety with the importance of making devices rapidly available.

After reviewing the status of circumcision programme design and delivery in the African region, the meeting reviewed experience with circumcision devices and considered the proposed steps for assessing devices in new populations. Three major types of study were outlined – clinical studies in country of origin, clinical studies in the country of intended final use, and field studies of actual devices use in programmes. A progression of clinical studies in the country of intended use was outlined, ranging from case series to obtain initial acceptability and performance data, formal (preferably randomized) comparison with an established method of circumcision, and acceptability studies. It was recognized that while rates of adverse events and device-related incidents were of prime interest, studies of practical and acceptable size were not sufficiently large to demonstrate equivalence or improvements in such endpoints compared with standard surgical procedures. Thus primary endpoints should focus on issues relevant to the advantages of introducing a device, such as reduced operation time, pain scores, costs, or training requirements.

Participants in the meeting recognized that the agreed circumcision device evaluation framework went beyond minimum requirements for registration of medical devices, particularly devices that presented a low risk to the patient or provider. However, the objective was not only to permit safe and effective male circumcision devices to be registered in countries expanding male circumcision services for HIV prevention, but also to gather sufficient evidence to determine whether and how best they could be used within national programmes of male circumcision for HIV prevention.



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## Background

Male circumcision devices have been successfully and safely used in babies and young boys and men, particularly in the United States of America (USA) and the Asian region. Circumcision devices have the potential to reduce the time to complete the circumcision operation, might be safely used by providers with less training than surgeons, may reduce the incidence of complications following the procedure, and decrease the time to full wound healing. However, most of the clinical experience with male circumcision devices has been from the Asian region and involved babies or young boys. There is little information on the acceptability, safety, practicality and effectiveness of devices to perform circumcisions in adolescents and adults in African countries, where governments are planning rapid expansion of male circumcision services in order to reduce HIV incidence.

While there is considerable pressure to move rapidly to clinical testing of devices in this population, the right sequence of steps and information necessary before moving to the next phase of evaluation has not been mapped out. A draft framework that discussed the regulatory and clinical testing requirements for advancing male circumcision devices through testing to introduction in programmes had been developed and the consultation involving regulators from African and developed countries, surgeons, programme managers, product developers and sponsors was convened to review the framework. The objective was to reach a consensus on appropriate clinical evaluation pathways, balancing the requirements of safety with the importance of making devices available rapidly if their potential to enhance circumcision programme delivery is supported by evidence.

## Meeting

### **Objectives**

The objectives of the meeting were to:

- Review the current knowledge on male circumcision devices and their potential to support rapid programme scale-up in high HIV incidence settings in Africa;
- Review regulatory criteria for devices to be used in male circumcision programmes;
- Review the clinical criteria and clinical testing pathways to assess acceptability, safety and effectiveness of male circumcision devices in African populations; and
- Reach consensus on the evaluation framework.

### **Background papers and documents**

Background papers available for meeting participants included the following:

- (1) Lagarde E, Taljaard D, Puren A, Auvert B. High rate of adverse events consecutive to circumcision of young male adults with the Tara KLamp technique. Results from a randomized trial conducted in South Africa. Typescript, subsequently published *S Afr Med J* 2009;**99**:163-169.
- (2) Peng Y-F, Cheng Y, Wang G-Y, et al. Clinical application of a new device for minimally invasive circumcision. *Asian J Androl* 2008;**10**(3):447-454.

- (3) Meeting the Demand for Male Circumcision. Report. Kampala Uganda, March 2008. Forum for Collaborative HIV Research; The Bill and Melinda Gates Foundation; WHO, UNAIDS
- (4) WHO. Framework for Evaluation of Devices for Adult Male Circumcision. Draft for Discussion, dated 3 March 2009

## ***Participants***

The meeting brought together clinicians working on male circumcision service delivery in Kenya, Uganda and Zambia, representatives from Ministries of Health from Botswana, Kenya, Uganda and Zimbabwe, teams of clinicians and researchers involved with evaluation of circumcision devices, consultants and sponsors. The full list of participants is given in Annex I.

## **Introduction**

Meeting participants were welcomed by Dr Kimani, Director of Medical Services, Kenya Ministry of Medical Services, who thanked the various organizations present for organizing and supporting the initiative to examine the role of circumcision devices to accelerate circumcision programme scale up. He stressed three main points regarding circumcision in Kenya:

1. Safety was a critical component of the national male circumcision program. The Ministry's goal was that both traditional and modern medical male circumcision is safe for everybody – every boy and man should have access to safe services.
2. Male circumcision must be promoted as part of a mix of other HIV prevention and health interventions, and must not be presented as a “silver bullet” to prevent HIV infection as this might encourage people to forgo other prevention methods.
3. It was important to maintain a dialogue with the media to ensure that accurate information about circumcision and the circumcision programmes is disseminated. The media and the Ministry should work together to ensure dissemination of accurate information, so that people can make informed choices about male circumcision. This was particularly important with regard to new circumcision devices which needed to be carefully evaluated and their safety and acceptability assessed before introducing them into the national programme. The way in which the media reports new technologies and devices could have a large impact on the subsequent acceptability and uptake of the innovation.

In conclusion, Dr Kimani stressed that the best male circumcision methods and technologies should be made available so that adult males seeking circumcision could be circumcised safely. This also applied to circumcision of male infants and children that should be performed under optimal conditions, even if this was only rarely practiced in the country at present.

Dr Muraguri, Director of NASCOP, Ministry of Public Health and Sanitation, reiterated that the Kenyan Ministries were very committed to the adult male circumcision programme. At the time of the meeting 20 000 men had been circumcised yet demand was far in excess of the available resources. The Ministries were both committed for male circumcision coverage to reach at least 80% in all provinces of Kenya, and for all men to have access to safe medical male circumcision services. The Ministries had developed the National Guidance for Voluntary Male Circumcision in Kenya that defined the goal, purpose and guiding principles for the expansion of



medical male circumcision. The current focus of the programme was in those areas where male circumcision was not culturally practiced, but the programme of safe medical circumcision would be progressively extended to other areas of the country. In addition to safety and integration within a comprehensive package of HIV prevention interventions, Dr Muraguri added that the Ministry would ensure strong linkages between HIV prevention and the HIV care and treatment services.

The Ministries were committed to reduce the incidence of HIV infection by 50% within four years as the current treatment programme was not sustainable. Hence it was placing great emphasis on HIV prevention interventions, and male circumcision in particular. The Ministries were looking for innovative circumcision service delivery models as well as new technologies to support the programme, in order that the full public health impact could be realized. Circumcision devices had a potentially important role within the programme if they were safe, acceptable and could reduce the time of the operation or the recovery time after the operation.

The objectives of the meeting, background documents and agenda (Annex II) were reviewed and agreed by participants.

## **Summary of male circumcision scale up in Africa**

Before proceeding to a review of circumcision devices and their potential to accelerate programme scale up, participants briefly reviewed the status of male circumcision programmes in countries in the African region. All country presentations emphasized the importance of integrating an adult male circumcision programme within the context of the country's HIV prevention programme and services and stressed that circumcision should not be offered without comprehensive counselling on HIV risk reduction, HIV testing, safe sex and condom promotion. All country programmes included a strong emphasis on the safety of clinical (or medical) male circumcision and proper training and supervision to ensure safety. In addition all presenters emphasized the need to work with the media to provide accurate and appropriate messages to the public about male circumcision, in particular to stress that while circumcision reduced the risk of HIV infection it was only partially protective and other risk reduction strategies must continue to be followed. The different cultural contexts of each country had to be considered, for example the current prevalence of circumcision and existence of traditional circumcision providers. These meant that countries would have different policies and approaches to scaling up adult male circumcision services, and the speed of scale up needed to be adapted to the acceptability of the program. The lack of health infrastructure and skilled clinicians, long duration of each procedure and cost were major hurdles to scaling up adult male circumcision services in all settings, and thus circumcision devices had a potential place within the programmes if they could result in cost and/or time savings, or facilitate service provision by nurses or other mid-level providers.

### ***Botswana***

Dr Hilda Matumo, focal person for the programme summarized the status of the Botswana circumcision programme. The government underlined the safety of the programme and procedure by defining the Safe Male Circumcision (SMC) Strategy. In 2008 the key messages and materials on SMC had been developed, pre-tested and distributed to health facilities. The Standard Operating Procedures and a manual had been developed and pilot tested in the Northern and Southern regions of the country in November 2008 and February 2009. A media training workshop had been held in March. The surgical approaches chosen for the country were the dorsal slit and forceps guided methods, the latter expected to be the most commonly used. The training programme required five days, of which two were devoted to practical

issues. The first series of 105 circumcisions had been uneventful. Only medical doctors were allowed to perform surgery in the country, so nurses could only support the operation. An ambitious national target of reaching 80% of the adult male population (current size approximately 500,000 men) with circumcision within 5 years had been set. There was no issue of combining or integrating traditional circumcision services with the national safe male circumcision programme as traditional circumcision had been prohibited by the High Commissioner in 1917.

A feasibility and acceptability study of infant circumcision had been completed and revealed high acceptance by parents (over 96%). A formal comparison would be made between the Mogen Clamp and Plastibell devices for this age group, with key outcomes being provider and parent acceptability and ease of the procedure. Additional research included a population-based survey of Knowledge, Attitudes and Practices on circumcision that would be shortly completed, as well as the analysis of a facility-based needs assessment in order to strengthen the health facilities with the Ministry of Health as required.

## **Kenya**

Dr Masasabi Wkesa and Dr Fred Kambuni summarized the status of the Kenya male circumcision programme which had been launched in 2008 with the release of the male circumcision policy, guidelines and technical manual. Circumcision was most commonly performed around the age of 12 years. No devices were currently used in the country except for the Plastibell which was used by some urologists for infant circumcision. The Ministry was currently considering an application to register the Tara KLamp and was looking for scientific evidence to support the application. All circumcision providers should be trained in the surgical method and associated procedures for circumcision, and such training should be integrated with other medical and nursing training.

Traditional male circumcision was very common in certain areas of the country and was primarily performed in 13-20 year old boys in annual or semi-annual ceremonies. Each tribe had slightly different variants and ways of performing circumcision and the Ministry was trying to standardize the approach as well as improve the safety of the procedure. The pain associated with traditional circumcision performed without anaesthesia was considered an important rite of passage. It appeared that the majority of the complications associated with traditional circumcision were attributable to circumcisers with inadequate training or background, particularly if they worked in areas without established traditional circumcision practices.

Other challenges mentioned regarding the safety and quality of circumcision services related to the lack of formal quality assurance procedures and requirements for medical devices in the country and the need to build good referral networks between the different levels of health providers and health facilities so that all complications associated with circumcision could be swiftly managed and statistics collated.

## **Uganda**

Dr Jackson Amone, Ministry of Health, summarized the progress in developing and implementing a programme for circumcision in Uganda. The government had decided to use the phrase Medical Male Circumcision (MMC) to distinguish the procedure from traditional circumcision and female circumcision that was still practiced in some parts of the country. Although one of the three adult male circumcision randomized controlled trials had been performed in Uganda, the government was moving cautiously in development and implementation of the

programme so as to avoid potential mismatch between demand and resources, and possible popular misconceptions about the benefits and risks of MMC.

A National Task Force for MMC had been formed, a communication strategy drafted and a Situation Analysis conducted to assess the degree of support for MMC, and mechanisms for integrating MMC with other services. The Situation Analysis was based on the WHO generic protocol using qualitative and quantitative methods and covered four districts (Kampala, Gulu, Kumi and Rukungiri). The Situation Analysis, had been presented and discussed in November 2008 and showed good support for MMC in the country, but currently limited capacity to offer MMC services, and no policy or legal framework to support implementation. The cost of the procedure to the clients ranged from US\$ 10 to US\$ 200 with a median of US\$ 30. Circumcision was being offered to all age groups.

While awaiting a more detailed policy and implementation strategy for MMC, the government was building consensus among key stakeholders for circumcision at national and provincial levels, and making available information on the risks and benefits of MMC, informing people where they could access services if they so wished and stressing that MMC was not a magic bullet – it must be seen in the context of other HIV risk-reduction strategies and behaviours.

The most commonly used circumcision procedures were the dorsal slit and sleeve methods. There was no experience with devices, other than in the hands of a limited number of private practitioners. Nurses were currently not allowed to perform surgical procedures in Uganda. Training in circumcision services and procedures was being provided in Rakai using the WHO technical standards and Jhpiego training tools. Teams consisting of clinical officers, doctors, and assistants (counsellors, nurses) from various countries were being trained with support of fellowships provided by WHO. The linkages between medical male circumcision services and traditional providers had not been adequately investigated and defined. Circumcisions were performed by traditional providers in several parts of the country (overall 55% prevalence of circumcision in Eastern, 35% in East Central 30% in Western and 24% in Central Provinces).

There was a brief discussion about recording of complications in a standardized format in all countries implementing circumcision programmes. Good data on incidence and severity of complications were important in order to counteract potential bad publicity on MC. Reference was made to the vasectomy programmes in India where press reports of high complication rates had undermined the national programme. In Uganda, as part of training, providers were noting and compiling information on complication rates. In Kenya, collation of information on complications was the responsibility of the national task force and similar mechanisms and responsibilities could be set up in other countries.

## **Zambia**

Dr Kasonde Bowa, University Teaching Hospital, Lusaka gave an overview of the circumcision programme in Zambia. A pilot feasibility study of circumcision for improved sexual health had been developed in 2004, and a national task force for male circumcision had been established once the results from the randomized controlled trials showing a lower HIV incidence had become available. Overall about 14-18% of men in Zambia were circumcised, mostly in rural areas. The highest prevalence of circumcision was in the northwest of the country (about 80%), but few complications associated with circumcision were reported.

The most commonly used method of medical circumcision was the dorsal slit, though there was interest in using other methods as recommended in the WHO technical

manual. Circumcision devices (Gomco clamp, Mogen clamp and Plastibell) were available for infant circumcision and a pilot study for research on an (unnamed) adult circumcision device was under consideration by the university ethics committee.

To date about 100 providers had been trained, primarily in teams consisting of nurses, doctors, clinical officers and surgeons. In Zambia nurses were not formally allowed to perform surgery, but the nursing council was supportive in the expectation that suitably trained nurses should be able to perform the procedure. Currently there were five fixed and two mobile sites providing services, run by non-governmental organizations. These were linked to HIV testing and counselling services, and the minimum package of services as defined by WHO was provided. A pilot programme at the University Teaching Hospital in Lusaka combines adult and neonatal circumcision and HIV testing. Plans are underfoot to establish male circumcision service sites in nine provinces in the country. Traditional male circumcision is quite widely practiced in the North West of the country.

### **Zimbabwe**

Dr Christopher Samkange and Christopher Tapfumaneyi summarized the status of male circumcision scale up in Zimbabwe. In 2007 the Ministry of Health had convened a consensus building meeting in which it was agreed to scale up services. The programme was overseen by a Steering Committee to assess service delivery and the positioning of the programme which should be integrated with the other HIV prevention programmes and strategies in the country. The priority age group for services would be 13 to 29 year old boys and men and it was noted that the MC programme was a rare opportunity to bring these young men into the health system. Roll out was planned for September 2009. Currently no devices were used in the country.

Traditional circumcision was performed in certain tribal groups, but other tribes had an aversion to the procedure. In 2008 a study of traditional circumcision practices and attitudes revealed that two main types of traditional circumcision were performed – one with full removal of the foreskin and the other in which just a dorsal slit was performed without foreskin removal. The circumcision process and accompanying ceremonies were seen as an important rite of passage to adulthood. A consensus had been reached that traditional circumcisers would continue the ceremonious part of the procedure while the medical providers would perform the procedure under safe and hygienic conditions.

### **Other countries**

The status of circumcision programme roll out in other countries was briefly summarized by Dr Tim Farley. In Lesotho, a situation analysis had been completed and had revealed a large gap in perceptions, attitudes and needs for a circumcision initiative between traditional and formal medical sectors. Dialogue between these groups was difficult, though there had been initiatives to close the gap. Circumcision was almost universal in the mountainous regions of the country, performed by traditional providers, though with very variable amounts of foreskin removed. Indeed it was questionable whether sufficient foreskin was removed in many traditional procedures in the country. The Tara KLamp device had been promoted by the manufacturer and distributor among traditional providers, but there was little documentation about the extent of use, acceptability and/or safety of the device used in this way.

In Namibia, the country was developing a national policy that would involve offering circumcision to all adults within five years. There were currently no plans for use or interest in devices.

In Rwanda services were being developed to systematically offer circumcision to young adult men recruited to the uniformed services (army, police force) as well as university students. A parallel neonatal programme was under development. There was no experience with adult circumcision devices, though neonatal devices were used in the country in limited numbers.

In Swaziland a National Task Force had been established to define the policy framework. Limited numbers of circumcisions were being provided through the NGO sector. There was potential interest in devices, should they be shown to accelerate service delivery.

In the Republic of South Africa there were large differences between ethnic groups in circumcision prevalence with the procedure almost unknown among the Zulus while almost universal among the Xhosa. Despite the male circumcision randomized controlled trial in Orange Farm to have been the first to report results in 2005, the country had not moved rapidly to develop a national programme. Acceleration was expected with the recent change in government in the country. High complication rates (including deaths) have been reported with traditional circumcision, though many of these were probably attributable to the enforced period of seclusion following the traditional initiation ceremonies rather than to the circumcision procedure itself. The Orange Farm team had assessed the Tara KLamp device in a formal randomized trial and shown high complication rates (discussed in detail on page 8 below).

## **Male circumcision devices**

### ***Potential of devices to facilitate scale up***

Dr Stephen Watya summarized key points regarding circumcision scale up and the potential for devices to facilitate this process. Large numbers of circumcisions are required over the next 5 years in Africa – by some estimates as much as 35 million – if the potential impact of circumcision on the HIV epidemic is to be realized. Key challenges to offering large numbers of circumcisions include the lack of surgical resources, the large burden on already stretched health systems, management and distribution of the necessary supplies and reusable equipment, and the ability to manage complications and ensure adequate follow up. Large efforts are being made to meet the anticipated demand for circumcision that has been shown in several countries to be highly acceptable. Key innovations include accelerated training programmes, task shifting of appropriate procedures to non-surgeons and mid-level providers, and arranging high throughput circumcision camps or weekend initiatives.

Male circumcision devices had the potential to facilitate rapid expansion of circumcision services. An ideal device would minimally affect routine provision of health care, be inexpensive, easy to use, safe, permit replicable procedures and easily taught to mid-level providers. At present there was limited clinical experience among adults in Africa with only three devices (Sunathrone Clamp, SmartKlamp and Tara KLamp).

During the meeting the importance of considering the full cost of a circumcision device was stressed. Such costs should include not only the cost of the device, but also its distribution and disposal. It was noted that many items in Africa were reused, even if not specifically intended as such. Thus auto-destruction of single-use devices

or safe cleaning and sterilization of reusable devices needs to be carefully considered.

Participants also stressed that devices may not be suitable for all patients presenting for circumcision, for example in men with congenital or acquired abnormalities of the penis or hereditary bleeding disorders. These men would have to be screened out and referred to appropriate surgical services for their circumcision. Thus a device, even if shown to be safe, effective and acceptable, would still require locally available conventional surgical facilities for men with contraindications to use of the device, and to manage any complications that might arise during the procedure, and would not obviate the requirement for careful screening of patients.

### ***Key recommendations from Kampala meeting on circumcision devices***

A previous meeting in Kampala Uganda in March 2008 had discussed *inter alia* the potential for devices to accelerate male circumcision scale up. A scoping of available devices had been completed and it was noted that there was very little clinical experience with devices in young men and adults in African settings. Most devices had been designed for neonatal, infant or young boy circumcision and the majority of the clinical experience had accumulated in Moslem and Jewish countries and communities as well as the USA for neonatal procedures. The importance of ensuring data on the acceptability and performance of the device collected independently from the manufacturer was stressed, as well as progressively accumulating clinical experience in the populations where the devices would ultimately be used. An initial study of 30-40 procedures in the hands of experienced providers was recommended. It was also important to clarify the pathway for regulatory approval of new circumcision devices or the approval of devices in new countries. The meeting urged the development of a consensus among regulators, policy makers, clinicians and programme managers on the minimum requirements for male circumcision devices so that their clinical evaluation could advance progressively, with due attention to the acceptability and safety of the device.

Of the devices considered in Kampala, the SmartKlamp was the only device with USA FDA approval. In addition, the Tara KLamp had not performed successfully in the one formal clinical study conducted in Africa (see below).

### ***Leading candidate devices for assessment***

There were three options for developing devices for use in circumcision programmes in Africa – taking an existing device used in other settings and populations, modifying an existing device to improve safety or performance, and/or developing a device *de novo*. The first approach would be the quickest to scale up use in the target populations, though there may be developments and improvements that could be introduced as clinical experience in the target populations expanded. Currently there were no new devices advancing through the product development pipeline, while the potential to make minor modifications to existing devices to improve performance were being considered. In order to inform the discussion about the appropriate clinical evaluation pathways and steps, two particular devices for which clinical data existed (Tara KLamp and Shang Ring) were considered in detail.

Devices could be considered in different categories – those that were applied to facilitate the surgical operation and designed to be removed after wound closure, and those that crushed the foreskin and blood vessels thus achieving haemostasis. While crushing devices in infants could achieve haemostasis within a short period (e.g. several minutes with the Mogen Clamp), in adults they would need to remain *in*

*situ* for several days (possibly up to a week) to have the desired result. The Plastibell device, included in the WHO Technical Manual for paediatric circumcision, was an example of a crush device in which the remaining tissue necrosed and fell off with the device after several days.

### Experience with Tara KLamp in South Africa

Dr Tim Hargreave summarized the clinical experiences reported with the Tara KLamp device in a randomized controlled trial conducted in South Africa. This device had been developed in Kuala Lumpur, Malaysia, and the majority of the clinical experience had been accumulated among young adolescent boys (ages 8 or 9 years).<sup>1</sup> The device could only be used once and came in a range of sizes, the choice of which was determined from a simple graduated measuring tape that was wrapped around the penis prior to surgery. Adult sizes had been developed and the device had been promoted by the distributor in South Africa as well as in Lesotho, though it was not clear how frequently the device was used. The device involved a short sleeve that was placed between the glans and foreskin with a clamping mechanism that crushed the foreskin and blood vessels outside the sleeve. Surplus foreskin tissue was then trimmed using scissors or a scalpel and the device remained locked in situ until released about one week later. Releasing the device rendered it unusable for any further operation. Careful inspection of the devices revealed theoretical concerns, notably several crevasses that could lead to infections, potential pressure on the glans if a too small device was used, adult sizes being quite large and bulky to wear for a week which may lead to low acceptability and/or potential wound disruption. There were concerns whether the device would be sufficiently strong to crush adult foreskin tissue that was thicker than in young boys.

A non-randomized comparison between conventional surgery and the Tara KLamp device had been completed in 275 young boys the Netherlands (median age 3 years) showing low rates of complications in each group, and a somewhat shorter operative time and improved cosmetic result with the KLamp.<sup>2</sup>

A randomized trial of the device had been conducted in Orange Farm, South Africa, among men originally allocated to the delayed circumcision group in the randomized controlled trial of immediate versus delayed circumcision and HIV infection.<sup>3</sup> Men presenting for circumcision were invited to participate in the randomized trial comparing circumcision with the Tara KLamp and conventional surgery (forceps guided method).<sup>4</sup> Of 166 men invited to participate in the trial, 97 preferred not to be randomized and chose conventional surgery. The median age of the volunteers was 22 years. Adverse events were experienced by 12 men allocated to the Tara KLamp

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<sup>1</sup> Schmitz RF, Abu Bakar MH, Omar ZH, Kamalanathan S, Schulpen TW, van der Werken C. Results of group-circumcision of Muslim boys in Malaysia with a new type of disposable clamp. *Tropical Doctor* 2001; **31**: 152-4.

<sup>2</sup> Schmitz RF, Schulpen TWJ, Redjopawiro MS, Liem MSL, Madern GC, Van Der Werken C. Religious circumcision under local anaesthesia with a new disposable clamp. *BJU International* 2001; **88**(6): 581-585.

<sup>3</sup> Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: The ANRS 1265 Trial. *PLoS Medicine* 2005; **2**(11): e298.

<sup>4</sup> Lagarde E, Taljaard D, Puren A, Auvert B. High rate of adverse events following circumcision of young male adults with the Tara KLamp technique: A randomized trial conducted in South Africa. *S Afr Med J* 2009; **99**: 163-169.

compared with none allocated conventional surgery. The most common problems were cellulitis, septic wound, swelling, erythema and adherence of the device to the penile tissue. The local distributor suggested that the difficulties encountered were due to inexperience with the device and arranged a retraining session by an experienced practitioner. However, the trial was abandoned as no improvement in performance was seen in the last group of 15 patients circumcised.

While the surgeons were much more experienced with the forceps-guided method than the Tara KLamp, the low acceptability and high complication rates illustrate the difficulties of introducing a device in a new population and the need for careful evaluation by clinicians independent of the device manufacturers. Although the limited data on the device in the South African setting were worrisome, it was agreed that they did not necessarily exclude the Tara KLamp device from further assessment in an adult African population, nor imply that similarly high complication rates would be seen in younger men or adolescents. Any further research on this device would preferably include careful documentation of wound healing and complications so that an independent assessment could be made.

### **Experience with Tara KLamp in Kenya**

Dr Wasasabi Wekesa and Dr Peter Cherutich summarized the status of the Tara KLamp device in Kenya. The distributor had been granted preliminary approval to market the device in the country based on a presentation made to the Ministry, but very little clinical data had been provided. It appeared that the device was being promoted in Nyanza province, but the extent of use, acceptability and possible complication rates were not clear.

This experience underscored the importance of formal assessment of male circumcision devices and careful progressive clinical evaluation if a device was to become part of a national scale-up strategy for male circumcision. While the formal procedures for regulation and approval of medical devices must be followed, these may not give sufficient reassurance that a device was suitable for use in a programme. Considerations of acceptability, costs, training, reliability of supply, and the potential impact on effective programme scale-up were additional important considerations that were not usually part of the device approval process. It was not clear which body should be responsible for such an assessment – possible structures included the National Circumcision Task Force or the local surgical or medical society.

Since the device was being used in the country, there was an opportunity for a formal pilot evaluation and a direct randomized comparison with another device or conventional surgery. It was agreed that any such evaluation must be conducted independently of the manufacturer under conditions that would reflect the eventual use of the device in a programme. In addition a mechanism needed to be established to compile comprehensive information on complications with the device.

### **Experience with Shang Ring in China**

Dr Philip Li summarized the clinical experience with a new circumcision device, the Shang Ring, developed in China. This had been developed in 2005 and over 40,000 circumcisions had been performed with the device. A specially designed measuring tape was used to select the correct size device which was 10-20% larger than actual penile circumference to accommodate erections while the device remained in situ.

The device had a unique feature in that the foreskin was everted over the inner ring placed just below the coronal sulcus and a second ring applied to crush the foreskin once it had been correctly adjusted. The excess foreskin was cut away distal to the



glans, thus reducing the chance of injury. Four to eight small slits were made on the foreskin on the underside of the closed ring to allow for expansion during erections and facilitate the healing process. For well-trained physicians the average total operation time was about five minutes. Although the procedure to apply the device was straightforward and rapid, Dr Li stressed the importance of appropriate training to minimize potential complications.

The ring was removed after 7-8 days using a small tool (similar to a screw driver) to unclip the lock on the outer ring and special scissors to cut the inner ring. The penis was wrapped in a small self-adhesive dressing after removal.

Peng and colleagues had published their clinical experience with the device in China in 1200 patients,<sup>5</sup> but the quality and completeness of the data were unclear. This particular report was not likely adequate to support a regulatory review of the device. A better protocol including systematic data recording and collation using standardized forms was currently under way in China involving support from Philip Li, David Sokal and other clinicians with experience of international regulatory requirements.

An additional study reported use of the Shang Ring from a series of 328 men age 18-58 (mean 28) years from Ningbo First Hospital, Zhejiang Province, China.<sup>6</sup> The mean procedure time was 4.7 (SD 1.3) minutes. Pain scores on a visual analogue scale 0 (no pain) to 10 (extreme pain) were 0.2 (0.6) during surgery, 1.6 (1.0) 24 hours postoperatively, 1.7 (1.1) 24 hours prior to ring removal, and 2.7 (1.4) during ring removal. Complications were rare – bleeding 0.6%, local infection 0.6%, wound oedema 4.9% (which resolved following ring removal) and wound dehiscence (0.6%). The median ring size was 30 mm diameter, with 90% of patients requiring a ring diameter between 28 mm and 35 mm. No data were available on sizes in non-Chinese populations.

Dr Philip Li listed several advantages and disadvantages of the Shang Ring device, some of which were theoretical and not yet well documented (Table 1).

**Table 1: Potential advantages and disadvantages of the Shang Ring device**

Potential Advantages	Potential Disadvantages
<p><b>General</b></p> <ul style="list-style-type: none"> <li>- Simple effective MC technique in China</li> <li>- Significantly reduces operative time</li> <li>- Few complications</li> <li>- Can be performed by minimally experienced healthcare providers</li> <li>- Minimally invasive surgery – reduces potential surgical errors</li> <li>- No sutures for haemostasis or wound closure</li> <li>- Disposable and sterile package</li> <li>- Relatively painless</li> <li>- Coronal sulcus is open and clean</li> <li>- Glans and frenulum are well protected</li> </ul> <p><b>Post surgery</b></p> <ul style="list-style-type: none"> <li>- No need to use antibiotics</li> </ul>	<ul style="list-style-type: none"> <li>- Too many sizes</li> <li>- Device is left on patient 7-10 days</li> <li>- Requires second visit for device removal</li> <li>- Potential oedema and pain</li> <li>- No data from outside of China</li> <li>- Extensive training extremely important to reduce complication rates (even though procedure simple to perform)</li> <li>- Requires special scissors for removal</li> </ul>

<sup>5</sup> Peng Y-F, Cheng Y, Wang G-Y, et al. Clinical application of a new device for minimally invasive circumcision. *Asian J Androl* 2008;**10**(3):447-454.

<sup>6</sup> Cheng Y, Peng Y-F, Liu Y-D, et al. Adult male circumcision using the Chinese Shang Ring: results of 328 cases and a recommended standard surgical protocol in China. *National Journal of Andrology* 2009;**15**(7):584-592.

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- No need to delay or avoid washing or showering following surgery
  - Excellent cosmetic results, little wound scar
  - Rare bleeding and infection
  - Low complication rate
  - High satisfaction with result
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### **Pilot Study of Shang Ring in Kenya**

As part of the progressive evaluation of a device in a new clinical setting, Mr Mark Barone summarized a planned study on the Shang Ring device in Kenya designed to examine clinical outcomes and patient satisfaction in a small group of Kenyan men and lay the ground work for a more extensive randomized controlled trial. The specific objectives included:

1. Safety: Immediate, early post-operative complications (within 30 days), excessive pain and/or need to remove device before scheduled date (possibly due to erections)
2. Effectiveness (successful circumcision): Ease of use (during circumcision procedure and removal), procedure and removal time, surgical difficulties (i.e. thickness of foreskin), removal problems, healing time, cosmetic results
3. Acceptability/satisfaction: Meet recruitment target; problems while device in situ, pain score (during circumcision procedure and removal), pain/discomfort while device in place, cosmetic results, overall satisfaction

The study design was a prospective non-comparative study of 40 men at one site in Nyanza Province currently providing a male circumcision service. There would be a phased enrolment of an initial five cases followed until complete healing, and ongoing enrolment if no complications occurred. The circumcisions would be performed by a provider experienced in conventional circumcision surgery who would be trained as part of a team in China. Follow-up visits (clinical examinations and interviews) were scheduled for day 0 (immediately following circumcision), day 2 (device in situ), day 7 (device removal and interview), day 9 (post-removal visit), then weekly until healing was complete.

Meeting participants welcomed the carefully designed protocol and progressive evaluation of the device. In discussion about the study, they suggested:

- Documentation of complications and wound healing with systematic photographs labelled with patient identification and date.
- Theoretical concerns with penile strangulation which would require immediate presentation to the health facility and prompt ring removal. Suturing of the wound might be necessary so it was important the study was conducted in a setting where such skills were available. Some notes on this issue needed to be included in the protocol.
- Since this was the first study of the device in an African population, it was important to have very strict medical eligibility criteria. These would be based on the criteria for surgery defined in the WHO Technical Manual and additionally exclude HIV-positive men. Social and environmental eligibility criteria (e.g. proximity and ease of access to health facility, washing facilities and hygiene in the home) could be progressively relaxed as experience with the device accumulated and no complications were seen.
- Acceptability could be assessed by the refusal rate and from specific questions during the follow-up and exit interviews.

- Resumption of sexual activity should be documented.

### ***Assessing new technology for adult male circumcision***

Ms Emily Gumkowski summarized the steps in the assessment of new or existing technologies in male circumcision, in order to identify areas for improved design, reduced operative time or avoiding potential risks. She noted that circumcision was probably the most widely performed minor surgical procedure worldwide with which there was considerable experience. The three methods included in the WHO Technical Manual (dorsal slit, forceps-guided and sleeve methods) were all skill based. The greatest skill was required during the haemostasis (identifying and tying the bleeders) and wound closure steps (10-20 sutures) which were also the most time consuming steps.

To develop new or improved technology for circumcision, it was important to examine the different steps (isolate foreskin, cut away foreskin, achieve haemostasis, and ensure wound closure) for their potential to develop faster, safer and easier procedures.

The different perspectives of the clinician, patient and supplier in developing new or improved technology needed to be considered. For the clinician these included safety (reliable haemostasis, good infection control, protection of glans) and simplicity (easy to use, train, reproducible results, shorter procedure). From the patient's perspective these included the cosmetic result, satisfaction with the procedure, completed operation by end of visit and acceptable pain control and healing time. For the supplier, key considerations included device sterilization, sterile packaging, disposable or self-destruct device, or easy cleaning, disinfection and sterilization of a reusable device, built-in failure mode protection (e.g. sharp edges supplied with protective cover or inaccessible), and acceptable cost for the end user. Non-clinical factors relevant to any new technology included regulatory considerations, manufacturing and distribution costs, and simplicity of manufacture.

There were several technologies that could be applied to or further developed for the circumcision procedure. These included devices, adhesives, tapes, haemostatic dressings, as well as the development of completely new devices. Some aspects could be assessed with bench top models – compression forces exerted by the device can be measured and with and without artificial skin, shearing during wound healing could be assessed with artificial skin. However, other characteristics required clinical evaluation on actual patients – potential wound disruption with device in situ during an erection, clear understanding of when it was safe and appropriate to remove the device for optimal wound healing, tolerance of different device sizes according to dimensions of non-erect penis.

The example of potential evaluation of surgical grade glue was discussed. There was clinical experience with this approach<sup>7</sup> including a randomized trial in 162 young boys.<sup>8</sup> The authors had shown that operative time was reduced and with less postoperative pain than with sutures. While used fairly extensively in wound closure in resource-rich settings, glue had not been studied for adult circumcision. A brief discussion ensued on the potential for this technology to facilitate circumcisions in African settings ensued. The glue was used to approximate the foreskin tissues and achieve wound closure but would have to be combined with diathermy or

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<sup>7</sup> Fraser ID, Goede AC. Sutureless circumcision. *BJU Int* 2002;**90**(4):467-8.

<sup>8</sup> Subramaniam R, Jacobsen AS. Sutureless circumcision: a prospective randomised controlled study. *Pediatr Surg Int* 2004;**20**(10):783-5.

haemostatic sutures, thus undermining the potential advantage of this approach by enabling providers not skilled in suturing to become involved with circumcision provision.

## **Review of draft evaluation framework**

The remainder of the meeting was spent reviewing the draft *Framework for Evaluation of Devices for Adult Male Circumcision* in the light of the discussion and the experiences with the development and clinical testing of circumcision devices in the African context. Specific technical and textual issues were mentioned, particularly with regard to the context, regulatory requirements, manufacturing, marketing and surveillance of product use. These clarifications were introduced in the updated framework document. The majority of discussion focussed on the clinical evaluation of circumcision devices to meet regulatory requirements as well as public health goals of accelerating circumcision programme scale up. It was noted that the regulatory requirements to introduce new circumcision devices to the market or to make improvements to existing devices did not necessarily provide sufficient information as to whether the device would be acceptable to providers and clients, result in net cost savings, increase the rate at which circumcisions could be performed in country programmes, and be a cost-effective addition to the method mix. Such additional information was critical to making recommendations and policy decisions on the role of devices for expansion of circumcision services and sustaining those services in the long term.

In order for WHO and national health authorities to assess a device for general use in low-resource settings and in national circumcision programmes, the following research studies should be considered:

- clinical studies by skilled surgeons in the country of origin or manufacture,
- clinical studies by skilled surgeons in the country of intended use,
- comparative clinical study by skilled surgeons in a low resource setting, and
- field studies by trained clinical personnel in a low resource setting, reflecting anticipated conditions of intended use.

The body of evidence and experience so generated would form the basis of guidelines and recommendations on the use of the device(s) within programmes in resource-limited settings that are offering adult male circumcision for HIV prevention.

## ***Collation and review of data from country of origin***

As a first step, it would be important to gather relevant clinical data on a device and establish its clinical profile of the device on the basis of published and unpublished data. Some of these data could have been generated during the device development process and would form the basis of an initial device approval dossier. However, data from sources independent of the manufacturer would carry greater weight, unless high-quality and comprehensive data could be documented. A review of clinical adverse events and device-related incidents, together with the related actions taken by the manufacturer, should also be available.

Initial clinical data that should be available from country of origin before a device could proceed to evaluation in a low resource setting are summarized in Table 2. While demonstrated reductions in adverse event rates compared with conventional surgery were important, it was recognized that studies of practical size could not expect to show such differences, particularly since large-scale comparative studies were not appropriate until adequate information on safety and effectiveness of the

device had been collected. There were other considerations that could justify proceeding further with a new device, such as anticipated improvements in the operative procedure, reduced costs, reduced operative times, reduced pain, improved patient or provider satisfaction, higher acceptability or reduced healing time. These endpoints could be considered as the primary outcomes for sample size assessment.

**Table 2: Clinical data on device from country of origin**

Type of study	Sample size (range)	Endpoints	Notes and comments
Case series (non-comparative study)	50 (25 – 100)	Primary endpoints: <ul style="list-style-type: none"> <li>- Clinical adverse events</li> <li>- Device-related incidents</li> </ul> Secondary endpoints: <ul style="list-style-type: none"> <li>- Technical difficulty and complications during procedure and removal process*</li> <li>- Pain assessment at key time points (using e.g. Visual Analogue Scale)</li> <li>- Cosmetic results*</li> <li>- Healing process*</li> <li>- Time to complete healing</li> </ul>	Conducted with appropriate attention to data quality and integrity  Defined stopping rules for serious and/or severe adverse events  Phased recruitment  Intensive follow-up for a minimum of 6 weeks
Comparative study	~100 (50 – 300)	Primary endpoints: <ul style="list-style-type: none"> <li>- Operative and removal times</li> </ul> Secondary endpoints: <ul style="list-style-type: none"> <li>- Difficulties and complications during procedure and removal process*</li> <li>- Pain assessment at key time points</li> <li>- Clinical adverse event rates</li> <li>- Device-related incident rates</li> <li>- Patient satisfaction</li> <li>- Cosmetic results*</li> <li>- Healing process*</li> <li>- Time to complete healing</li> </ul>	Randomized concurrent comparison group preferable but not required. Alternative is larger case series with historical comparison group  Comparison method should be well-established and documented circumcision procedure  Could consider unbalanced randomization, e.g. 2:1 to accumulate more data on new device  Defined stopping rules for serious and/or severe adverse events  Superiority trial  Follow-up for a minimum of 6 weeks

\* documented photographically

### ***Clinical studies in country of intended final use***

Following documentation on the clinical performance of the device in the country of origin or manufacture, it was important to progressively accrue clinical experience and data in the country or setting of intended final use. In addition, it was important to note that the patient population may be very different from the types of patient in the country of origin, particularly with respect to age, motivation and clinical indications for circumcision, and social environment. These could lead to unexpected and new difficulties with the device that investigators must be able to respond to. Concern for rapid progress through the different stages of clinical evaluation needed to be balanced by the importance of progression from assessment under well controlled conditions in the hands of experienced providers with backup in case of problems to the eventual target population and providers in resource-limited

settings with little access to additional support. The proposed types of study and key elements are summarized in Table 3. It was noted that not all steps and studies had to be completed in every country where a new device might be used – the main issue was whether the populations studied in the assessment of safety, effectiveness and acceptability of the device were relevant to the intended patient population. This would have to be determined in each country by the public health authorities on the basis of the available data.

### **Case series**

The first study should be non-comparative in order to collect preliminary information on the ease of use and performance of the device in the new population and setting. There should be phased enrolment with completion of an initial small cohort of men to wound healing (or at least device removal) before enrolling the next cohort of men. As more experience accumulated with the device, enrolment of new patients while others are still under follow up would be acceptable, but ought to be sanctioned by an independent group of experts overseeing the study, such as a formal Data Monitoring Committee. It would be important to collect systematic data on all procedure starts and outcomes with the new device, even if it was decided to abandon the device and/or complete the circumcision with a conventional surgical approach.

Considerable discussion centred on the importance of ensuring that patients enrolled in the first studies of the device be documented as not infected with HIV. Since male circumcision services were being expanded as an HIV prevention intervention, uninfected men were the primary target population. However, when a device was used in programmes it may be used in men of unknown HIV status or with HIV infection, even if not specifically intended for such groups. Thus it was important at some point to establish safety information among men with HIV infection, not that major differences in complication or adverse event rates were expected. However, the group recommended that safety and effectiveness first be established in men known to be free of HIV before including men with HIV infection or those of unknown HIV status in any research studies.

### **Comparative study**

After successful completion of the first clinical studies, a formal trial comparing the device against one of the established methods of circumcision should be conducted by providers experienced with both methods. Only surgeons who are competent and have successfully performed a minimum of five of each of the two procedures under study should be involved in such a comparative trial. While the incidence of adverse events and device-related incidents were important in the assessment of the devices, other outcomes should be considered primary endpoints and drive the sample size requirements. The exact choice of endpoint would be determined by the expected advantages of the new device over conventional surgery. However, the total operation time was considered to be one key measure by which to compare the approaches. This should be “skin-to-skin” time measured from the first touch of the surgeon to the final wound closure, but excluding anaesthesia time.

Studies directly comparing adverse event (AE) rates between the new device and conventional surgery would require sample sizes of 800 – 1500 patients as the incidence of AEs in clinical environments with properly trained and equipped providers was low. Studies of such size were neither realistic nor appropriate, particularly since they would need to be conducted by providers who were skilled in both methods of circumcision. Yet the purpose of developing and assessing new devices was to allow providers not necessarily skilled in conventional surgery to perform circumcisions with a device, once shown safe and effective. The relevant

testing pathway was to establish that the device performed well and presented several advantages in the hands of skilled providers and then proceed to clinical evaluation in populations of intended final use and providers with limited surgical skills.

In order rapidly to accumulate experience with the new device unbalanced randomization (e.g. 2:1) could be considered. In addition several sites could be included in order to have a broader patient population and larger range of providers involved in the formal assessment.

### **Acceptability studies**

Acceptability of the device among the new patient population was an important consideration that should be evaluated in parallel with the clinical studies. An indirect measure of acceptability was the acceptance rate of volunteers approached to participate in the studies, but more direct measures should be used, possibly in a subset of patients. Understanding reason(s) for refusal, comfort with the device while *in situ*, attitudes of family and/or partners and final cosmetic result would inform eventual decisions on programme design, communications, and selection of suitable patient populations where the device could be used. Longer term issues related to erection and sexual function, while important, were likely beyond the scope of the initial comparative studies and would require long follow-up periods.

**Table 3: Clinical studies in country of intended final use**

Type of study	Sample size (range)	Endpoints	Notes and comments
Case series (non-comparative study)	50 (25 – 100)	Primary endpoints: <ul style="list-style-type: none"> <li>- Clinical adverse events</li> <li>- Device-related incidents</li> </ul> Secondary endpoints: <ul style="list-style-type: none"> <li>- Technical difficulty and complications during procedure and removal process*</li> <li>- Pain assessment at key time points</li> <li>- Patient satisfaction</li> <li>- Cosmetic results*</li> <li>- Healing process*</li> <li>- Time to complete healing</li> </ul>	Conducted with appropriate attention to data quality and integrity Defined stopping rules for serious adverse events including independent review by, for example, an independent Data Monitoring Committee Phased recruitment Intensive follow-up for a minimum of 6 weeks Document ease of training new providers and time required to achieve adequate competency with the new device and procedure Collate data on reasons to decline participation as indirect measure of acceptability
Comparative study	~ 100 (50 – 300)	Primary endpoints: <ul style="list-style-type: none"> <li>- Operative and removal times</li> </ul> Secondary endpoints: <ul style="list-style-type: none"> <li>- Technical difficulty and complications during procedure and removal process*</li> <li>- Pain assessment at key time points</li> <li>- Clinical adverse events</li> <li>- Device-related incidents</li> <li>- Patient satisfaction</li> <li>- Cosmetic results*</li> <li>- Healing process*</li> <li>- Time to complete healing</li> </ul>	Randomized controlled trial comparing new device with a standard surgical procedure as defined in <i>WHO Technical Manual for Male Circumcision under Local Anaesthesia</i> or other well standardized and documented circumcision method. Could consider unbalanced randomization, e.g. 2:1 to accumulate more data on new device. Superiority or non-inferiority trial Defined stopping rules for serious adverse events and device-related incidents including review by an independent Data Monitoring Committee Consider accumulating data and experience from more than one site in a series of coordinated single site trials with standardized definitions and procedures Use appropriate methods to measure procedure and removal times. Document ease and duration of training. Follow-up for a minimum of 6 weeks, but can be less intensive than previous study since more clinical experience available Collate data on reasons to decline participation as indirect measure of acceptability
Acceptability sub-studies		Assess acceptability: <ul style="list-style-type: none"> <li>- During procedure to place device</li> <li>- While device in situ, including during (nocturnal) erections</li> <li>- During removal</li> <li>- Cosmetic finish</li> </ul>	Assessment of acceptability needs to be built into all clinical research in country of intended final use. Could be based on subgroups of men involved in the case series or the comparative trials, as well as assess acceptability in partners and/or parents of any minors undergoing circumcision.

\*: Documented photographically



### ***Field studies in country of intended final use***

Field studies would provide data on whether the device is sufficiently safe and cost-effective to warrant expansion to a wider population. The third type of study should be a non-comparative field trial of the device, with procedures performed by trained mid-level providers or non-physicians. The objective of this study would be to evaluate the training needed for health providers to learn the device procedure, the cost-effectiveness of the device compared with the standard surgical technique, the safety of the device when used by non-physicians, the practicality and acceptability of the device and procedures (e.g. need to return to the clinic for device removal, tolerance for leaving device *in situ* for longer than intended). The characteristics of the field studies are listed in Table 4.

Before implementing a large cohort study, it may be useful first to conduct a pilot study to evaluate training requirements, acceptability to providers and patients, logistics and costs. An alternative approach would be a pilot run-in phase to a larger field study. Since not all men would necessarily be suitable for circumcision with the new device (either because they have “standard” contraindications to circumcision at a peripheral facility and thus need referral to a higher level of care, or because they have device-specific contraindications), links with facilities providing conventional surgical approach need to be defined and established. Similarly, any complications occurring during or after circumcision with the device will need to be referred to a conventional surgical facility.

After completion of a pilot study, a relatively large sample size should be chosen in order carefully to evaluate the safety profile of the device in the context of routine use. Follow-up would be less intense, with less frequent follow-up visits but appropriate to the anticipated clinical schedule of the device, and with detailed data collection on adverse events, especially any unexpected or serious adverse events. It would be important to collect systematic data on all procedure starts and outcomes, even if it was decided to complete the circumcision using a conventional surgical approach.

There should be a formal mechanism to review clinical adverse events and device-related incidents according to type and experience of the provider, after, for example, every 100 device starts. As experience with the device increases and more information was available on the incidence and types of adverse events, it may be appropriate to reduce the intensity of follow-up of each patient and increase the interval between formal safety reviews.

Before being widely adopted in a national public health programme as one of the standard circumcision methods, the benefits, costs and risks of the new procedure compared with conventional surgery need to be assessed against objective criteria and supported by quality data. The field studies should be designed to collect data that could inform such policy decisions. Additionally acceptability of the device for the provider, the patient, his female partner and caregivers (in case of adolescent boys) should be evaluated, possibly on subset of participants.

Post-marketing surveillance of medical devices is normally the responsibility of the manufacturer or distributor which must establish mechanisms to collate reports of adverse events and device-related incidents, and demonstrate that they have been considered and acted on if relevant. Since male circumcision is a public health intervention targeting large numbers of healthy men, monitoring of incidents and adverse events and a robust reporting system is critical even if such systems do not exist for other medical devices. Dedication of resources for gathering adverse events and developing an adequate reporting system should be a priority for countries considering scale up of male circumcision in general, and particularly where devices are to be used. At the same time it will be important to know the number of devices

used, so that the incidence of adverse events can be computed. An additional risk with devices is that, once available in the country, they may be used outside the formal health sector by providers who have not received adequate training. Not only must such use be monitored where possible, but adverse events occurring outside the formal health sector should be included in the monitoring system.

**Table 4: Field studies, surveillance and post-marketing studies in country of intended final use**

Type of study	Sample size (range)	Endpoints	Notes and comments
Pilot field study	100 (50 – 200)	Primary endpoints: <ul style="list-style-type: none"> <li>- Provider training needs</li> <li>- Provider acceptability</li> </ul> Secondary endpoints: <ul style="list-style-type: none"> <li>- Adverse events and device-related incidents</li> <li>- Procedure and removal times</li> </ul>	Train at least 10 providers to determine training and support needs Ensure good data quality and integrity, including recording outcomes on all procedure starts Collate data on reasons to decline participation in the study as indirect measure of acceptability
Cohort study	~ 500 (300 – 800)	Primary endpoints: <ul style="list-style-type: none"> <li>- Procedure and removal times</li> </ul> Secondary endpoints: <ul style="list-style-type: none"> <li>- Training needs of providers</li> <li>- Safety of procedure/removal</li> <li>- Clinical adverse events and device-related incidents</li> <li>- Practicality of device use (i.e. need to return to clinic for removal)</li> </ul>	Systematic review of clinical adverse events and device-related incidents after every 100 procedure starts; interval between reviews can be increased as more experience with method becomes available. Ensure mechanisms in place to capture information on all adverse events, even if men are not followed systematically to complete wound healing. Importance of enhanced surveillance of outcomes, especially AEs and losses to follow-up. Collate data to inform cost-effectiveness assessment: <ul style="list-style-type: none"> <li>- Cost of device</li> <li>- Cost of training to use device compared with standard surgical method</li> <li>- Cost of provider's time</li> <li>- Staff time for follow-up visits</li> <li>- Equipment and supplies needed</li> </ul> Collate data on reasons to decline participation in the study as indirect measure of acceptability Include assessments of acceptability among subset of patients, their partners and care givers (minors only), with respect to device placement, wearing the device and device removal
Post-marketing surveillance		Serious adverse events and device-related incidents	Mechanisms available to collect, collate and act on adverse event reports, including ensuring potential modifications to the procedures, device or packaging

## Conclusions and Recommendations

Key recommendations from the meeting included:

1. Male circumcision devices have potential to accelerate programme scale up and expansion to areas not well served by existing surgical services.
2. While circumcision devices have been successfully used in other populations, experience with their use among adults in Africa has not been encouraging. It is important to proceed in a cautious yet progressive fashion, ensuring that the safety, effectiveness and acceptability of the devices in populations with good access to care are established before proceeding to more widespread implementation.
3. Since male circumcision is being implemented as a public health intervention for HIV prevention among healthy men, it is important to proceed cautiously and avoid any major complications or adverse events. Public acceptance of circumcision devices and confidence in the male circumcision programme could easily be undermined if adverse events occur and are widely publicized.
4. Requirements outlined for evaluation of male circumcision devices are more stringent than requirements for registration of medical devices that present minimal risks to the provider or patient. However, the desired end result is to ensure that safe, effective and acceptable devices could be introduced rapidly into national programmes. This requires more extensive data on clinical experience and acceptability than required for a device to be authorized for distribution in the country.
5. Preliminary data on the Shang Ring device developed in China are encouraging and the device should be tested in a progressive manner in men in Africa.
6. Critical steps in testing new devices in new populations were agreed and summarized for incorporation into the *Framework for Evaluation of Devices for Adult Male Circumcision* that will be updated.
7. Other technologies that might accelerate male circumcision service delivery should be considered in addition to circumcision devices, though no cost-effective innovations had been identified to date. These should be evaluated in a progressive manner, considering the advantages and potential risks associated with their use.



## Annex I: Participants

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## Annex II: Agenda

**Wednesday 11 March 2009**

Time	Topic	Speaker/discussant
0800 – 0830	Registration	
0830 – 0900	Opening of meeting Welcome and introductions  Welcome on behalf of Kenya Ministry of Public Health and Sanitation and/or Ministry of Medical Services Objectives and expected outcomes Overview of background documents	Christine Rousseau Tim Farley   Tim Farley Ariane van der Straten
0900 – 1000	Summary of male circumcision programme scale up in African region and potential demand for services  Brief summaries from each country represented Botswana Kenya  Uganda Zambia Zimbabwe Other countries	   Hilda Matumo Masasabi Wekesa, Fred Kambuni Jackson Amone Kasonde Bowa Christopher Samkange Tim Farley
1000 – 1030	Male circumcision devices  Potential to facilitate programme scale up Key points regarding device evaluation from June 2008 Kampala meeting	  Stephen Watya Tim Farley
1030 – 1100	Break	
1100 – 1230	Leading candidate devices to advance through assessment steps  Rationale for considering selected devices Tara KLamp Experiences in South Africa Promotion in Kenya and other countries Shang Ring Experience in China Proposed clinical research in Africa	  Tim Farley Tim Hargreave  Masasabi Wekesa  Philip Li Mark Barone
1230 – 1400	Lunch	
1400 – 1430	Assessing the Application of Technology for Adult Male Circumcision  Bioengineering aspects of circumcision devices, potential for adhesives and other technologies to facilitate scale up	  Emily Gumkowski

<b>Time</b>	<b>Topic</b>	<b>Speaker/discussant</b>
1430 – 1530	Draft evaluation framework for male circumcision devices	Discussant
	Overview	
	Chapter 1: Prioritization of devices for evaluation	Stephen Watya
	Chapter 2: Regulatory issues in development, testing and registration of devices	Tim Farley
	Chapter 3: Clinical issues in development and evaluation of devices	David Sokal
	Chapter 4: Manufacturing and marketing of male circumcision devices	Emily Gumkowski
	Chapter 5: Monitoring use and safety of circumcision devices	Kawango Agot
1530 – 1600	Break	
1600 – 1730	Discussion of evaluation framework (continued)	
1730	Closure for day	

### ***Thursday 12 March 2009***

<b>Time</b>	<b>Topic</b>	<b>Speaker/discussant</b>
0830 – 1030	Break-out groups (maximum 3) to review and comment on different chapters	Chair and rapporteur to be nominated by each group
1030 – 1100	Break	
1100 – 1230	Report back from breakout groups, review of recommendations, prioritization of next steps	Rapporteur reports
1230 – 1400	Lunch	
1400 – 1530	Review of meeting recommendations, specific next steps to progressively advance clinical assessment of male circumcision devices and their introduction into programmes	
1530 – 1600	Closure of meeting and thanks	Tim Farley Christine Rousseau, Ministry of Health