MALE CIRCUMCISION FOR HIV PREVENTION

MEETING REPORT

WHO TECHNICAL ADVISORY GROUP ON INNOVATIONS IN MALE CIRCUMCISION:

EVALUATION OF TWO ADULT DEVICES

JANUARY 2013

World Health Organization

HIV/AIDS Programme

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ACRONYMS

AE	adverse events
EMP	Department of Essential Medicines and Pharmaceutical Policies
FMEA	failure modes and effects analysis
GHTF	Global Harmonization Task Force
HIV	human immunodeficiency virus
IFU	Instructions for Use
ISO	International Organization for Standardization
PEPFAR	US President's Emergency Plan for AIDS Relief
PQ	prequalification
SAE	serious adverse event
TAG	Technical Advisory Group on Innovations in Male Circumcision
UNAIDS	Joint United Nations Programme on HIV/AIDS
VAS	Visual analogue score
VMMC	Voluntary medical male circumcision
WHO	World Health Organization

EXECUTIVE SUMMARY

The World Health Organization (WHO) Technical Advisory Group on Innovations in Male Circumcision (TAG) met at WHO headquarters in Geneva in January 2013. The focus of the meeting was a review of the clinical performance of two specific male circumcision devices (PrePex and ShangRing) as part of the product review in the WHO Prequalification of Male Circumcision Devices Programme. This review was based on clinical data collected in the context of the *Framework for clinical evaluation of male circumcision devices* (WHO), which stipulates a progressive series of clinical studies to establish the efficacy, safety, acceptability and clinical performance of the device when used by trained mid-level providers. The evaluation was also informed by the failure modes and effects analysis conducted by WHO for the collar clamp and elastic collar compression type devices. The meeting discussions also provided inputs on programmatic considerations for guidance under development on the use of devices, information gaps and research needs.

The ShangRing (collar clamp) device had been evaluated in five studies in Kenya, Uganda and Zambia, involving almost 2000 device placements. These clinical studies met the minimum requirements necessary before a device can be considered for prequalification. The overall estimated proportion of clients not eligible for male circumcision with the ShangRing device was about 1%. In about one of every 200 clients, it was not possible to complete the circumcision procedure with the device alone. Some men required immediate conversion to conventional surgical circumcision to avoid any serious complications. The conventional surgery was performed by a person experienced in standard surgical circumcision who was available on site, together with appropriate instruments and supplies. The data demonstrated that the ShangRing was efficacious and safe when used by suitably trained and equipped providers, with a circumcision success rate of over 99%. No serious adverse events occurred in 1983 successful device placements. A total of 20 men (1.0%) experienced moderate adverse events. All adverse events were managed with, at most, minor intervention and resolved, leaving no long-term sequelae. The adverse event rates were similar to those observed with conventional surgical circumcision.

The TAG considered the ShangRing to be clinically efficacious and safe for use in healthy men age 18 years and older, when performed by trained providers in public health programmes. Skills and surgical facilities should always be available to safely convert technical failures of device placement to a conventional procedure. The TAG based its conclusion on the data currently available and recognized that this is only one component of the prequalification assessments. This conclusion must be reassessed in about one year as more experience with use of the device accumulates in diverse programmatic settings outside the context of studies.

The PrePex (elastic collar compression) device had been evaluated in eight studies conducted in Rwanda, Uganda and Zimbabwe involving about 2400 device placements. The range and scope of these studies met the criteria established in the WHO *Framework for clinical evaluation of devices for male circumcision*. About 7% of clients could not have the PrePex device placed for various anatomical and technical reasons but would have been eligible for conventional surgical circumcision. Circumcision was successfully completed using the PrePex in 99.5 % of clients on whom the device was successfully placed. Adverse events occurred in 1.7% of clients, the majority of which were mild or moderate. Serious adverse events occurred in 0.4% of clients, some of whom required prompt intervention to prevent potentially serious long-term sequelae. Over half of these serious events were due to device displacement or to device removal (including self-removal) secondary to pain or discomfort. These cases resulted in pain, swelling and occasional blistering of the partially necrosed foreskin tissue, requiring urgent intervention by a skilled surgeon to prevent severe local or systemic infection and/or permanent disfigurement of the penis. In the studies conducted to date, appropriate surgical facilities have been available, and all cases were successfully managed with no long-term sequelae. Client instructions must clearly describe safe use of the device, symptoms that may develop with device displacement or early removal, as well as the possible serious outcomes and surgical interventions that may be needed if instructions on abstinence and wound care are not followed. Similarly, PrePex providers must be appropriately trained to recognize the rare serious complications that can occur if the device is displaced and must ensure that such clients are rapidly provided appropriate management.

On the basis of the clinical evaluation, the TAG concluded that the requirements for clinical studies necessary before a device is considered for WHO prequalification had been satisfactorily met. The TAG considered the device to be clinically efficacious in male circumcision and safe for use among healthy men 18 years and older when used by trained mid-level providers in public health programmes, provided that surgical backup facilities and skills are available within 6–12 hours to manage events that could lead to serious complications. The TAG based its conclusion on the data currently available. This conclusion must be reassessed in about one year as more experience and data accumulate with use of the device in diverse programmatic settings outside the context of studies.

INTRODUCTION

The HIV Department at the WHO headquarters convened a meeting of the WHO Technical Advisory Group (TAG) on Innovations in Male Circumcision in Geneva, Switzerland, 29–31 January 2013. The purpose of the meeting was to provide programmatic and technical updates and to evaluate and advise on the clinical efficacy and safety of two devices for adolescent and adult male circumcision that have formally entered the WHO prequalification process. The three-day meeting brought together members and observers of the TAG along with the WHO Secretariat and staff from the HIV Department, the Department of Essential Medicines and Pharmaceutical Policies, the WHO Regional Office for Africa, and the Intercountry Support Team.

Background

In March 2007, responding to compelling evidence from three randomized controlled clinical trials confirming the results from ecological studies, WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS) issued recommendations that medical male circumcision be considered as part of a comprehensive HIV prevention package in countries with generalized epidemics. Since then, 14 countries in east and southern Africa have taken action towards the scale-up of voluntary medical male circumcision (VMMC) for HIV prevention.

Modelling studies indicate that national male circumcision programmes will have the greatest public health impact in these 14 priority countries, averting up to 3.4 million HIV infections through 2025, and will provide the largest cost-saving (USD 16.5 billion) if services are scaled up rapidly. However, currently recommended surgical methods for adult male circumcision involve considerable time and skill. Thus, innovations in the procedure, including male circumcision devices, have been under study over the past few years.

In 2008 and 2009 initial consultations reviewed the landscape of technologies for male circumcision. In 2010 the WHO established a *Technical Advisory Group on Innovations in Male Circumcision* (henceforth "the TAG") for the purpose of reviewing and advising the WHO on innovations in male circumcision, including devices. The *Framework for the clinical evaluation of devices for male circumcision (1)*, published in 2012, describes the clinical evaluation pathways required to provide sufficient evidence of efficacy and safety of a new male circumcision device. These studies include:

- initial studies to establish safety and acceptability;
- at least two independent randomized controlled trials comparing the device against an established method of circumcision performed by providers skilled to offer either method of male circumcision in settings of intended final use; and
- at least two field studies of procedures involving relevant populations, types of facilities and performed by suitably trained and qualified mid-level or non-physician providers in settings of intended final use.

The information generated from these studies forms the basis for WHO to assess and provide advice on the use of a device in adult and adolescent VMMC programmes for HIV prevention in high HIV prevalence, resource-limited settings.

WHO also established the Prequalification (PQ) of Male Circumcision Devices Programme for HIV Prevention in the Department of Essential Medicines and Pharmaceutical Policies (EMP). The TAG reviews the clinical data on a specific product and advises the Department of EMP whether the evidence demonstrates that a specific device is efficacious in removal of the foreskin and safe for use in the intended population. The Department of EMP assesses the product to see that it meets international standards (through a review of the product dossier) and inspects the manufacturing site(s) to assess the adequacy and effectiveness of the manufacturer's quality management system and the correct implementation of their documented procedures.

By the end of 2012, three manufacturers had entered the PQ Programme; sufficient data was judged to be available on two devices—the ShangRing and PrePex. The TAG was, therefore, convened in January 2013 to review all available data on these devices, to advise on the clinical evaluation component of PQ and highlight programmatic considerations in the use of each device and to advise on priority research needs.

Objectives

The objectives of the meeting were to:

- update the TAG on the:
  - status of devices in the WHO PQ of Male Circumcision Devices Programme
  - device risk assessments and
  - development of guidance on use of devices and issues from the research that will inform the guidance.
- review all available clinical research findings on two male circumcision devices for adolescents and adults, specifically the PrePex and the ShangRing, to inform prequalification decisions;
- advise the WHO on:
  - review of study requirements for clinical evaluation of devices of the same category;
  - operational and programmatic considerations on use of devices to be addressed in the guidance;
  - additional technical innovations that WHO should assess, or should stimulate further development of, to improve coverage and/or accelerate scale-up of male circumcision in priority countries; and
  - priority research to further advance work on male circumcision for HIV prevention.

Meeting process and roles of participants

The TAG is comprised of internationally recognized experts including representatives of research institutes, clinical scientists, statisticians, medical device regulators and programme managers in the field. The TAG is composed of members and observers. Members of the TAG are experts appointed because of their expertise in the field and are involved in the formulation of recommendations. Observers from collaborating partners with an interest in expanding male circumcision programmes for HIV prevention represent the perspective of their institutions as well as contribute their technical knowledge. Observers do not directly participate in formulating the advice and recommendations of the TAG. Given the nature of the meeting documents that were reviewed, TAG participants agreed to strict standards of confidentiality and submitted signed confidentiality agreements.

Declaration of interests

At the beginning of the meeting, the WHO secretariat explained the reasons for the written and verbal declarations of interests and summarized the pertinent interests that had been declared in writing prior to the meeting. All participants were invited to declare verbally to the group any other conflicts, or potential conflicts, of interest. No other members stated any current or potential conflicts of interest that might affect their impartiality, judgment or advice. Review of the declarations by the secretariat and the TAG chairs identified no significant conflicts or potential conflicts of interest that would disqualify or restrict participation.

The primary types of potential conflicts were due to participants' involvement on research teams that had or were currently studying one or more devices, involvement in modelling studies and a declared advocacy of "cautious optimism in favour" of devices. One participant had been previously employed by a company that worked on the development of male circumcision devices, two currently or previously worked on male circumcision device technologies, and one worked with and currently consults for the Bill and Melinda Gates Foundation, which has supported device development and research.

PROGRAMME AND TECHNICAL UPDATES

WHO HIV Department progress during 2012 and planned guidance

The WHO Secretariat provided programmatic updates on the work of the WHO HIV Department during 2012. WHO remains fully committed to identifying and assessing priority technical innovations in male circumcision, including devices that have the potential to:

- make the male circumcision procedure safer, easier and quicker than current methods;
- facilitate more rapid healing and/or entail less risk of HIV transmission or acquisition in the immediate post-operative period;
- be used safely by (mid-level) health-care providers with a shorter period of training than required for conventional surgical male circumcision; and
- be more cost-effective for male circumcision scale-up than standard surgical methods.

Given that a number of devices were available on the market, the WHO, with the inputs of the TAG, had produced the following guidance products to inform evaluation and use of devices:

- *Framework for clinical evaluation of devices for male circumcision (1)*, which:
  - outlines the clinical pathway for assessing suitability of a device, including the minimum requirement for WHO consideration of efficacy and safety (two comparative studies in different settings and two field studies in settings of intended use);
  - lists ideal device characteristics and potential evaluation criteria;
  - provides suggestions for the stepwise introduction of a new device, with scale-up in mind; and
  - highlights regulatory considerations and the WHO Prequalification Programme.
- *Use of devices for adult male circumcision in public health HIV prevention programmes: conclusions of the WHO Technical Advisory Group on Innovations in Male Circumcision (2)*, which provided initial conclusions based on limited evidence on the use of the PrePex device in early 2012.
  - As the data reviewed were from a series of three clinical studies conducted in only one low-resource country (Rwanda), the TAG concluded that additional studies were needed before advice could be generalized beyond Rwanda.

During 2012 the WHO PQ of Male Circumcision Devices Programme reviewed two device products and responded to requests from manufacturers of two other devices. More details on PQ are noted below. The link to the PQ documents is: http://www.who.int/diagnostics_laboratory/evaluations/prequalification_male_circumcision_devices.

WHO also convened a small expert group to conduct a risk analysis of devices in mid-2012. The outputs of this exercise (see below) helped to identify key potential risks associated with use of devices. WHO is preparing guidance on the use of devices for adolescent and adult VMMC for HIV prevention in accordance with the WHO guideline review processes.

The conclusions of this TAG meeting will inform several guidance products on devices and device use, in particular:

- The WHO PQ Programme component on clinical safety and efficacy of the ShangRing and PrePex devices. This is one part of the full product review and contributes to the decision whether or not to prequalify a particular device. A summary report will be provided on the clinical evaluation of each specific device.
- Programmatic and operational considerations in the WHO guidance on use of devices for adolescent and adult VMMC for HIV prevention.

The WHO also sought inputs from the TAG on additional technical considerations, including a review of the clinical evaluation requirements to demonstrate equivalent efficacy and safety of a similar product, further research to be catalysed, and additional promising technologies that should be considered.

Prequalification of male circumcision devices

The WHO PQ of Male Circumcision Devices Programme undertakes a comprehensive assessment of the applications submitted by device manufacturers through a standardized procedure based on international best practices and WHO PQ requirements, which include three main components:

- Review of the application form with summary information about the product
- Review of the product dossier, including review of clinical evidence, and
- Inspection of the manufacturing site(s).

The role of the TAG in the PQ of Male Circumcision Devices Programme process is review of the clinical safety and efficacy of the device based on clinical evidence generated within the clinical evaluation framework described earlier.

To date, three devices—namely the PrePex, ShangRing and AlisKlamp—have entered the WHO PQ Programme. The manufacturer of a fourth device, the TaraKlamp, has expressed interest but has not yet submitted an application. Review of the PrePex device has moved the most swiftly through the stages of PQ and is the closest to meeting clinical evaluation and other requirements. Once a product has been prequalified, it will be included on a list of devices published on the WHO web site (see above). This paves the way for procurement by UN agencies,

WHO Member States, donors and other interested purchasers. Prequalification does not imply WHO approval to import or to use the device in any particular country, as this the prerogative and responsibility of the national regulatory authorities.

The main points from discussions that followed these updates included:

- The steps in the PQ process require significant staff time and financial resource investments.
  - These financial resources have been provided by donors and the public sector, and the manufacturer is not charged by WHO for work performed for PQ of a product.
  - The process can take many months before the manufacturer satisfactorily meets requirements. It involves the manufacturer submitting complete documentation, responding to requests for clarification, and implementing suggested corrective actions following WHO site inspections.
- A PQ decision is time-limited. WHO will arrange for the products and manufacturing sites included in the WHO list of prequalified male circumcision devices to be reassessed at regular intervals. Prequalified diagnostic products are reassessed usually every three to five years, or sooner if warranted, such as in the case of reports of product defects. If, as a result of reassessment, it is found that a product and/or specified manufacturing site no longer complies with the WHO requirements, such products and manufacturing sites will be removed from the list. Failure of a manufacturer to participate in the reassessment procedure also will lead to removal from the list. For prequalified devices the same principle will be applied, with re-inspection occurring sooner as indicated, including for a new product and manufacturer.
- A PQ decision can be retracted if concerns with safety are substantiated. Once a product is prequalified, International Organization for Standardization (ISO) 13485 requires the reporting of serious adverse events and post-market surveillance. Since national adverse event monitoring systems are often weak, the TAG urged the standardization of post-market surveillance and that countries improve the reporting of adverse events. PEPFAR will collaborate with WHO to support national programmes in post-market surveillance of the use of male circumcision devices.
- The manufacturer must report, in addition to serious adverse events, change(s) in the design or manufacturing (material or process) of the device to the PQ Programme. It is not the manufacturer but rather the WHO programme that decides what constitutes a "significant" change in the design of the product or the manufacturing process, and if a re-evaluation is needed.

Technical update 1: Risk analysis of male circumcision devices

The WHO held a technical consultation in Geneva, 6–7 August 2012, to reach consensus on the classification scheme for male circumcision devices and to conduct a risk analysis on of devices.

Three categories of in-situ devices (i.e. devices that remain in place for some period of time) for adolescent and adult male circumcision were agreed upon based on their mechanism of action:

- Clamp, with subcategories: a) collar clamp (e.g. ShangRing); b) vice clamp (e.g. TaraKlamp)
  The mechanism of action consists of rapid, tight compression between hard surfaces to achieve haemostasis. Compression is sufficient to prevent slippage of tissue such that the foreskin can be removed at the time of, or soon after, application of the device. Part or all of device is left in situ for more than 24 hours. Injection with local anaesthesia is required.
- Ligature compression (e.g. Plastibell for infants)
  The mechanism of action consists of a rapid, tight compression between a hard surface and a non-rigid ligature that is tied to hold the foreskin in place between the hard surface and the ligature. Compression is sufficient to achieve haemostasis and prevent slippage of tissue such that the foreskin can be removed at the time of, or soon after, application of the device. Part or all of the device is left in situ for more than 24 hours. Local anaesthesia is required. The compression force and the security of the knot depend on the provider.
- Elastic collar compression (e.g. PrePex).
  The mechanism of action consists of slow compression between an elastic ring and a hard surface that is sufficient to occlude circulation and produce tissue ischaemia. Part or all of the device and the foreskin are left in place for more than 24 hours, thereby causing ischaemic necrosis of the foreskin. The device and the foreskin are removed at a later date. Such devices can be applied without the need for injected local anaesthetic.

The consultation then used the Failure Modes and Effects Analysis procedure (FMEA) which is one of the techniques specified in ISO 14971, the international standard for the application of risk management to medical devices, to systematically analyze, evaluate and propose control measures on use of devices. According to ISO 14971, the manufacturer is responsible for establishing, documenting and maintaining a continuous process of risk management/quality feedback for the lifetime of a device, including identifying hazards associated with a medical device, estimating and evaluating the associated risks, controlling these risks and monitoring the effectiveness of these controls. Feedback information is obtained from the market in the form of customer complaints and proactive post-market surveillance as well as internally from production processes, if a problem is encountered before the product or lot reaches the market.

The WHO consultation applied the FMEA technique to a device category: identifying failure modes associated with the specific device category, quantifying the risk and identifying actions to mitigate risks. The exercise focused on device categories for use in adolescents and adults (rather than infants) and on those that had entered the WHO PQ Programme. The FMEA technique takes into account three factors:

- potential severity of an outcome (consequence of the harm)
- frequency of occurrence (per client procedure) and
- detectability of any potential failure (ease with which the failure can be detected at time of deployment or while the device is in situ).

Individual scores were assigned to each potential failure mode for each of the three factors, using a scale of 1 to 5. A total risk score was calculated by multiplying the individual factor scores (highest score possible risk score is 125). A risk score of 25 or above was considered by the participants as a priority, warranting that actions to mitigate risk be identified. Such actions could be through:

- Provider instructions, warnings and contraindications on use
- Client information on use
- Specification of the device (in its design and/or the material(s) used or testing)
- Process and quality controls in manufacturing

Tables 1 and 2 summarize the results of the risk analysis of two male circumcision device categories.

Some key points for programme introduction were noted. As devices are rolled out from study to field conditions and with broader use, more failures and failure modes can be expected to occur. When the device is procured and used in a programme supported by a government or donor, it is more likely that safety will be monitored through standardized serious adverse event (SAE) reporting than when it is procured and used by the private sector. User instructions are critical. Clinicians will need to be educated not to use devices that have not been clinically evaluated and are not prequalified. Devices that fail should be sent back to the manufacturer for analysis.

Technical update 2: Clinical evaluation of the PrePex and the ShangRing devices

The TAG conducted a detailed review of all available clinical safety, efficacy and acceptability data on two male circumcision devices for adolescents and adults, the ShangRing and the PrePex. Data on the safety and efficacy of the PrePex were available from eight studies conducted in three countries in east and southern Africa (Rwanda, Uganda and Zimbabwe). These studies included an initial safety and efficacy study, two randomized comparative trials, two completed field studies and interim analyses from two ongoing field studies. Safety and efficacy data for the ShangRing included data from five studies conducted in three countries (Kenya, Zambia and Uganda). Data from studies conducted in China were summarized (3–6), but the TAG decided these data were not directly relevant to the population where the intervention is prioritized. In addition, it was not clear whether the version of the device used in these studies was the same as that used in the African studies.

DEVICE EVALUATIONS

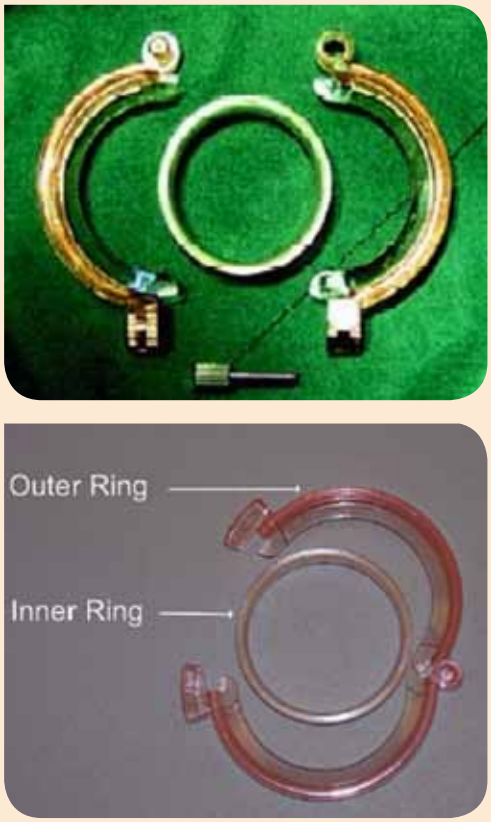
1. ShangRing

The ShangRing is produced by Wuhu Snnda Medical Treatment Appliance Technology Co. Ltd, Wuhu City, China. It is a minimally invasive method for boys and adult men undergoing circumcision for phimosis or electively and was first described in the international literature in 2008 (7). The ShangRing is a collar clamp circumcision type of device. The device consists of two concentric plastic rings that sandwich the foreskin of the penis. The mechanism of action consists of a rapid, tight compression of the foreskin between the hard surfaces to achieve haemostasis. The compression is sufficient to prevent slippage of tissue such that the foreskin can be removed at the time of device application. The device must be sterile. Anaesthetic injection is required.

The device is applied by placing the inner ring over the shaft of the penis at the height of the coronal sulcus. The foreskin is everted over the inner ring and then clamped in place and crushed by the outer ring. The foreskin distal to the device is then cut away. The device is removed at seven days by releasing the clamped outer ring, gently separating the inner ring from the healing wound, and then cutting the ring in two places to remove it from the shaft of the penis.

The original device used in China is shown on the top in Figure 1. It was available in different diameters, ranging from 13 mm to 40 mm in 2 or 3 mm increments. The device used in all the African studies is depicted at the bottom in Figure 1. It differed from the original design only with regard to the mechanism to secure the outer ring—the threaded locking mechanism in the original design was replaced with a ratchet that facilitated positioning and adjustment of the device over the everted foreskin. Also, the device was available in 26 mm to 40 mm diameter sizes in 1 mm increments. The correct device size is selected based on measurement of the penile circumference at the level of the coronal sulcus with a specially marked tape.

Figure 1: The original design of the ShangRing is shown at the top (7). The design used in the African studies is shown at the bottom (8).



2. PrePex™

The PrePex™ is produced by Circ MedTech Limited in Israel. The device was specifically designed to be used by mid-level providers in resource-limited settings and to avoid the need for local anaesthesia during device placement. The device is an elastic collar compression type of device. It consists of an inner ring placed under the foreskin at the level of the coronal sulcus and an elastic O-ring that is aligned and released over the groove of the inner ring using an applicator (Figure 2). Blood flow to the foreskin is restricted by compression of the elastic ring on the inner ring, resulting in ischemia and necrosis of the foreskin. The device and necrotic residual foreskin are removed at seven days. Since there is neither cutting nor crushing of live tissue that would result in intense pain, there is no need for injectable local anaesthesia. The absence of bleeding means that there is no need for suturing and the device does not have to be sterile at the time of use.

Figure 2: The PrePex device

Process of evaluation of study data on specific devices

Retrieval of the evidence

In preparation for the TAG meeting, WHO staff searched the PubMed database for all published studies on the two circumcision devices and contacted investigators known to be studying the devices in African countries. WHO staff reviewed all published reports. Investigators made available to WHO secretariat confidential final reports from completed studies and interim reports from ongoing studies for review by the TAG. WHO secretariat extracted key features of each study into a standard format and compiled these to report the most important clinical outcomes regarding safety and efficacy of the device in different populations and in the hands of different providers. During the latter part of 2012, a subgroup of the TAG reviewed and commented on all data available. WHO sought clarifications from the study investigators where necessary.

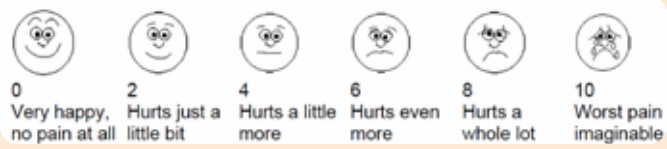
As the review of the clinical data by the TAG informs the development of guidance on use of devices, the process followed was similar to that recommended by the WHO Guideline Development Committee, including specifying outcomes of interest. The evaluation criteria were in line with those identified in the *Framework* (1). External audits conducted either on behalf of the study sponsor or by a team designated by the WHO secretariat independently verified the quality of the research study and the completeness of the data and reports.

Standardization of the priority outcomes

The TAG meeting evaluated the devices on the basis of the following critical outcomes and definitions:

- Eligibility for male circumcision with the device. All men must be screened for medical eligibility for circumcision, in particular the absence of any penile abnormalities and current genital infections. For a particular device, use may be further restricted due to: a) additional anatomical reasons, such as phimosis (inability to retract the foreskin), a narrow foreskin opening or a short frenulum; or b) technical reasons that preclude device placement such as unavailability of a correct device size or inability to complete the device placement procedure. Therefore, device eligibility was defined as the proportion of men who met the criteria for conventional surgical circumcision, who were also eligible for circumcision with the specific device and in whom the device could be successfully placed.
- Successful circumcision was defined as removal of sufficient foreskin such that the coronal sulcus was visible with the penis in a flaccid (non-erect) state. Circumcision failures included clients who needed an additional intervention to complete the circumcision and those with insufficient foreskin removed. The proportion of successful circumcisions was computed only on clients on whom the device was successfully placed.
- Procedure time was computed for devices as the sum of the preparation and procedure times for placement and removal, not counting the time period between the two. Times were measured from start of the surgical procedure to completion of wound dressing (first to last touch) for conventional surgery or to end of device placement (last touch) for device application, but did not include the time for induction of anaesthesia, where used. Removal times were measured from first touch to completion of wound dressing after device removal.
- Time to complete wound healing was defined as the number of days from the date of conventional surgical circumcision or device placement (not from the date of intended or actual device removal) to the first date when complete wound epithelialization was observed. Not all study teams used identical definitions of complete wound healing, and the long intervals between visits in some studies prevented a precise estimate of the duration of healing.
- Pain was measured in most studies using a Visual Analogue Score (VAS) with a range of 0–10, where 0 corresponds to "no pain at all" and 10, to "worst pain imaginable", with clients shown pictograms for six different rating levels (Figure 3), with text usually translated into the local language. Depending on the study and the follow-up schedule, the pain assessments were made at specified time points, such as before or during device placement; specified times after placement; while wearing; before, during and after removal; and at selected follow-up visits. Additionally, some studies assessed the duration of the pain. Not all studies assessed pain at the same time points; the most comparable times have been selected in order to facilitate comparisons between devices and with conventional surgical circumcision.

Figure 3: Visual analogue pain scale and pictograms



Definitions and classification of adverse events

Although there had been attempts to standardize terminology and classification of adverse events (AEs) in studies of conventional male circumcision and circumcision devices, the classification schemes evolved as more information about the types and timing of AEs became available. The different mechanisms of action of the devices and the differences from conventional surgical circumcision techniques have led to differences in the types of AEs and characterization of the AEs. This required that all observed AEs be reviewed and classified by the TAG in a uniform manner. In doing so, the TAG was guided by internationally recognized principles and definitions of AEs and serious adverse events (SAEs).

The Global Harmonization Task Force (GHTF) (9) and the International Organization for Standardization define an AE as: "Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device". This definition includes events related to the investigational medical device or the comparator and events related to the procedures involved.

In addition, an SAE is defined as an AE that:

1) led to a death; or,
2) led to a serious deterioration in the health of a patient, user, or others that:
   a. resulted in a life-threatening illness or injury
   b. resulted in a permanent impairment of a body structure or body function
   c. required inpatient hospitalization or prolongation of existing hospitalization
   d. resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function.

The International Organization for Standardization document 14155 additionally defines an adverse device effect as an AE related to the use of an investigational medical device, which includes:

- AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device; and,
- Any event resulting from use error or from intentional misuse of the investigational medical device.

In consideration of the above international definitions and the importance of ensuring a uniform classification that can be applied to clinical research on male circumcision, the WHO TAG closely followed GHTF definitions and the following principles (for the two circumcision devices for which data were available for review as well as other devices that may become available with different mechanisms of action):

- Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the conventional surgical procedure or to the medical device used for performing or assisting in the male circumcision procedure was considered an AE.
- Any AE that was definitely not related to the circumcision procedure or to handling or operating the medical device was not considered further.
- Any AE that satisfied the GHTF definition of an SAE was considered a serious adverse event (SAE).
- Any AE not classified as an SAE but that required an intervention by a health care provider or medication (parenteral, oral or topical) was considered a moderate AE.
- All other AEs were considered mild AEs. None of these events would require any intervention.

In order to compile AEs over the different clinical studies and circumcision procedures, each AE was classified according to its underlying cause or clinical presentation. It is important to note that the classification adopted is designed to assess and compare complications that occurred during the clinical research on male circumcision devices. While the overall principles underlying the classification are likely to apply to programmes, the details will have to be assessed for relevance in classifying AEs that occur in male circumcision programmes. Table 3 lists all AEs observed to date according to category.

Clinical evaluation of the ShangRing

1.Overview of the studies

The TAG reviewed clinical data on the safety, efficacy and acceptability of the ShangRing from studies conducted in China and three countries in Africa. Table 4 summarizes the studies conducted in five sites in Africa (in Kenya, Uganda and Zambia). Early studies in China demonstrated that the device was safe when applied under local anaesthesia by skilled providers in Chinese study participants (ages 5 to 95 years across studies), resulted in a neat and complete circumcision, and was potentially faster and simpler than conventional surgical circumcision, as no suturing was required for haemostasis or wound closure. These studies formed the basis for proceeding in a stepwise manner to clinical research in African countries where public health male circumcision programmes are being implemented.

In its review of evidence, the TAG placed emphasis on the studies conducted in the African region, which provided directly relevant information on the clinical performance of the device when used in public health HIV prevention programmes: two initial safety and efficacy studies, two randomized controlled trials and two field studies. All the studies conducted in Africa with the ShangRing device used the same device design, which differed from the original device only with regard to the mechanism to secure the outer ring (see Figure 1). Safety and effectiveness of the ShangRing device have been studied only in men age 18 years and older. There was consensus among the TAG members that the range and scope of the studies conducted on the ShangRing met the requirements set forth in the *Framework*.

2. ShangRing study results

Eligibility

The overall estimated proportion of clients eligible for conventional male circumcision who were also eligible for Shang Ring circumcision and in whom the device could be placed was 98.8%. The proportion of clients eligible for Shang Ring circumcision was 99.6%, due to a small number of clients excluded for minor foreskin abnormalities (e.g. short frenulum) that precluded device placement. These men could be circumcised using a conventional surgical approach. Shang Ring device placement procedures were started in 1998 clients and were completed in all but 15 (99.2%) due to correct ring size not being available at the time of the procedure (8), the foreskin slipped from the outer ring (3), the foreskin was too short (1) or damaged (2), or the outer ring could not be closed (1).

Successful circumcision

Circumcision was achieved in all clients on whom the device was successfully placed with the exception of three men (0.15%) who were considered to have insufficient skin removed.

Some clients with moderate or severe phimosis required a small dorsal slit to be made in the foreskin to facilitate eversion over the inner ring (range across studies of 10%-28% of men).

The spontaneous detachment study showed that, if the device is not removed as scheduled at seven days, the device begins to detach spontaneously and may come off without removal by a medical provider. Partial detachments appear to be painful, cause discomfort as the partially detached device may snag and cause tearing of tissue and bleeding. Therefore, the device should ideally be removed at seven days.

Procedure times

The overall mean placement time was 6.4 (SD 3.8) minutes, excluding the time for injection and induction of local anaesthesia. The mean removal time was 3.1 (SD 1.8) minutes. The total of the mean placement and removal times (mean 10.3 minutes) was less than the mean procedure time in the randomized comparison with conventional surgery in Kenya and Zambia (mean 20.3 minutes).

Adverse events

Adverse events in all the African ShangRing studies combined are summarized in Table 5. Based on a total of 1983 successful device placements, there were:

- no SAEs—proportion 0.0% (95% confidence interval 0.0%-0.2%)
- a total of 20 moderate adverse events—proportion 1.0% (0.6%-1.6%) and
- a total of 43 mild adverse events—proportion 2.2% (1.6%-2.9%).

The ShangRing device is designed to avoid the need for haemostasis during surgery and to clamp the skin edges firmly together to fuse as part of the healing process. Because of the tight clamping mechanism, local injectable anaesthesia is required before device placement and then the foreskin is cut away distal to the device. The greatest proportion of moderate AEs was associated with pain during the anaesthetic administration and device placement, requiring additional medication for control in some instances, pain while wearing the device, or partial device detachment or minor wound disruption before device removal. Nevertheless, complications requiring intervention were rare (less than 1 in every 100 procedures).

It is important to note that the seven clients (0.4%) in whom the device placement procedure was started but could not be completed were all immediately converted to conventional surgical circumcision. Had facilities not been immediately available to safely complete the open circumcision (sterile field, sutures or electrocautery for haemostasis and sutures for wound closure), complications that would have resulted in serious adverse events might have occurred. A small number of wound disruptions occurred several weeks after device removal; these were clear departures from the normal healing process.

In the randomized controlled trial comparing ShangRing with conventional surgery, there were no serious AEs, 2 moderate AEs (both in the surgery arm) and 23 mild AEs (15 in the ring arm and 8 in the surgery arm) in 197 ring placements and 198 surgical circumcisions, P=0.40.

Healing

Healing following male circumcision with the ShangRing device is by secondary intention and takes about one week longer than with surgery. In the comparative study, the mean time to complete healing was 44.1 (SD 12.6) days following ShangRing placement compared with 38.9 (SD 12.6) days following surgery (mean 5.2 days longer, 95% confidence interval 2.7–7.7 days). Thus, ShangRing circumcision requires a longer period of post-circumcision sexual abstinence than standard surgical methods.

Pain

The ShangRing device requires injectable local anaesthesia before placement. The pain experienced during device placement and in the post-operative period is similar to that reported after conventional surgery. Men reported some pain while wearing the device and a somewhat higher rate of pain during erection than at comparable times after conventional surgery. There is a risk of minor injury to the penis from the device itself and discomfort from catching or snagging the device while wearing it. Partial detachment of the devices is associated with some discomfort and pain, but this is rare if the device is removed as scheduled at seven days. There is short, transient discomfort and pain as the device is removed. In one study local anaesthetic spray was used prior to removal. This seemed to lessen but not completely eliminate pain.

Key points on the ShangRing made by the TAG

(Programmatic considerations are included in the next section).

The TAG reviewed clinical data on the safety, efficacy and acceptability of the ShangRing device from five studies conducted in three African countries that resulted in device placements on nearly 2000 men.

- The TAG advised that the clinical studies necessary before a device is considered for prequalification by WHO per the *Framework for clinical evaluation of devices for male circumcision* (2012) have been satisfactorily conducted.
- The evaluation, and thus advice on use, is currently limited to data on healthy males 18 years and older, as data were not available on men under 18 years or on men living with HIV.
- A small proportion of men were not eligible for device use. Provision of or referral to conventional surgical male circumcision would be needed. Some of the cases required immediate conversion to a conventional surgical circumcision. A person experienced in standard surgical circumcision must, therefore, be available on site, together with appropriate instruments and supplies.
- Circumcision using the ShangRing was demonstrated to be safe and successful in over 99% of clients.
- Healing is by secondary intention. It requires about one week longer than after conventional surgery. The TAG considered that there is a risk of HIV acquisition if men engage in unprotected sex before the wound is healed, but the magnitude of risk is unknown. While this is also true of circumcision by conventional surgery, because of the longer healing time, the group stressed the importance of good counselling about sexual activity and condom use.
- Adverse events associated with ShangRing procedures were rare. In a total of 1983 successful device placements, there were no deaths or serious adverse events (95% confidence interval 0.0%–0.2%). The most common AEs were related to pain. All AEs were managed with, at most, minor intervention and resolved with no long-term sequelae. Although definitions of serious and moderate AEs in the three randomized controlled trials that demonstrated the efficacy of male circumcision for HIV prevention in Kenya, South Africa and Uganda are not directly comparable to those adopted in the device studies, the proportions are in a similar range—0.0% to 0.6%.
- Phased implementation with careful monitoring and reporting of device events and AEs is recommended in order to better understand the frequency of technical failures of the ShangRing and how best to manage such failures.
  - Programmes must conduct active surveillance of the first 1000 clients to identify and record AEs based on standardized definitions. The active surveillance may change to passive surveillance after the first 1000 clients, if the incidence of events is reassuringly low as determined by independent review. Ongoing reporting of serious adverse events as part of post-market surveillance will need to be systematized.
- The TAG considered the ShangRing to be clinically efficacious and safe for use in men 18 years and older, when the procedure is performed by trained providers in public health programmes. Skills and surgical facilities should be available to safely convert technical failures of device placement to conventional procedures. The TAG recognizes that this conclusion on clinical efficacy and safety is only one component of the prequalification decision. The TAG based its conclusion on the data currently available. This conclusion must be reassessed in about one year as more experience with use of the device accumulates in diverse programmatic settings outside the context of studies.

Clinical evaluation of the PrePex

1. Overview of the studies

Table 6 summarizes the eight studies conducted in three countries, Rwanda, Uganda and Zimbabwe (interim analyses on two ongoing field studies were included). The device was first clinically tested in Rwanda in a study that established the natural history of the necrotic process in 50 volunteers. A second study investigated alternative forms of topical anaesthesia at the time of placement before a formal randomized comparison with the dorsal slit conventional surgical approach was made. The next study to be completed was a field study in Rwanda in which the device was placed and removed by trained nurses instead of physicians. In order to comply with the requirements in the WHO *Framework*, a second series of studies was independently conducted in Zimbabwe, starting with a small safety study followed with a randomized comparison and a second field study.

2. PrePex study results

Eligibility

The overall estimated proportion of clients eligible for conventional male circumcision who were also eligible for PrePex circumcision and in whom the device could be successfully placed was 92.6%. The proportion of clients considered eligible for PrePex circumcision was 94.1%, due a number of clients excluded for phimosis, narrow foreskin opening, tight frenulum, or small wounds on the foreskin or penile shaft. PrePex placement procedures were started in 2268 clients and were completed in all but 38 (98.3%) due to narrow foreskin opening (16), tight or short foreskin (15) or adhesions (4), and three clients with a penis circumference size outside the range of available ring sizes.

Successful circumcision

A total of 2417 PrePex devices were successfully placed in the eight studies. For a large majority of clients (99.5%), the PrePex circumcision was successful, leaving a neat circumferential wound resulting in a final cosmetic appearance without suture marks. Circumcision had to be completed by conventional surgery in a total of 12 clients (0.5%)—four removed the device themselves on Day 1 , two returned to the clinic on Day 2 requesting removal because of pain, discomfort or inconvenience, and in five clients the device became displaced on Day 1 (1), Day 2 (2), Day 4 (1) or Day 5 (1), following erection, masturbation, sexual intercourse or an assault. In one client surgery under local anaesthesia was required to remove the band of necrotic foreskin that had everted over the outer ring and prevented device removal.

Procedure times

There was considerable variation in placement and removal times over the different studies, with more experienced providers having lower procedure times. After the initial training and familiarization process, mean placement preparation times were 2.0 (SD 0.8) minutes, placement procedure 1.5 (SD 1.0) minutes, removal preparation 0.4 (SD 0.2) minutes and removal procedure 2.0 (SD 1.1) minutes. In the two comparative studies, the mean total procedure time (placement preparation and procedure time and removal preparation and procedure time) was 5.7 (SD 1.4) minutes compared with 19.2 (SD 3.9) minutes for conventional surgery.

Adverse events

AEs occurred in 42 men in whom the device was successfully placed (1.7%); the majority of AEs were mild or moderate, while 9 (21%, or 0.4% of device placements) were considered serious, as prompt surgical intervention was required to prevent potential serious long-term sequelae. The nine adverse events categorized as serious resulted from device displacements during sexual activity, masturbation, erection, possible placement error, or accidental dislodging by another person; early removals (including self-removals) secondary to pain; meatal injury at removal; and difficult removal due to necrotic tissue everted over the elastic ring requiring surgical intervention, and wound dehiscence. Some of the displacements were associated with painful oedema, blistering and swelling as the blood flow returned to the partially necrotic foreskin and required prompt surgical intervention to remove the foreskin and avoid serious infection or injury to the penis. No mechanical device failures were reported.

Healing

Healing following male circumcision with the PrePex device is by secondary intention and takes about one week longer than with surgery. In the comparative study in Rwanda, the mean time to complete healing was 38.0 (SD 12.1) days following PrePex placement compared with 23.0 (SD 7.5) days following surgery (mean 15 days longer, 95% confidence interval 12 to 18 days). In the comparative study in Zimbabwe, the difference in healing times was less pronounced, but interpretation of the data from this study is limited by the absence of follow-up visits between days 7 and 42 post-procedure in the surgical circumcision arm. The overall mean healing time after placement recorded over five studies was 42.3 days (standard deviation 7.8 days). Almost all men healed by 8 weeks. Thus, healing following PrePex circumcision requires a longer period of post-circumcision sexual abstinence than standard surgical methods.

Pain

The PrePex device does not require injectable anaesthesia during placement. Comparing the pain scores is difficult because the pain control protocols evolved as the studies progressed and more information on pain became available. In none of the studies was any injectable anaesthesia used for placement or removal of the PrePex device (excluding the men with complications that required surgical intervention). A topical anaesthetic cream containing 5% lidocaine was first introduced in the Rwanda field study and has been adopted in all subsequent studies.

Summary results of the VAS pain scores in the Rwanda studies showed that pain at the time of ring placement was minimal. The period of greatest discomfort and pain was in the 3–6 hours after placement, with ischaemia induced by the device. Most study participants were provided with analgesics to take as needed at home after placement; pain during the early ischaemic process appeared to be adequately controlled in a large proportion of clients with readily available medications such as paracetamol or ibuprofen. There appears to be less pain while the device is worn than at comparable times after conventional surgery, even during erections. Study participants reported transient pain (short duration but quite severe) during device removal as the elastic and inner rings were detached from the healing wound.

Acceptability

Objectively assessing client acceptability in the early research studies is difficult. However, a large proportion of clients expressed satisfaction with the aesthetic result. Pain, discomfort or user behaviour led to device displacements or early removals. Providers in at least three studies noted a strong odour in several clients at the time of removal. Studies with the PrePex assessed loss of working days, which appeared to be fewer than following conventional surgery.

Key points on the PrePex made by the TAG

(Key programmatic considerations are noted in the next section.)

The TAG reviewed clinical data on the safety, efficacy and acceptability of the PrePex device from eight studies conducted in three countries with device placement on 2417 men.

- The range and scope of these studies met the criteria established in the WHO *Framework for clinical evaluation of devices for male circumcision.*
- The TAG advised that the clinical studies necessary before a device is considered for prequalification by WHO have been satisfactorily conducted.
- Evaluation and any advice are currently limited to healthy males 18 years and older, as the device has not yet been evaluated for use among younger ages or among men living with HIV.
- About 7% of clients eligible for conventional surgical circumcision could not have the PrePex device placed for various anatomical or technical reasons, including a narrow preputial opening or the correct device size outside range of five sizes produced. Circumcision was completed using the PrePex in 99.5 % of clients on whom the device was successfully placed.
- AEs occurred in 1.7% of clients; the majority were mild or moderate. AEs in 0.4% were considered serious, and prompt intervention was required to prevent potential serious long-term sequelae.
- In a small number of clients (about 1 in every 200), the device became displaced and /or was removed (including self-removal) due to client activities, pain, discomfort or personal inconvenience wearing the device. Some of these cases resulted in pain, rapid swelling and/or blistering of the partially necrotized foreskin tissue, requiring urgent surgical intervention by a skilled surgeon in order to avert permanent disfigurement of the penis and/or severe local or systemic infection. In the studies conducted to date, appropriate surgical facilities have been available; all cases were successfully managed, with no long-term sequelae.
- Client instructions must clearly describe safe use of the device, symptoms that may develop with device displacement or early removal as well as the possible serious outcomes and surgical interventions that may be needed if instructions on abstinence and wound care are not followed or if the device becomes displaced (see next section).
- The PrePex device was reportedly acceptable to a large proportion of study participants. In contrast to conventional surgical circumcision and other circumcision devices that have been reviewed by the TAG, the PrePex device has the advantage of not requiring injectable anaesthesia or suturing at the time of placement, thus requiring less time for the procedures and causing less pain.
- PrePex providers must be appropriately trained to recognize the potential serious complications that can occur if the device is displaced or removed early, and must ensure that such clients are rapidly assessed for appropriate management (within 6–12 hours), including referral when necessary.
- If countries decide to introduce the PrePex device into their public health programme, introduction should be done in a phased approach after the device is prequalified.
- Careful monitoring and reporting of AEs is necessary in order to better understand the frequency of device displacement and self-removals and how risks can best be mitigated.
  - Programmes must conduct active surveillance of the first 1000 clients to identify and record AEs based on standardized definitions. The active surveillance may change to passive surveillance after the first 1000 clients, if the incidence of events is reassuringly low as determined by independent review.
- The TAG considered that there is an enhanced risk of HIV acquisition if men engage in unprotected sex before the wound is healed, but the magnitude of risk is unknown. Therefore, the group stressed the importance of good counselling about sexual activity and condom use.
- The TAG considered the device to be clinically efficacious in male circumcision and safe for use among healthy men 18 years and older when used by trained mid-level providers in public health programmes, provided that surgical backup facilities and skills are available within 6–12 hours to manage events that could lead to serious complications. This conclusion is time-limited and must be reassessed in about one year as more experience with use of the device in diverse programmatic settings is accumulated and reported.

PROGRAMMATIC CONSIDERATIONS IN DEVELOPING WHO GUIDANCE ON THE USE OF MALE CIRCUMCISION DEVICES

During the course of the meeting and the session focused on programmatic considerations, the TAG noted the following key points. In general, evidence on devices is currently available from use in research conditions, in which many of the providers are highly skilled. As use expands and shifts from study populations receiving "ideal care in well-resourced settings" to more real-world conditions, the TAG considered phased implementation critical to determine the best and safest approaches for addition of a new device method. Pilot studies are planned in a number of the priority countries. The information from these studies will further inform the use of the devices. Implementation plans must be tailored to the specific characteristics of each device.

Clinical skills and competencies for device placement, removal and management of AEs should be available within an 'individual' and/or a 'team'. For conversion to a surgical procedure after commencement of a device circumcision, surgical staff may need skills beyond those needed to perform conventional surgical circumcision. Required clinical skills and training will differ according to device. For example, ShangRing placement requires skills similar to those required for conventional surgery, but more advanced skills and experience are required to manage the rare cases when the ShangRing placement procedure cannot be completed; these skills should be available on site. The surgical intervention necessary after PrePex device displacement or self-removal after the ischemic process has started requires a surgeon experienced with managing swollen tissue and abnormal foreskin anatomy. These skills and facilities must be available or obtainable within 6 to 12 hours. All providers must be knowledgeable and trained to manage potentially life-threatening complications as well as the expected and foreseeable side-effects.

Considerations related to delivery site requirements that the TAG identified included:

- The unique requirements of a device will need to be considered in the context of each type of service delivery site (e.g. fixed, mobile, outreach, routine versus campaign).
- At the initial introduction of a new device, it is advised to have both conventional surgery and device methods available.
- A second visit is definitely required for device removal; services must be organized to meet the requirements of both visits.
- The type of surgical back-up skills and facilities must be clearly specified, depending on device type, and available:
  - "Immediate/on-site" surgical skills will be necessary at the time of ShangRing placement.
  - "Within 6–12 hours timeframe" surgical skills must be available during the week that men have a PrePex device in situ, in case of an AE requiring urgent intervention.
- Referral systems and contact numbers should be in place prior to adding a device to any service.
- For men not eligible for a device (such as those under 18 years old or HIV-positive), service sites must determine if conventional surgery is to be available on site or through a functioning system of referral to services at another location.
- Programmes need to indicate pain management protocols for each specific device and for all stages of device use (pre-, in situ, at removal and post removal); these protocols must be resourced appropriately.

Male circumcision is one essential component of the "minimum package" of services, and all other components also must be available.

Information should be available for providers, including a training manual and instructions for use of the device. The EMP Department stated that the evaluation of the manufacturer's instructions for use (IFU) is part of the PQ programme. The IFU should include pictures and step-by-step instructions from beginning to end (placement and removal) and should list the equipment that is provided in procedure package and additional accessories that are required. The TAG asked to review the IFUs prior to a PQ decision. Considering the limits of any IFU, programmes will still be responsible for the training and for developing manuals that will address specific issues such as pain management.

Client counselling and education is an essential activity for good clinical practice, informed consent and mitigation of risks related to client behaviours. Client instructions must clearly indicate the process and requirements of use of a specific device. Clients' partners should also be provided instructions. Points that should be included in client instructions include the following:

- Once placed, a device must remain for seven days. In case a client desires to remove the device early, clients must be instructed to return to the clinic. For the PrePex device early removal would likely require a conventional surgery to safely complete the circumcision.
- Clients must understand that wound healing may take about one week longer than following surgery, and that, until complete healing, they should continue abstinence or use a condom to protect the wound and reduce HIV transmission risk. Also, the nature and appearance of secondary healing should be described to men.
- Accurate messaging is needed on care and hygiene, possible symptoms and management of device use, including the likely event of some pain. Symptoms such as pain, odour, bleeding and swelling should be clearly described.
- Clients must also be instructed on safe behaviours while the device is worn, including avoidance of sexual activity and masturbation and the risks associated with such activity (with the PrePex risk of displacement, bleeding, swelling and ulceration and need for surgical circumcision).
- If a device displaces or becomes dislodged, clients must know where to return to receive skilled surgical care or referral and transport arrangements to such care, within 6–12 hours.

There are a number of other issues that programmes will need to consider prior to introduction and use of a device, including:

- The organization of the supply chain and logistics will be needed. Multiple device sizes will be required and must be sufficiently stocked through good supply management and forecasting. The choice of the correct device size is likely to be critical for avoiding adverse outcomes, but as yet the tolerance margin for using a device one size too small or too large is not known.
- Effective training and training materials will need to be available.
- Sterility requirements and accessories required will need to be available.
- Regulations/policies will be needed on product approval in the country and on which providers are permitted to perform male circumcision with a device.
- Post-market surveillance will need to be set up in a standardized manner.

INFORMATION GAPS AND NEEDS

The TAG discussed research gaps that should be addressed in the near future. Over the next 12 months, PEPFAR and the Bill and Melinda Gates Foundation will support pilot studies on the use of the ShangRing and the PrePex devices in VMMC programmes in most of the countries in eastern and southern Africa. These pilot projects will have monitoring components, particularly the monitoring and analysis of AEs, which will provide more data on their frequency and more detailed information on causes of serious AEs, such as PrePex displacement or ShangRing device failures.

The following additional gaps regarding the use of male circumcision devices were identified:

- Bridging studies are required to establish performance and safety in younger populations since neither the ShangRing nor the PrePex have been evaluated in men under the age of 18 years.
- Since there are limited data in HIV-infected adolescent males and adult men, it is important to document the safety of the device in such clients. Risk of HIV transmission during wound healing should be assessed through modelling studies to better inform the consideration of risks and benefits.
- Studies are needed to assess the acceptability of the devices, particularly regarding the recommended period of sexual abstinence and the presence and management of pain, odour and urination problems while the devices are in situ.
- More research is required to identify the best protocol for managing pain at each point in the device use process.
- The frequency of SAEs in non-study settings needs to be measured.
- As full healing and resolution of scarring may take up to one year, outcomes one year after circumcision is performed with a device should be assessed to document long-term wound healing and final cosmetic result.
- Sizing studies are required, as the choice of the correct device size is likely to be critical for avoiding adverse outcomes.

A brief update on ongoing/planned studies on the use of male circumcision devices for infants such as AccuCirc compared with Mogen and Plastibell in Botswana, Zimbabwe and Uganda was provided by the WHO secretariat. TAG members expressed interest in moving forward infant circumcision, but WHO noted that due to limited resources the focus would be on review of data when it becomes available.

Addressing other technical issues

Due to the limited time available, two items on the agenda were not completed:

- review of the study requirements for clinical evaluation of devices in the same category;
- advise on additional technical innovations that WHO should assess or should stimulate further development of in order to improve coverage and/or accelerate scale-up of medical male circumcision in priority countries.

The TAG will address these items through telephone and electronic communications during the year.

NEXT STEPS

Key activities for the coming year include:

- Complete the summary reports on the clinical performance of each device as part of the prequalification process;
- Finalize the tables and summaries of adverse events and provide feedback to the study investigators on the classifications adopted by TAG;
- Review the Instructions for Use submitted by the device manufacturers in accordance with the TAG recommendations;
- Incorporate feedback from the TAG into the generic guidance on use of devices by the Guideline Development Group;
- Follow up with other technologies that have the potential to accelerate public health male circumcision programmes, specifically use of the Gomco clamp and surgical adhesive;
- Collate and monitor the incidence of device-related SAEs occurring in programmes and provide regular updates to the TAG chairs;
- Convene the next TAG meeting in early 2014 when sufficient additional data on male circumcision devices used in programmatic settings is available, and review the TAG conclusions on the clinical performance of the PrePex and Shang Ring devices.

TABLES

Table 1: Key risks of elastic collar compression devices as identified by WHO failure modes and risk analysis, August 2012

Characteristic	Potential failure mode	Event	Effect	Mitigation
Instructions and warnings	Untrained provider	Incorrect use	Penile damage Excessive blood loss	Clear and detailed instructions
Device size	Incorrect gauging	Wrong size used	Penile strangulation Insufficient foreskin removed	Training and user instructions
Device profile	Snagging	Device displacement Trauma	Damage to penis Excessive bleeding	Device design Instruction Patient selection
Applied pressure	Insufficient pressure applied	Partial necrosis	Septicaemic shock	Matching components O-ring properties
Properties of O-ring	Stress relaxation	Partial necrosis	Septicaemic shock	O-ring properties
Material for O-ring	Adverse reactions	Irritation and/or sensitisation	Anaphylactic shock	Biocompatibility (ISO 10993)
Properties of inner ring	Inadequate strength	Ring breaks after a period of time	Damage to penis/glans or urethra	Specification and material testing at end of shelf-life
Contact duration	Accumulation of debris	Colonisation of device	Local and systemic infection	Device design Instructions for patients
Contact duration	Inappropriate cleaning	Damage to tissue Damage to device	Ulceration, pain infection Device failure	Information for patients Choice of materials
Reasonably foreseeable misuse by patient	Masturbation Intercourse Self-removal of device or foreskin	Device displacement Injury to self or partner	Bleeding, damage to penis, infection	Patient instructions, appropriate selection of patients (user instructions)
Reasonably foreseeable misuse by clinic or hospital	Reuse of device components	Components break	Damage to penis, glans and/or urethra	Design of components Instructions

Table 2: Key risks of clamp collar devices as identified by WHO failure modes and risk analysis, August 2012

Characteristic	Potential failure mode	Event	Effect	Mitigation
Instructions and warnings	Untrained provider	Incorrect use	Penile damage Excessive blood loss	Clear and detailed instructions
Device sterility	Inadequate sterilization	Microbial contamination	Potential infection	SAL <10-6 Sterilization validation
Device sterility	Packaging breached	Microbial contamination	Potential infection	Packaging validation Seal integrity testing
Device size	Incorrect gauging	Wrong size used	Penile strangulation Insufficient foreskin removed	Training and user instructions
Device profile	Snagging	Device displacement Trauma	Damage to penis Excessive bleeding	Device design Instruction Patient selection
Material for O-ring	Adverse reactions	Irritation and/or sensitisation	Anaphylactic shock	Biocompatibility (ISO 10993)
Latch or hinge	Failure after placement and foreskin removed	Collar detaches	Severe bleeding	Design verification Product testing
Components not matched for size	Outer ring too loose	Device displacement	Damage to penis, bleeding	Manufacturer's quality management system and product inspection Instructions for use
Properties of inner ring	Inadequate strength	Ring breaks after a period of time	Damage to penis, glans and/or urethra	Specification and materials testing at end of shelf-life
Applied pressure	Inadequate force applied	Excessive bleeding Device displacement	Shock, blood loss, infection	Set appropriate lower limit for applied pressure
Properties of outer ring/clamp	Inadequate strength	Ring breaks after 6–8 hours	Excessive bleeding Shock	Supplier evaluation Testing and inspection
Contact duration	Accumulation of debris	Colonization of device	Local and systemic infection	Device design Instructions for clients
Contact duration	Inappropriate cleaning	Damage to tissue Damage to device	Ulceration, pain, infection Device failure	Information for clients Choice of materials
Reasonably foreseeable misuse by patient	Masturbation Intercourse Self-removal of device	Device displacement Injury to self or partner	Bleeding, damage to penis Infection	Patient instructions, appropriate selection of patients (user instructions)
Reasonably foreseeable misuse by clinic or hospital	Reuse of device components	Components break	Damage to penis, glans and/or urethra	Design of components Instructions

Table 3: Classification of serious, moderate and mild adverse events for review of clinical data on device safety by the WHO TAG, 2013

Serious adverse event **Required surgical intervention to prevent permanent impairment to a body structure or a body function**	**Code**
Displacement	DISP
Pain or discomfort resulting in early removal	PREM
Difficult removal	DIFR
Injury to penis	INJP
Wound disruption requiring suturing	WNDD
Moderate adverse event **Required intervention or medication**	
Severe pain at time of, or soon after, device placement or surgery	PAIN
Displacement	DISP
Bleeding	BLDD
Infection requiring medication	INFD
Pain or discomfort resulting in early device removal	PREM
Wound disruption	WNDD
Difficult removal	DIFR
Insufficient skin removed	ISKR
Mild adverse event **Did not require intervention**	
Anaesthetic complication	ANAE
Pain at time of, or soon after, device placement or the surgical operation	PAIN
Oedema	OEDP
Displacement requiring repositioning	DISP
Burn blister	BLIS
Abscess	INFD
Bleeding or oozing (pressure and/or dressing)	BLDD
Exudate	EXUD
Injury to penis	INJP
Wound disruption	WNDD
Partial detachment	DETD
Insufficient skin removed	ISKD

Table 4: ShangRing clinical studies in Africa

Study [type of study] (reference number)	Location	Number and type of client	Type of providers
Safety Study (Kenya) [case series] (8)	Homa Bay District Hospital, Kenya	40 healthy HIV-negative men	Physicians and nurses experienced in conventional surgical circumcision
Spontaneous Detachment Study (Kenya) (10, 11)	Homa Bay District Hospital, Kenya	50 healthy HIV-negative men	Physicians and nurses experienced in conventional surgical circumcision
Randomized Comparison with Surgery (Kenya and Zambia) [comparative trials] (12–14)	Kenya: Homa Bay District Hospital Zambia: University Teaching Hospital (UTH), Lusaka	400 healthy HIV-negative men (200 allocated to ShangRing, 200 to conventional surgery)	Non-physicians under supervision, physicians and non-physicians, all with extensive experience with surgical male circumcision (>500 surgical procedures each)
Field Studies (Kenya and Zambia) [field studies] (15, 16)	Kenya: seven sites in Homa Bay Zambia: Male Circumcision Centre and UTH, Lusaka	1256 healthy men	Non-physicians and physicians, all with extensive experience with surgical male circumcision
Acceptability and Safety (Rakai) [field study] (17)	Rakai Health Sciences Programme, Kalisizo, Rakai District, Uganda	621 health HIV-negative men, 508 of whom chose ShangRing	Clinical officers in sterile conditions in outpatient operating rooms

Table 5: Adverse Events in all Shang Ring studies combined

Type of Event	Number		Per cent	
Number of device placements	1,983			
Serious AEs	**0**		**0.0%** [0.0%, 0.2%]	
Moderate AEs	**20**		**1.0%** [0.6%, 1.6%]	
Pain placement (PAIN)		8		0.4%
Pain leading to early removal (PREM)		2		0.1%
Infection (INFD)		4		0.2%
Bleeding (BLDD)		1		0.1%
Wound disruption (WNDD)		2		0.1%
Insufficient skin removed (ISKR)		3		0.1%
Other events		0		
Mild AEs	**43**		**2.2%** [1.6%, 2.9%]	
Anaesthetic complication (ANAE)		1		0.1%
Pain placement (PAIN)		13		0.7%
Oedema (OEDP)		3		0.2%
Injury (INJP)		3		0.2%
Partial detachment (DETD)		3		0.2%
Bleeding (BLDD)		2		0.1%
Wound disruption (WNDD)		15		0.8%
Insufficient skin removed (ISKR)		3		0.1%
Other events		0		

Table 6: PrePex™ clinical studies in Africa

Study [type of study] (reference number)	Location	Number and type of client	Type of providers
Safety and Efficacy Rwanda [case series] (18)	Kanombe District and Military Hospital, Kigali, Rwanda	50 generally healthy HIV-negative men	Physicians and nurse operators
Randomized Comparison of PrePex and Surgery Rwanda [comparative trial] (19)	Nyamata District Hospital, Rwanda	217 generally healthy men (144 allocated to PrePex, 73 allocated to dorsal slit surgery)	Physicians and nurse operators
Pilot Study with Nurse Providers Rwanda [case series]	Kanombe District and Military Hospital, Kigali, Rwanda	49 healthy HIV-negative men age 21–54 years	Nurses
Field Study with Nurse Providers Rwanda [field study] (20–22)	Kanombe Military Hospital, Kigali, Rwanda	666 generally healthy men	Lower cadre nurses with no previous experience of PrePex circumcision
Phase 1 Safety Study Zimbabwe [case series] (23)	Harare Central Hospital, Zimbabwe	53 HIV-negative men	Physicians (urologists, general surgeons and general practitioners) and assistants (senior registered general nurses)
Phase 2 Randomized Controlled Trial Zimbabwe [comparative trial] (24)	Harare Central Hospital, Zimbabwe	240 HIV-negative men	As above
Phase 3 Field Study Zimbabwe [field study] (25)	Harare, Kadoma and Mutare, Zimbabwe	641 HIV-negative men	Nurses with physician back-up support
Field Study, Kampala, Uganda [field study] (26)	International Hospital Kampala, Uganda	634 healthy men	Surgeons, medical officers, clinical officers and nurses
Field Study, Rakai, Uganda [field study] (27)	Rakai Health Sciences Program, Uganda	187 HIV-negative men	*Not stated*

Table 7: Adverse Events in all PrePex studies combined

Type of Event	Number		Per cent [95% CI]	
Number of circumcisions	2,417			
Serious AEs	**9**		**0.4%** [0.2%, 0.7%]	
Displacement (DISP)		4		0.2%
Premature removal (PREM)		1		0.0%
Difficult removal (DIFR)		1		0.0%
Injury (INJP)		1		0.0%
Wound disruption (WNDD)		2		0.1%
Other events		0		
Moderate AEs	**18**		**0.7%** [0.4%, 1.2%]	
Displacement (DISP)		2		0.1%
Bleeding (BLDD)		5		0.2%
Infection (INFD)		2		0.1%
Premature removal (PREM)		8		0.3%
Difficult removal (DIFR)		1		0.0%
Other events		0		
Mild AEs	**15**		**0.6%** [0.3%, 1.0%]	
Mild pain (PAIN)		2		0.1%
Oedema (OEDP)		9		0.4%
Burn blisters (BLIS)		3		0.1%
Abscess (INFD)		1		0.0%
Other events		0		

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ANNEX: MEETING AGENDA

Day 1: Tuesday 29 January 2013		
Time	**Topic**	**Presenter/Facilitator**
8:00–8:30	Registration	
8:30–9:15	**Opening** Welcome and introductions Objectives and expected outcomes, review of agenda Roles of members and observers, declaration of interests	**Rachel Baggaley** **Julia Samuelson**
09:15–10:30	**Session I: Brief updates** WHO guidance on use of devices for male circumcision Prequalification status of devices Discussion	**Chair: Tim Hargreave** **Julia Samuelson** **GabyVercauteren/** **Irena Prat**
10:30–11:00	Coffee Break	
11:00–12:30	**Session II: Technical updates** Recapitulation of research available on male circumcision devices for adolescents and adults Risk assessment of devices Clinical studies–is there a need to review requirements? Discussion	**Tim Farley** **Bill Potter** **Nicola Magrini**
12:30–13:30	Lunch Break	
13:30–15:30	**Session III: ShangRing** Detailed review of research findings Discussion	**Co-chair:Tim Hargreave** **Tim Farley**
15:30–16:00	Coffee Break	
16:00–18:00	Con't: review evidence Discussion	**Tim Farley**
18: 00	Reception (WHO D building cafeteria)	

Day 2: Wednesday, 30 January 2013		
Time	**Topic**	**Presenter/Facilitator**
9:00–10:30	**Session III: ShangRing (cont'd)** Conclusions	**Co-chair:Tim Hargreave** **Tim Farley**
10:30–11:00	Coffee Break	
11:00–13:00	**Session IV: PrePex** Detailed review of research findings Discussion	**Co-chair: Stephen Watya** **Tim Farley**
13:00–1400	Lunch	
14:00–15:30	Con't: Review evidence Discussion	**Tim Farley**
15:30–16:00	Coffee Break	
16:00–18:00	Discussion (cont'd)	

Day 3: Thursday, 31 January 2013		
Time	**Topic**	**Presenter/Facilitator**
9:00–10:30	**Session IV: PrePex (cont'd)** Conclusions	**Co-chair:Stephen Watya** **Tim Farley**
10:30–11:00	Coffee Break	
11:00–13:00	**Session V: Implications for WHO Guidance on use of devices** Highlights of Day 1 & 2 to address guidance on use of devices: operational and programmatic considerations, and recommendations Discussion	**Co-chair:Stephen Watya** **Doris Mugrditchian/** **Nicola Magrini**
1300–1400	Lunch	
14:00–15:30	**Session VI: Additional technical innovations and research priorities** Bridging studies and special safety studies Other male circumcision technologies including Gomco and glue Discussion	**Co-chair: Steve Watya** **Tim Hargreave**
15:30–16:00	Coffee Break	
16:00–18:00	**Closing** Next steps Closing	**Julia Samuelson** **Rachel Baggaley**

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