

FRAMEWORK FOR CLINICAL EVALUATION  
OF DEVICES FOR MALE CIRCUMCISION



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OF DEVICES FOR MALE CIRCUMCISION**

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## ABBREVIATIONS AND ACRONYMS

AE	adverse event
CFR	Code of Federal Regulations
EU	European Union
FDA	US Food and Drug Administration
GHTF	Global Harmonization Task Force
HIV	human immunodeficiency virus
HPV	human papillomavirus
HSV-2	herpes simplex virus-2
ISO	International Organization for Standardization
MDD	Medical Device Directive (European Union)
PMA	pre-market approval
SFDA	State Food and Drug Administration (People's Republic of China)
UNAIDS	Joint United Nations Programme on HIV/AIDS
VMMC	Voluntary medical male circumcision
WHO	World Health Organization

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## EXECUTIVE SUMMARY

Male circumcision has been shown to reduce the risk of heterosexually acquired HIV infection in men. The World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) recommend male circumcision as a priority intervention in countries and settings with a high incidence of HIV and a low prevalence of male circumcision.

Male circumcision devices have the potential to accelerate delivery of male circumcision programmes in resource-limited settings by reducing the time to perform the operation, by simplifying the procedure so that providers can perform it more easily and in some circumstances by making the procedure more acceptable to clients than a surgical approach. Devices are widely used for circumcision in infants and young boys, but experience in post-pubertal boys and adults is limited, particularly in the countries in the African region where rapid expansion of male circumcision programmes for HIV prevention is most urgent.

Regulations governing approval of medical devices require clinical evaluation but may only require limited clinical trials for devices that are used as aids to surgery or remain external to the body. This includes male circumcision devices. As male circumcision programmes for HIV prevention are a public health intervention and involve large numbers of healthy men, a more rigorous assessment of the clinical safety, efficacy, acceptability and cost-effectiveness of male circumcision devices is required. *The Framework for clinical evaluation of devices for male circumcision* is intended to be used by (a) product developers seeking to develop new male circumcision devices or to modify existing devices for use in adult male circumcision programmes in resource-limited settings; (b) clinicians involved in testing devices for acceptability and suitability for use in resource-limited settings, particularly by mid-level providers; (c) regulators responsible for overseeing the development, testing and evaluation of male circumcision devices; and (d) programme managers and sponsors supporting expansion of programmes for male circumcision to prevent HIV infection.

The framework focuses mainly on clinical requirements for assessing the suitability of a device for male circumcision within public health HIV prevention programmes in resource-limited settings and, secondarily, on regulatory and manufacturing considerations. A series of steps and clinical studies is described to evaluate the clinical performance, safety and acceptability of a new male circumcision device, as are the minimum sizes of these different studies. These studies include clinical studies in the country of origin or development, clinical studies in the countries or settings of intended final use (initial case series, comparative trials and acceptability studies) and field studies in settings of intended final use. The information generated by this research will form the basis of WHO decisions on the suitability of devices for use in male circumcision programmes in resource-limited settings. In addition, the framework describes bridging studies and special safety studies as well as initial implementation studies and monitoring as devices are introduced into programmes.



# 1. PURPOSE AND BACKGROUND

## 1.1 PURPOSE

The World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) recommend male circumcision as a priority intervention for the prevention of HIV in countries and settings with a high incidence of HIV and a low prevalence of male circumcision. Male circumcision devices, or other technologies, that make the procedure quicker, easier, more replicable, safer and more cost-effective may facilitate expansion of adult male circumcision programmes for HIV prevention. To support rapid scale-up of male circumcision services for HIV prevention, WHO and other health authorities seek to identify devices for male circumcision that:

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

### 1.1.1 Objective of this document

Research is required to assess the performance of male circumcision devices against these criteria. A uniform approach to this research should speed progress toward an adequate evidence base upon which decisions regarding new technologies can be taken. The objective of this document is to provide a framework for the clinical evaluation of devices for male circumcision. The framework defines the minimum extent of clinical data required for an assessment of the safety of devices when used by providers in settings of intended final use in male circumcision programmes for HIV prevention. It also defines the minimum criteria for bridging studies to extend recommended use to new populations and/or types of provider. Similar research and the minimum specified clinical data would also be required for assessment of the safety and suitability of other innovations to facilitate the male circumcision process, as well as for the assessment of new devices for use in paediatric and adolescent male circumcision in resource-limited settings.

This document was reviewed during a consultative meeting of interested parties from developed and developing countries in March 2009 in Nairobi, Kenya. The framework was disseminated for comment and then critically reviewed by the WHO Technical Advisory Group on Innovations in Male Circumcision and further revised based on that review.

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## 1.1.2 Target audiences

This document addresses:

- product developers seeking to develop new male circumcision devices or to modify or transfer existing devices for use in adult male circumcision programmes in resource-limited settings;
- clinicians involved in testing devices for acceptability and suitability for use in resource-limited settings, particularly by mid-level providers;
- regulators responsible for overseeing development, testing and evaluation of male circumcision devices; and
- programme managers and sponsors supporting the expansion of programmes for male circumcision to prevent HIV infection.

## 1.2 BACKGROUND

### 1.2.1 Male circumcision and prevention of HIV and other sexually transmitted infections

In March 2007 following release of compelling evidence from three randomized, controlled clinical trials, WHO and UNAIDS issued recommendations that male circumcision be considered as part of a comprehensive HIV prevention package (1). The clinical trials, conducted in Kenya, South Africa and Uganda, showed that male circumcision reduced the risk of heterosexually acquired HIV infection in men by about 60% (2-4). The clinical trial data were consistent with results from observational studies, which found, both at the population and individual levels, lower incidence and prevalence of HIV in circumcised men compared with those not circumcised.

Male circumcision does not provide complete protection from HIV infection and is therefore promoted as an *additional* (and not an alternative) strategy for the prevention of heterosexually acquired HIV infection in men. Other current interventions to prevent heterosexual transmission of HIV should continue, with male circumcision being considered part of a comprehensive HIV prevention package. All men opting for male circumcision and their sexual partners should be educated and encouraged to continue using other effective HIV prevention measures in combination with male circumcision.

Recently, results have been published from some of the above-mentioned male circumcision trials highlighting the additional role that male circumcision plays in the prevention of genital herpes simplex virus-2 (HSV-2) and human papillomavirus (HPV) infection in men. A meta-analysis of 21 studies, including two randomized controlled trials, found a robust inverse association between male circumcision and genital HPV prevalence in men (5). One trial, in Orange Farm, South Africa, demonstrated a 36% reduction in the prevalence of high-risk HPV in circumcised men (6). Another study, from the Uganda male circumcision trials, indicated that circumcised men had a 28% lower risk of HSV-2 acquisition and a 35% lower prevalence of high-risk HPV infection compared with uncircumcised men (7). These new results corroborate findings from previous observational studies and contribute to the mounting evidence of the benefits of male circumcision as a public health intervention for preventing sexually transmitted infections (STIs), including HIV, among men. Any direct long-term effects of male circumcision on women's sexual health are less well documented, but they include a reduced prevalence and incidence of high-risk HPV among female partners of circumcised men (8), a potentially lower incidence of HIV infection (observational study in Uganda (9) and the multi-country Partners in Prevention study (10)) and a lower incidence of bacterial vaginosis and severe bacterial vaginosis, *Trichomonas* infection and genital ulceration (randomized controlled trial in Uganda (11)). Indirect benefits to women following lower incidence and prevalence of HIV infection and other STIs in men in the community are predicted by epidemiological models (12) but have yet to be demonstrated in community studies.

### 1.2.2 Expansion of male circumcision programmes

Fourteen priority countries that have a high prevalence of HIV and a low prevalence of male circumcision are striving to scale-up voluntary medical male circumcision services for HIV prevention as an additional HIV prevention intervention (13). Epidemiological and economic modelling completed in 2011 determined that scale-up of voluntary medical male circumcision (VMMC) in appropriate settings constitutes a high-impact intervention with excellent value for the expenditure (14). Impact and costing estimates suggest that scaling up VMMC to reach 80% coverage among males 15–49 years old in the 14 priority countries in five years (by 2015) would entail performing about 20 million male circumcisions. An additional 8.4 million between 2016 and 2025 would be required to maintain the 80% coverage level. Such a scale-up would avert 3.4 million, or 22%, of new HIV infections through 2025. In addition, while the model shows that this scale-up would cost a total of US\$1.5 billion between 2011 and 2025, it would result in net savings (due to averted treatment and care costs) amounting to US\$16.5 billion.

While rapid programme expansion will have the greatest public health impact and provide the largest cost-savings, quality must be assured as countries scale up. Male circumcision procedures must be safe, performed under proper conditions and conform to all ethical and human rights guidelines and standards.

Furthermore, in the introduction and expansion of male circumcision programmes, socio-cultural issues have to be considered. Differences between and within countries will emerge, depending on male circumcision traditions and practices in the particular settings. There are a wide range of religious and cultural practices surrounding male circumcision. The majority of male circumcisions worldwide are performed for religious or cultural reasons, with smaller numbers performed for medical reasons. High rates of complications are associated with traditional male circumcision practices, and pain is associated with male circumcision performed without local anaesthesia (15). While this framework focuses on devices to be used to facilitate *medical* male circumcision through the formal health sector, consideration should be given to the development and evaluation of devices or surgical aids to make traditional circumcision safer in areas where this practice is common.

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### 1.2.3 Male circumcision procedures

Adult and adolescent male circumcision is most commonly performed using one of three surgical methods: dorsal slit, forceps-guided method or sleeve resection. All these methods have been used in low-resource settings, according to preference or training. All require a certain level of surgical skill. The latter two methods have been standardized and successfully used in the three randomized controlled trials of adult male circumcision—the forceps-guided method in Kenya (3) and South Africa (2); sleeve resection method in Uganda (4).

Each approach has advantages and disadvantages. For example, the sleeve resection method produces a good cosmetic result but requires higher-level surgical skill and may take longer to perform. The forceps-guided method may be the most suitable surgical approach for the training of mid-level providers in low resource settings, but the amount of foreskin removed is not standardized and may vary from surgeon to surgeon. In addition, there is potential for injury to the glans. All these methods require suturing for haemostasis and wound closure, although haemostasis can also be achieved with electrocautery where the availability of equipment in facilities and training permit.

Adult and adolescent male circumcision is more complex to perform than early infant male circumcision. Experienced health workers can perform infant male circumcision quickly and safely, especially with the aid of various devices that have been well studied, including in randomized, controlled trials (16). Early infant male circumcision, as performed with various devices, usually does not require any suturing. One surgical method (the dorsal slit) and three devices (the Plastibell, the Mogen Clamp and the Gomco clamp) were described in the WHO guidance on early infant male circumcision (17) on the basis of well-documented clinical experience with these methods in different regions of the world. Several other devices have been used for infant male circumcision, but their safety and performance have not been well documented.

In contrast to infant male circumcision, the currently recommended techniques for adult male circumcision require suturing for haemostasis and wound closure and thus are technically more difficult, take longer to perform, and have higher complication rates than those seen with infant male circumcision (18).

Little clinical experience with devices for male circumcision of adults currently exists. Since voluntary medical male circumcision for HIV prevention is a public health intervention performed on healthy men, evaluation of potential devices for male circumcision requires scrutiny beyond that typically required by standard medical device regulations, specifically with respect to clinical evidence of safety. Therefore, this framework focuses on the evaluation of male circumcision devices to be used post-puberty, in adolescent and adult male circumcision (referred to as “adult” male circumcision in this document).

## 1.2.4 Structure of document

Chapter 1 has provided an introduction and background to male circumcision for HIV prevention and male circumcision procedures,

Chapter 2 discusses the characteristics of male circumcision devices for use on adult men in resource-limited settings and the evaluation criteria.

Chapter 3 reviews medical device regulations in developed and developing countries that are relevant to the evaluation of male circumcision devices for use in public health HIV prevention programmes. In addition to meeting the regulatory requirements for device evaluation, a male circumcision device must be evaluated for acceptability to clients, providers, female partners of clients and parents of male adolescents and for clinical performance and safety in the country and setting of intended final use.

Chapter 4 describes a minimum series of steps and clinical studies to be completed that will determine whether a device is suitable for use in adult voluntary medical male circumcision programmes in resource-limited settings. Chapter 4 also describes bridging studies to extend the use of devices to populations beyond those included in the initial evaluation and safety studies in patients with specific clinical conditions.

Chapter 5 summarizes key elements of the WHO process for prequalification of male circumcision devices and issues related to manufacturing to ensure a sustainable supply of high-quality devices for use in male circumcision programmes for HIV prevention in resource-limited settings. It also discusses issues related to intellectual property, preferential pricing in the public sector in developing countries, and marketing, distribution and safety monitoring of devices.

Chapter 6 highlights supply and marketing issues including pricing and post-marketing surveillance in the context of public health programmes.

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## 2. EVALUATION OF ADULT MALE CIRCUMCISION DEVICES

Various devices have been widely used for circumcision in infants and young boys. Infant devices are usually multiple-use metal instruments that achieve haemostasis by crushing the tissue. They produce an even circumcision wound. Suturing is rarely necessary. An alternative, widely used infant device made of plastic stays in place for about a week; haemostasis is obtained by a compressive ligature. For older pre-pubertal or early adolescent boys, a number of clamp devices are used. These devices must stay on for about a week. The foreskin may be removed when the device is placed or, in some cases, when the device is taken off one week later.

There is much less experience with devices for adults. The surgical requirement is the same for all ages—adequate removal of foreskin, safe haemostasis, and a neat cosmetically acceptable wound with minimal pain or discomfort. The particular problem with adult male circumcision is ensuring haemostasis, because the blood supply is more developed. Also, if post-procedure penile erections occur, wound healing may be disturbed.

For adult male circumcision, devices that can be used by mid-level providers, reduce the time required per circumcision, require no suturing and/or allow faster wound healing with a good cosmetic finish are of particular value. Devices are quite commonly used for male circumcision of young boys in the Asian region, but there is limited evidence on their use for adult male circumcision. A number of existing male circumcision devices could be studied for use in adults, but there are currently few high-quality published clinical data to support their use. If a device is to be used in a different population or age group, it is necessary to carefully evaluate acceptability, safety and effectiveness (that is, effectiveness in ensuring a neat, full circumcision, as opposed to effectiveness for HIV prevention, which has already been clearly demonstrated).

Considerations for improving or facilitating use and development of adult male circumcision devices include:

- Existing devices have the advantage of being already available, with accessible clinical data to support their safety and effectiveness, although data may not always apply to the relevant age or population groups (i.e. adolescent and adult males).
- New devices would entail de novo development or the modification of existing devices. This may be time-consuming and may entail unforeseen costs.
- Aids to improve or facilitate standard surgical methods include existing materials (such as haemostatic gauze and surgical glue) and new techniques. These would require clinical evaluation and collection of data similar to the scheme for the evaluation of devices (see below).

The essential requirements for an adult male circumcision device in low-resource settings should take into consideration aspects relevant to several groups: (a) male circumcision providers (safety during handling, reproducibility and consistency of the final result, simplicity or ease of training and use, practicality and safety of cleaning and sterilization if the device is intended for multiple uses); (b) clients (acceptability during the procedure and post-operatively, minimal pain, good cosmetic final result, rapid healing and minimal complications); (c) suppliers (safety features, costs, shelf-life, sterilization); and (d) policy-makers (ease of training providers, ease of deployment and supply chain management, cost, cost-effectiveness and regulatory issues). Table 1 presents criteria for selecting devices for evaluation and assessment in countries wishing to expand adult male circumcision programmes for HIV prevention. These criteria have been adapted from those proposed in 2008 by Walsh and Gola (19), who performed an initial review of male circumcision devices.

**Table 1. Device characteristics and evaluation criteria for assessing male circumcision devices**

CHARACTERISTIC	EVALUATION CRITERIA
<p><b>1. SAFETY OF DEVICE</b></p> <ul style="list-style-type: none"> <li>▪ safe to use</li> <li>▪ reduces the chance of injury to the glans (compared with standard surgical technique)</li> <li>▪ consistent removal of an adequate amount of foreskin</li> <li>▪ protects the urethra</li> <li>▪ instructions for use of the device and its procedure include provision for dealing with a short frenulum</li> <li>▪ better haemostasis than with standard surgical technique</li> <li>▪ rapid, uncomplicated post-operative recovery period.</li> </ul>	<ul style="list-style-type: none"> <li>▪ equivalent to or safer than conventional surgical methods (similar or lower adverse event (AE) rates)</li> <li>▪ Data and Safety Monitoring Board independent from the manufacturer or sponsor to review safety data during trials of the device</li> <li>▪ good clinical profile of the device (published or unpublished data) among men or boys in the target age group or in other age groups</li> <li>▪ whether and how the device ensures haemostasis and prevents blood loss</li> <li>▪ whether the device protects the glans from any cutting or injury</li> <li>▪ requires minimal post-operative care</li> <li>▪ minimizes cross-infection by preventing reuse of non-sterile material (ideally, device should be disposable and should auto-destruct, but, if reusable, device should be easily cleaned and sterilized)</li> <li>▪ features to prevent reuse of single-use devices..</li> </ul>
<p><b>2A. CLIENT ACCEPTABILITY</b></p> <ul style="list-style-type: none"> <li>▪ to the client</li> <li>▪ to the sexual partner</li> <li>▪ to caregivers of male adolescents</li> <li>▪ to parents of baby</li> </ul>	<ul style="list-style-type: none"> <li>▪ minimal pain or discomfort while device in situ</li> <li>▪ quick resumption of daily activities</li> <li>▪ minimal length of time device in situ</li> <li>▪ acceptable cosmetic finish</li> <li>▪ minimal or no requirement for post-operative visits.</li> </ul>
<p><b>2B. PROVIDER ACCEPTABILITY</b></p>	<ul style="list-style-type: none"> <li>▪ ease of storage</li> <li>▪ reliability of distribution systems</li> <li>▪ ease of use and removal</li> <li>▪ provides reproducible results</li> <li>▪ ease of training.</li> </ul>

**Table 1. continued**

<b>CHARACTERISTIC</b>	<b>EVALUATION CRITERIA</b>
<p><b>3. EASE OF USE</b></p> <ul style="list-style-type: none"> <li>▪ device used easily by the provider</li> <li>▪ short procedure time</li> <li>▪ training completed effectively and easily</li> <li>▪ easy and practical removal</li> <li>▪ suitable for use by mid-level providers.</li> </ul>	<ul style="list-style-type: none"> <li>▪ minimum kit requirements: kit should be simple, with as few components as possible</li> <li>▪ simple to manipulate and use, thus minimizing opportunities for mistakes and injuries to the client during the procedure</li> <li>▪ does not require high-level medical training or advanced surgical skills, but rather can be used by specifically trained mid-level providers</li> <li>▪ simple removal: consideration should be given to the safety and practicality of removal at other health facilities and removal of the device by the client</li> <li>▪ clear disposal instructions</li> <li>▪ clear labelling to reduce chance of using wrong-sized device or other misuse of the device.</li> </ul>
<p><b>4. LOW COST/AFFORDABLE PRICE</b></p> <ul style="list-style-type: none"> <li>▪ cost advantage over conventional surgical methods</li> </ul>	<ul style="list-style-type: none"> <li>▪ does not require expensive infrastructure</li> <li>▪ requires a minimal amount of other consumables</li> <li>▪ single-use device has features to prevent reuse</li> <li>▪ multiple-use device is easy to clean and sterilize; must withstand many reuses</li> <li>▪ reduced provider time for procedure</li> <li>▪ efficient packaging, shipping and storage system</li> <li>▪ reasonable cost for a public health good.</li> </ul>
<p><b>5. REGULATORY AND MARKETING</b></p> <ul style="list-style-type: none"> <li>▪ approved in country of origin</li> <li>▪ marketed in country of origin</li> </ul>	<ul style="list-style-type: none"> <li>▪ high-quality clinical data to support its safety and effectiveness available</li> <li>▪ marketed and preferably used in an age group relevant for the country of intended use</li> </ul>



### 3. REGULATORY ISSUES IN THE DEVELOPMENT, TESTING AND REGISTRATION OF DEVICES

Regulations are developed and enforced to ensure the safety and effectiveness of a medical device designed for a specific procedure or purpose. It is important to note that all devices carry some risk and regulations alone cannot eliminate risk. Regulations consider the safety of a medical device throughout its lifespan, as gauged by a risk assessment of each phase (from design and development, manufacture to use to removal and ultimate disposal) that estimates the potential of the device to cause an adverse event (AE) (20).

The regulation of medical devices varies greatly among countries. In general, however, obtaining regulatory approval is much easier for devices than for drugs. In some countries there is no specific mechanism for approval of medical devices, and devices can be imported without any regulatory review. However, since adult male circumcision is a public health intervention for disease prevention and not a means to cure individual ill health, safety criteria when introducing adult male circumcision devices into male circumcision programmes for HIV prevention should be more stringent than current regulations on importation or approval for use of other medical devices in resource-limited countries.

For illustrative purposes a brief summary of the regulatory status of male circumcision devices in the United States of America (USA), Europe and China is provided below. More details are given on the relevant agencies' web sites (21-23).

In the USA the Food and Drug Administration (FDA) divides medical devices into three main classes. Class I has the fewest restrictions, while Class III is the most stringent. Male circumcision devices are considered Class II medical devices, with a device code "HFX" (circumcision clamp), and are cleared to market through a Premarket Notification, or 510(k), submission, generally without clinical data, although clinical data can be submitted if the manufacturer so desires. A number of different devices for male circumcision have been cleared to market in the USA in recent years.

US pre-market controls are specific to the device and classification. The controls can include clearance to market by either: (1) submitting the Premarket Notification, also known as a 510(k), for devices that are claimed to be "substantially equivalent" to an already approved product or (2) obtaining an approval to market through a Premarket Approval (PMA) for new devices or novel mechanisms of action. Manufacturers of medical devices must comply with premarket notification 510(k) requirements in accordance with 21 CFR 807 Subpart E as well as with the medical device general controls provisions of the Federal Food, Drug, and Cosmetic Act. The general controls provisions of this Act include requirements for registration and device listing (21 CFR 807 Subparts B & C), labelling (21 CFR 801) and good manufacturing practice requirements as set forth in the Quality System Regulation (21 CFR 820). Premarket Notification (510(k)) requires that descriptive data, and, when necessary, performance data be submitted to establish that the device is substantially equivalent to the predicate device (that is, the device for which equivalence is claimed). In contrast, a PMA application requires demonstration of reasonable safety and effectiveness. Clinical studies have to be conducted to support a PMA. Clinical evaluations must have an approved investigational device exemption (IDE) before the study is initiated.

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In the European Union, per the European Union Medical Device Directive (MDD) 93/42/EEC, medical devices are divided into four classes—Classes I, IIa, IIb and III. As in the US system, the stringency of the controls for oversight increases in each successive class, with Class III being most stringent. In the European community male circumcision devices are considered Class IIa or Class IIb devices. Rules for the classifications are derived from assessments of the following criteria: duration of contact with the patient, the degree of invasiveness and the anatomy affected by the use of the device. As in the USA the level of control is proportionate to the level of risk to patients. All medical devices are required to meet the Essential Requirements of the MDD and to comply with the “Conformité Européenne” (CE) marking requirements of the MDD, which means that the manufacturer satisfies the requirements essential for the product to be considered safe for its intended purpose, regardless of the classification.

In China the regulatory framework is governed by the State Food and Drug Administration (SFDA), which takes on the same tasks as the US FDA. The SFDA classification system has three classes. Devices in Classes I and II can be registered by provincial governments, while Class III devices are of high risk and are regulated at the national level by the SFDA. Male circumcision devices are considered Class II devices, which can be registered at the provincial level without clinical data.

For most of the African countries in the sub-Saharan region, regulations regarding medical devices in general are at their early stages of development. The process for marketing and use of such devices currently involves obtaining permission to import, either through the national regulatory body or the Ministry of Health. For South Africa, Zimbabwe and Zambia, although medical device regulations are not yet in full force, draft forms of the regulations are under development. The current approval process requires submitting a summary of the device, including manufacturing details, in order to obtain permission to import from the Medicines Control Council in South Africa, the Medicines Control Authority in Zimbabwe or the Pharmacy and Poisons Board in Zambia.

It is important for any country to review the following both before a device is registered for use and during the use of the device in the country:

- device registration status in the country of manufacture
- manufacturing standards and marketing of the device in the country of manufacture
- clinical profile of the device (published or unpublished data)
- known AEs, warnings or “recalls” in countries where the device is marketed
- systems required to monitor use of the device in the country.

Special consideration should be given if a device appears promising but is not registered in the country of origin or manufacture or by a recognized national regulatory body with international standing, such as the US FDA or a Notified Body in the European Union. In such a case it should be permissible to initiate research and clinical testing in the country of intended use concurrently with the completion of the registration process in the country of origin. In other words, registration in the country of origin may be required for marketing and use but not necessarily for research. An exception would be if there is no process or body for registration in the country of origin. Such cases could justify initiation of research in the country of intended use without full or adequate registration in the country of origin.

Additional special cases include the need for device modification in the country of intended use that is not needed in the country of origin (for example, change in the device due to variation in the thickness of the foreskin in different population groups). Such modified devices may not be registered in the country of origin. However, it would be appropriate to test and eventually register them in the country of intended use.

International sources of reference for regulatory considerations are the documents and other resources of the International Organization for Standardization (ISO) and the Global Harmonization Task Force (GHTF), which provide an international set of standards and regulatory guidelines developed to facilitate technology transfer and minimize regulatory barriers between countries. Standards are made specific to a particular product, material or service. Medical devices are covered in ISO 13485: 2003, which lays out quality management systems for the manufacture of medical devices. The emphasis of this standard is on patient safety, effectiveness, performance and quality of devices as well as information exchange. While countries maintain their own medical device regulatory systems and standards, countries at the early stages of developing medical device regulation can refer to and use ISO and GHTF resources to learn from established systems.

In 2011 WHO established a programme for prequalification of male circumcision devices, which aims to promote and facilitate access to safe, appropriate and affordable male circumcision devices of good quality in an equitable manner (24). The programme undertakes a comprehensive assessment of submitted products through a standardized procedure based on WHO prequalification requirements for medicines and diagnostics. This includes review of the application form and product dossier including clinical evidence of safety, and inspection of the manufacturing site(s). The application form provides summary information about the device and the manufacturer. The procedures and processes are described in further detail in Chapter 5.

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## 4. CLINICAL ISSUES IN DEVELOPMENT AND EVALUATION OF MALE CIRCUMCISION DEVICES

### 4.1 DEMONSTRATING SAFETY AND EFFECTIVENESS

While regulatory agencies in most countries may not require the submission of clinical data for approval of male circumcision devices, clinical data are necessary in order for WHO to assess the safety and effectiveness of male circumcision devices and to make prequalification decisions and recommendations on their use in programmes offering male circumcision for HIV prevention. Regulatory requirements to introduce new male circumcision devices to the market or to make improvements to existing devices in a specific country do not necessarily require information in support of clinical performance and utility. This information may address aspects such as whether the device would be acceptable to providers and clients, increase the rate at which male circumcisions could be performed in country programmes, result in net cost savings or be a cost-effective addition to a public health male circumcision programme. Such additional information is critical to making recommendations and national policy decisions on the role of devices for expansion of male circumcision services as a public health intervention and for sustaining those services in the long term.

In order to establish the clinical profile of a device, all relevant clinical data (published and unpublished) must be systematically compiled and assessed for quality. The following types and progression of studies must be available before WHO will assess a male circumcision device for general use in HIV prevention programmes in low-resource settings:

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

If clinical data on a device are available only for the country of origin, these need to be compiled and their relevance to the settings and populations of intended final use established. In any case, however, it is important that the safety, effectiveness and acceptability of the device are supported by clinical data generated in the country and setting of intended final use. Note that effectiveness in this context refers to ensuring a neat, full circumcision and not to the effectiveness of male circumcision in reducing the risk of HIV infection, which has been established in randomized controlled trials. The rationale for and issues to be considered in designing and implementing relevant studies are discussed below. The body of evidence and experience so generated will inform guidelines, recommendations and decisions on the use of the device(s) in programmes in resource-limited settings that offer adult male circumcision for HIV prevention and the prequalification of specific devices that have been formally assessed by WHO.

## 4.2 CLINICAL STUDIES IN THE COUNTRY OF ORIGIN

For WHO purposes, a study in the country of origin or manufacture, where surgeons are experienced with use of the device, should provide the best initial data on the device's clinical profile (clinical performance) and potential benefits (clinical utility). A manufacturer may have already performed such a study, although data from sources independent of the manufacturer would carry greater weight, unless it can be documented that the data are of high quality and comprehensive. A review of clinical AEs and device-related incidents, together with the related actions taken by the manufacturer, also should be available.

A new study will require a well-defined protocol for use of the device and selection of suitable clients (or exclusion of unsuitable clients), with well-documented outcomes, including cases in which the device procedures were started but not successfully completed. Where possible, the study participants should be representative of those in whom the device would eventually be used. The protocol should have defined stopping rules for high rates of serious adverse events. An initial study could be a case series using phased recruitment, with the first 5–10 clients followed through to study completion before new clients are enrolled. For this type of study, a small sample size of 25 to 100 clients would be adequate to provide information on the performance of the device. The primary end-point would be safety—clinical adverse events and device-related incidents—recognizing that rare complications will not be detected in such a limited study. The study also would provide preliminary information on the acceptability of the device to clients and providers. Selected secondary end-points, such as technical difficulty and complications with the procedure, cosmetic results and healing process, should be documented by digital photos preferably taken in a systematic manner of all clients. Ideally, photographs should present two views (dorsal and ventral sides of the penis) and be assessed by an independent reviewer who is not aware of the method used for circumcision. However, masking the method of male circumcision may be difficult.

For devices that are aids to surgery and do not stay on the penis after completion of the male circumcision procedure, study sizes at the lower end of the 25–100 range may be sufficient. Regulatory authorities might consider some devices that are used only during surgery to be Class I rather than Class II devices. Devices that remain on the penis for an extended period require more rigorous evaluation, including assessment of the timing, ease and duration of the removal procedure. Additionally, a device that is intended to be left on the penis until it falls off through necrosis will require an assessment of the time until spontaneous detachment.

Since data from the randomized controlled trial of male circumcision in HIV-positive men in Uganda suggest that the immediate post-operative period may be a time of high risk for HIV transmission from infected men to their uninfected partners (25), documenting the time course of wound healing after adult male circumcision deserves special attention. There may also be a period of high vulnerability to HIV acquisition in the immediate post-operative period due to the presence of a healing wound in newly circumcised uninfected men. While it may be challenging to operationalize measurements of the healing process and the time to complete healing, it is important to use objective criteria. Carefully documenting the healing process probably requires follow-up visits at weekly intervals in order to be able to compute estimates of the time to complete healing.

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Follow-up should be intensive and preferably include a post-operative visit about two days after the procedure and then weekly for at least six weeks or until wound healing (epithelium covering the entire wound) is documented, whichever is later. For devices that remain in place for an extended period, a follow-up visit should be considered at about two days after removal of the device in addition to two days after placement. Such intensive follow-up is essential in the early phases of research. The frequency may be reduced as more experience with the healing and removal processes accumulates and when a low rate of any adverse events has been documented.

Ideally, a second, larger study would compare the device with one or more of the current WHO-recommended conventional male circumcision surgical techniques, i.e. forceps-guided, sleeve resection or dorsal slit. While a randomized, controlled trial would be preferable, such a trial requires standardization of both study arms, in particular the standard surgical arm, even if randomization is not possible. This may be problematic if surgeons already have a preference for, and extensive experience with, the device being studied. A non-comparative study or a comparison with a well-documented historical case series using a conventional surgical approach could be considered, depending on the nature of the device and the location of the trial. The trial should be conducted to international standards and provide well-documented outcome data.

One challenge in performing a comparative study in the country of origin may be the need to establish a well-documented standard procedure for the comparison group. A non-comparative trial might be easier and quicker to implement in the country of origin, especially if the device is already marketed and/or if the developer has already obtained regulatory approval of the device.

Clinical parameters for study of a male circumcision device should clearly define the surgical techniques being used, preferably documented by video or photographs. If a comparative study is done, an unbalanced design, e.g. two-to-one randomization, could be considered, with more cases using the novel device, depending on various considerations such as anticipated speed of recruitment and the relative acceptability of the two methods among surgeons or clients. In addition to clinical adverse events and device-related incidents, the primary end-point would be the duration of the procedure, which would include the operative time plus, for devices that remain on the penis, the removal time. Secondary end-points are listed in Table 2. To enable comparability with other studies, the definitions of end-points should be similar to those used in other recent trials, such as the three randomized, controlled trials that established the protective efficacy of male circumcision (2,3,4) or other rigorous studies assessing devices with clear definitions for AEs.

While the suggested numbers of clients circumcised with the new device in the studies are too small to assess rare events and outcomes, such numbers will provide sufficient information to justify further clinical evaluation. It is not appropriate to expose large numbers of men to a new device until safety and clinical performance has first been established in a limited number of men.

**Table 2. Types of studies and information on male circumcision device from country of origin**

TYPE OF STUDY	SAMPLE SIZE (RANGE) <sup>#</sup>	END-POINTS OR ISSUES	NOTES AND COMMENTS
Case series (non-comparative study)	50 (25–100)	Primary end-points <ul style="list-style-type: none"> <li>▪ clinical adverse events</li> <li>▪ device-related incidents</li> </ul> Secondary end-points <ul style="list-style-type: none"> <li>▪ technical difficulty and complications during procedure and removal processes*</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>	Conduct with appropriate attention to data quality and integrity. Define stopping rules for serious adverse events. Phase recruitment. Follow up closely for a minimum of six weeks.
Comparative study	~100 (50–300)	Primary end-points <ul style="list-style-type: none"> <li>▪ operative and removal times</li> <li>▪ clinical adverse events</li> <li>▪ device-related incidents</li> </ul> Secondary end-points <ul style="list-style-type: none"> <li>▪ difficulties and complications during procedure and removal processes*</li> <li>▪ pain assessment at key time points (using e.g. visual analogue scale)</li> <li>▪ client 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 a larger case series with historical comparison group. Comparison should be a well-established and documented circumcision procedure. Could consider unbalanced randomization, e.g. 2:1, to accumulate more data on new device. Follow up for a minimum of six weeks or until epithelium covers the entire wound.

\* Requires documentation by photographs

# Number of clients circumcised with the new device

### 4.3 CLINICAL STUDIES IN THE SETTING OF INTENDED FINAL USE

Following documentation on the clinical performance of the device in the country of origin or manufacture, it is important to progressively accrue clinical experience and data in the country or setting of intended final use. In addition to the safety and the performance of the device, the time required to train providers and the ease of training should be documented. It is important to note that the client population may be very different from the types of client in the country of origin, particularly with respect to age, motivation, clinical indications for circumcision, and social environment. These differences could lead to new and unexpected difficulties with the device that investigators must be able to identify.

The types of study and key elements are summarized in Table 3. Concern for rapid progress through the different stages of clinical evaluation must be balanced against the importance of step-by-step progression from assessment under well-controlled conditions in the hands of experienced providers with backup in case of problems to eventual general use in the target population by providers in resource-limited settings with little access to additional support. Not all steps and studies need be completed in every country where a new device might be used; the main issue is whether the populations studied in the assessment of safety, effectiveness and acceptability are relevant to the intended final client population. This would be determined in each country by the public health authorities on the basis of available data.

**Table 3. Clinical trials in settings of intended final use**

TYPE OF STUDY	SAMPLE SIZE (RANGE)#	END-POINTS	NOTES AND COMMENTS
Case series (non-comparative study)	50 (25–100)	Primary end-points <ul style="list-style-type: none"> <li>▪ clinical adverse events</li> <li>▪ device-related incidents</li> </ul> Secondary end-points <ul style="list-style-type: none"> <li>▪ technical difficulty and complications during procedure and removal processes*</li> <li>▪ pain assessment at key time points</li> <li>▪ client 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 and independence from the manufacturer or developer. Define stopping rules for serious adverse events, including independent review by, for example, an independent Data Monitoring Committee. Phase recruitment. Follow up closely for a minimum of six weeks and then weekly to complete healing (epithelium covering entire wound). Document ease of training new providers and time required to achieve adequate competence with the new device and procedure. Collate data on reasons to decline participation as indirect measure of acceptability.
Comparative trial	~100 (50–300)	Primary end-points <ul style="list-style-type: none"> <li>▪ operative and removal times</li> </ul> Secondary end-points <ul style="list-style-type: none"> <li>▪ technical difficulty and complications during procedure and removal processes*</li> <li>▪ pain assessment at key time points</li> <li>▪ clinical adverse events</li> <li>▪ device-related incidents</li> <li>▪ client satisfaction</li> <li>▪ cosmetic results*</li> <li>▪ healing process*</li> <li>▪ time to complete healing</li> </ul>	Conduct randomized, controlled trial comparing new device with a standard surgical procedure as defined in <i>WHO 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. Define 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. Documentation of ease and duration of training. Follow up for a minimum of six weeks after device removal, but follow-up can be less intensive than in previous study since more clinical experience is 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>	Incorporate assessment of acceptability 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. Also assess acceptability to partners of clients and to parents of any minors undergoing circumcision.

\* Requires documentation by photographs

# Number of clients circumcised with the new device



### 4.3.1 Case series

The first study should be a non-comparative series of clients to collect preliminary information on the ease of use and performance of the device in the new population and setting. Enrolment should be phased, with completion of an initial small cohort of men to wound healing (or at least device removal, for devices that remain in place for several days or weeks after initial placement) before enrolling the next cohort of men. As experience accumulates with the device, enrolment of new clients while others are still under follow-up would be acceptable, provided that it is sanctioned by an independent group of experts overseeing the study, such as a formal Data and Safety Monitoring Board (DSMB). It is important to systematically collect data on all procedure starts and outcomes with the new device, even if it is decided to abandon the device and/or complete the circumcision with a conventional surgical approach.

In the initial case series and small proof-of-concept studies, it is best to start with clients who meet very stringent medical criteria. Clients with self-reported bleeding disorders or any potentially complicating medical condition (e.g. jaundice, diabetes) or observed abnormalities of the penis should be excluded from the initial clinical studies and referred to hospitals or clinics for conventional surgical male circumcision.

Also, it is important to collect information on refusals to participate in the study. Special consideration must be given to management of participants who do not return for post-operative visits, particularly with devices that require removal. Investigators should make all possible efforts to follow every single participant enrolled in the study until planned completion of follow-up.

Care should be taken to ensure that clients enrolled in the first studies of the device are known to be free of HIV infection. Since male circumcision services are being expanded as an HIV prevention intervention, uninfected men are the primary target population. However, when a device is used in programmes, it may be used in men of unknown HIV status or in men with established HIV infection, even if not specifically intended for such groups. It is important at some later point to establish safety among men with HIV infection, but safety and effectiveness should first be established in men known to be free of HIV.

### 4.3.2 Comparative studies

After successful completion of the first clinical studies, a formal trial comparing the device with one of the established conventional surgical male circumcision methods should be conducted by providers experienced with both methods. Only surgeons who are skilled in the standard surgical method and have successfully performed a minimum of five procedures with the device under study should be involved in such a comparative trial. While “skilled surgeon” is difficult to define, it is suggested that only surgeons who have successfully performed at least 200 standard surgical male circumcision procedures be involved in the trial, as adverse event rates in the randomized, controlled trial in Kenya of circumcision with the forceps-guided method were significantly lower after the first 200 procedures (18).

While the incidence of adverse events and device-related incidents is important in the assessment of the devices, other outcomes should be considered primary end-points and drive the sample size requirements. Studies involving about 100 men (range 50–300) circumcised with the new device are suggested as a compromise between assessing safety, documenting the presumed advantages of the new method, and ensuring rapid progress through the different stages of clinical assessment.

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The exact choice of end-points will be determined by the expected advantages of the new device over conventional surgery, but the total operation time is likely one key measurement by which to compare the approaches. Total operating time must be separated into the various stages of the male circumcision procedure—preparation, anaesthesia, “skin-to-skin” operation time (from first touch to final wound closure) and removal time. Objective methods for measuring times—for example, from a video recording of the procedure—should be used where possible. At a minimum, to ensure unbiased assessment, the procedure times should be assessed, using clear standardized definitions, by an observer who is not a member of the team performing the male circumcision.

Follow-up of all clients should be for a minimum of six weeks after the device is removed, and then continue weekly until healing (epithelium covering the entire wound) is documented. In general, follow-up can be less intensive than in the previous study since more clinical experience is available.

Studies to demonstrate differences in adverse event rates between the new device and conventional surgery would require sample sizes of 800–1500 clients, as the incidence of AEs in clinical environments with properly trained and equipped providers is low. Studies of such size are neither realistic nor appropriate, particularly since they would need to be conducted by providers who were skilled in both methods of male circumcision. The purpose of developing and assessing new devices is to allow providers not necessarily skilled in conventional surgery to perform circumcisions with a device. Therefore, once the device is shown to be safe and effective, the more relevant testing pathway is to establish that the device performs well and offers a number of advantages in the hands of skilled mid-level providers. Then clinical evaluation should proceed to populations of intended final use with trained mid-level providers and careful monitoring for rare adverse events.

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

### 4.3.3 Acceptability studies

In addition to the safety and performance of the device, an important consideration is the acceptability of the device—during the placement and removal procedures, during the period that the device remains in situ, during healing and regarding cosmetic result. Assessments should gauge acceptability not only for the client, but also for his sexual partner and (in case of adolescent boys) for caregivers as well as for the provider. This information could be collected from a subset of participants included in the clinical studies, recognizing that this is a small non-randomly selected sample that may not represent the population at large. An indirect measure of acceptability is the acceptance rate among volunteers approached to participate in the studies; however, this also is a non-randomly selected sample that may not represent the general population. An understanding of reason(s) for refusal, comfort with the device in situ, attitudes of family and/or partners and satisfaction with the final cosmetic result will inform eventual decisions on programme design, communication, and selection of suitable client populations where the device could be used.

#### 4.3.4 Field studies

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

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

After completion of a pilot field study, a larger sample size should be chosen in order to evaluate carefully the safety profile of the device in the context of routine use. Follow-up would be less intense, with follow-up visits less frequent but on a schedule appropriate to the anticipated clinical schedule of the device, and with detailed data collected on adverse events, especially any unexpected or serious adverse events. It is important to systematically collect 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 becomes available on the incidence and types of adverse events, it may be appropriate to reduce the intensity of follow-up of each client and increase the interval between formal safety reviews.

The benefits, costs and risks of the new procedure, compared with conventional surgery, need to be supported by quality data and assessed against objective criteria. Additionally, acceptability of the device for the provider, the client, his female partner (and in the case of adolescent boys, parents or guardian) should be evaluated, possibly with a subset of participants.

**Table 4. Field studies: pilot and cohort studies in settings of intended final use**

TYPE OF STUDY	SAMPLE SIZE (RANGE)	END-POINTS	NOTES AND COMMENTS
Pilot field study	100 (50–200)	Primary end-points <ul style="list-style-type: none"> <li>▪ provider training needs</li> <li>▪ provider acceptability</li> </ul> Secondary end-points <ul style="list-style-type: none"> <li>▪ adverse events (AEs) and device-related incidents among all men in whom the device procedure was planned or started, even if subsequently abandoned</li> <li>▪ procedure and removal times</li> </ul>	To determine training and support needs, train at least 10 providers. Ensure good data quality and integrity, including recording outcomes on all procedure starts. Collate data on reasons for declining participation in the study, as an indirect measure of acceptability. This may be a run-in phase to the cohort field study.
Cohort field study	~500 (250–1000)	Primary end-points <ul style="list-style-type: none"> <li>▪ procedure and removal times</li> </ul> Secondary end-points <ul style="list-style-type: none"> <li>▪ training needs of providers</li> <li>▪ safety of procedure and removal</li> <li>▪ clinical adverse events and device-related incidents among all men in whom the device procedure was planned or started, even if subsequently abandoned.</li> <li>▪ practicality of device use (i.e. need to return to clinic for removal)</li> </ul>	Systematic review of clinical AEs and device-related incidents after every 100 procedure starts; interval between reviews can be increased as experience with method grows. Ensure mechanisms in place to capture information on all AEs, even if men are not followed systematically to complete wound healing. Monitoring of outcomes, especially AEs and losses to follow-up, is important. Collate data to compare costs of: the device training to use device compared with cost of training in standard surgical method provider's time staff time for follow-up visits equipment and supplies needed for placement and removal. Collate data on reasons for declining participation in the study, as indirect measure of acceptability. Include assessments of acceptability among subset of clients, their partners and, for adolescents, their parents, with respect to device placement, wearing the device and device removal.

#### 4.4 MINIMUM CLINICAL STUDIES FOR REVIEW OF SAFETY AND EFFECTIVENESS

The types and extent of clinical studies defined in this framework form a progressive series of steps that should lead to timely generation of data on the safety, efficacy and acceptability of a device for use in resource-limited settings by mid-level providers. The ultimate purpose is to provide sufficient data for a formal clinical assessment of a device to determine whether it is suitable for wider use in male circumcision programmes for HIV prevention. The result of an assessment by the WHO Technical Advisory Group on Innovations in Male Circumcision of the clinical studies on a specific device is one element in the WHO process for prequalification of male circumcision devices. Since devices will be used in settings and client populations beyond those included in the initial studies, it is important that the data generated from the clinical studies can be generalized to wider populations. This is best achieved through replication of the pivotal clinical trials and field studies in different countries or settings and client populations by teams working independently of the product developer or manufacturer.

The WHO Technical Advisory Group on Innovations in Male Circumcision, which reviews the clinical information on male circumcision devices, has defined minimum requirements for clinical data from pivotal studies to establish the safety and efficacy of the device in settings of intended final use. These studies balance the requirement of establishing safety with the importance of accelerating deployment of new safe, effective and acceptable devices. In exceptional circumstances, fewer or smaller clinical studies may be appropriate, but this would need to be carefully justified and agreed by the Technical Advisory Group in advance of a formal review of the evidence.

In addition to the initial safety and training studies (“case series” in Table 3), typically involving 50 clients (range 25–100), the pivotal studies should include:

- at least two randomized, controlled trials (“comparative trials” in Table 3), in two different countries or settings, comparing a new device with a standard surgical male circumcision method, conducted by providers skilled and equipped to offer either method of male circumcision, with a minimum of 100 clients receiving the new device in each trial; and
- at least two field studies, in two different countries or settings, under conditions of intended final use (“cohort field study” in Table 4) involving relevant client populations, types of facility and types of provider, with a minimum of 500 clients receiving the new device in each field study, without necessarily including a concurrent comparison arm of men circumcised by a recommended standardized surgical method.

Data generated independently of the developer or manufacturer will be given more weight in any assessment of a new device. Provided the safety of the device is adequately supported by the data in the randomized trials and field studies, such information should be sufficient to assess its suitability for use in public health programmes of voluntary male circumcision for HIV prevention with similar client populations, types of facility and types of provider in other countries or settings. In the absence of a second series of studies, a recommendation for use in public health programmes would be restricted to the country or setting where the first field study had been conducted, as it is not possible to generalize with confidence to other countries or settings.

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## 4.5 STUDIES TO EXTEND USE TO OTHER POPULATIONS OR TYPES OF PATIENTS

### 4.5.1 Bridging studies to extend use to additional types of clients

Initial clinical studies of a new device are performed by well-trained and well-resourced providers on clients who are healthy and at low risk of complications. The field studies will establish the safety and efficacy of the device in the hands of selected cadres of mid-level providers and in less well-resourced settings. It is also important to conduct studies that assess device safety in a wider range of clients than those included in the pivotal trials and studies, where inclusion and exclusion criteria may have restricted participation to males over a certain minimum age and without known medical conditions that could result in complications. Such bridging studies must be conducted on at least 200 clients to justify extending a recommendation to use a device in new populations or by providers with very different levels of training, resources or medical backup. For example, bridging studies would be required to extend use to younger age groups than those included in the pivotal studies, such as adolescents under 18 years old. In particular, the safety and acceptability of devices that remain in situ for an extended period are not known in younger clients, who may be more likely to dislodge the device through manipulation or masturbation. (This concern would not be relevant for devices that are used as aids to surgery and removed after completion of the surgical procedure.)

### 4.5.2 Safety studies in special patient groups

The initial safety and efficacy studies will have been performed in healthy men who satisfied stringent screening criteria and were without potentially complicating medical conditions. However, the same level of screening procedures for all clients in a male circumcision programme would not be feasible or justifiable due to cost and burden on clients and the programme, while not necessarily improving the quality of clinical outcomes. There are some medical conditions for which there are special safety concerns, based on the mechanism of action of a device, theoretical considerations and/or clinical experience from other settings.

One important condition is HIV infection. Studies in Uganda showed that healing times following conventional surgery were somewhat longer in HIV-infected men than uninfected men (26). These studies did not show a higher rate of adverse events in HIV-infected men, but surgery was performed in HIV-infected asymptomatic men only if their CD4 cell counts were over 350 cells/mm (8). Safety in men with more advanced HIV infection or in routine service delivery has not been documented. In addition, complication rates following other types of surgery are higher in people with HIV infection (27). The safety of circumcision devices among HIV-positive men needs to be established as programmes scale up, since a device is likely to be used in some men with HIV infection. Specifically designed safety studies should be conducted among men living with HIV in order to quantify the risks involved and determine whether any cautions need to be applied. The WHO Technical Advisory Group on Innovations in Male Circumcision recommended that studies with a minimum sample size of 200 participants would be necessary to establish safety, recognizing nonetheless that rare complications are not likely to be detected in a study of such limited size; however, this number would be sufficient to exclude high complication rates. It may be difficult to recruit this number of men living with HIV into a single-site safety study. The most practical way to accumulate sufficient safety data may be to conduct a multi-site study using standardized and well-documented procedures.

Depending on the design and mechanism of action of the device, there may be other specific conditions or populations for which there may be safety concerns. For example, diabetics have been identified as a special population as this condition predisposes to infection. Would a device that leaves the foreskin in situ during the necrosis process be safe for use by diabetics? Anecdotally, there is evidence of increased infection risk in diabetics undergoing surgical male circumcision; the incidence and severity of complications with device use may be higher than in non-diabetics (28, 29). As indicated above, a study or series of studies involving a minimum sample size of 200 participants will be necessary to establish safety and the need for specific measures to reduce risks. The most practical approach may be to accumulate study data from several sites, as indicated above for assessing device use among men living with HIV.

## 4.6 ASSESSMENT OF OTHER INNOVATIONS IN MALE CIRCUMCISION PROCEDURE

Other innovations in the male circumcision procedure—for example, the use of medical-grade adhesive for wound closure or different approaches to anaesthesia—should also be formally evaluated for their suitability in public health programmes following steps similar to those outlined above for devices. Before the innovation is widely deployed, efficacy, safety and acceptability in settings of intended final use must be established. The recommendations on minimum number of clients in the pivotal studies and the number and type of pivotal studies also apply. Any exceptions would have to be carefully justified.

## 4.7 PAEDIATRIC DEVICES

Three circumcision devices and aids to surgery (Mogen Clamp, Gomco Clamp and Plastibell device) are included in the WHO guidance on early infant male circumcision based on the clinical data and extensive experience with these devices (17). However, improvements to these devices, development of new devices, or extension of clinical data from developed countries to resource-limited settings on other devices may lead to better, simpler, faster and safer deployment of infant circumcision. To this end, the series of steps outlined above for adult devices also applies to paediatric devices, including the minimum size of pivotal clinical studies—at least two randomized, controlled trials in two different settings, with at least 100 clients in each receiving the new device, and at least two field studies in two different settings or countries involving at least 500 clients in each. Data generated independently of the developer or manufacturer will be given more weight in any assessment.

## 4.8 INFORMING PROGRAMME IMPLEMENTATION

### 4.8.1 Implementation process

Once the safety and efficacy of a device has been established in comparative trials and field studies in two different settings or countries, it is reasonable to assume that the similar clinical performance will be found in other settings. It is not necessary to repeat the same series of randomized controlled trials and field studies described above. Countries and programmes should prepare in a stepwise manner for introduction and implementation of a new technology using a participatory planning process that includes all key stakeholders, as described in one of several well-established frameworks. The *ExpandNet: scaling up health innovations* network ([www.expandnet.net](http://www.expandnet.net)) provides guidance on a participatory approach to introduction of a new technology and discusses considerations in developing pilot projects and scaling up innovations

tested in experimental, pilot and demonstration projects. The document *'Beginning with the end in mind: planning pilot projects and other programmatic research for successful scaling up* (WHO 2011) offers 12 recommendations on how to design pilot projects with scaling up in mind (30) to increase the likelihood that they can be implemented on a large scale if proven successful (see Table 5). Piloting is not only testing and demonstrating a model but also refining it through an on-going learning process.

The pilot implementation project should be led by a country team. It should be informed by strategic and participatory assessments and the experience in other countries and settings. Pilot implementation should be conducted under routine operating conditions with the types of providers, clients and settings that will be part of programme implementation. Key stakeholder discussions will inform the pilot implementation project and any other operational studies. Most likely, a mix of physicians and mid-level providers who may offer services or lead programme delivery would need to be involved. Their perspectives, buy-in and endorsement are critical to programme success. The assessment process increases buy-in, including that of senior decision-makers, and it assists in co-ordinating the responses of many players.

**Table 5. Twelve recommendations on designing pilot projects with scaling up in mind (WHO/ExpandNet, 2011)**

STEP	RECOMMENDATIONS
1	Engage in a participatory process.
2	Ensure the relevance of the proposed innovation.
3	Reach consensus on expectations for scale-up.
4	Tailor the innovation to the sociocultural and institutional settings.
5	Keep the innovation as simple as possible.
6	Test the innovation in the variety of sociocultural and institutional settings where it will be scaled up.
7	Test the innovation under the routine operating conditions and existing resources constraints of the health system.
8	Develop plans to assess and document the process of implementation.
9	Advocate with donors and other sources of funding for financial support beyond the pilot stage.
10	Prepare to advocate necessary changes in policies, regulations and other health systems components.
11	Develop plans on how to promote learning and disseminate information.
12	Be cautious about initiating scale-up before the required evidence is available.



## 4.8.2 Pilot implementation studies

The main objectives of pilot implementation studies are to establish the feasibility and the acceptability of the new device for the programme, providers and clients, their families and partners. Aspects of feasibility include costs, policy and regulatory issues (such as the scope of practice of various cadres of health-care provider), training requirements, costs (e.g. unit costs), service delivery configurations that provide the minimum package of services, service settings for various male circumcision methods, programme logistics such as procurement and supply chain management. Incorporating a new technology into current services should consider the changes that will be required. Countries and programmes will need information on the acceptability of the new device or innovation among diverse cadres of health-care providers, programme managers, clients, and clients' partners and families as well as on community values and preferences.

While the exact studies will depend on local circumstances and consultations with key stakeholders, one approach would be to carry out two phases of pilot implementation studies, analogous to the field studies described in Table 4. These two phases are summarized in Table 6 as an example to guide and facilitate planning for the introduction of devices. A formal evaluation plan, with assessment criteria defined in advance, should be a part of a pilot implementation study. It is not appropriate to relax any screening or eligibility criteria that have been applied to the selection of clients in the formal comparative trials or field studies at initial implementation—for example, by expanding the age range of the clients. The safety and acceptability of the device in such an extended population should be assessed first in bridging studies, as described above.

The first phase of a pilot implementation study might involve about 100 completed procedures and 10 providers. A smaller number (e.g. 50 procedures) could be chosen if a country or programme wished to take a more limited approach, which may be more appropriate once several countries or programmes have successfully introduced the innovation or device. The size will depend on the country context and global experience with the device. A country may choose to conduct training of providers separately, prior to pilot implementation studies, or incorporate training into the first phase of study. Phase 1 outcomes should be evaluated; one approach would be to conduct ongoing review once Phase 1 clients have reached relevant milestones (e.g. one, three or six weeks after placement) without suspending implementation.

A second-phase pilot implementation study may take place if considered necessary. It could be planned to continue directly on from the first phase and might involve about 500 clients (ranging from 250 to 1000 clients). The exact size will be determined by the specific objectives and sample sizes needed to achieve the objectives. The second phase may involve a follow-up schedule like that expected in routine service delivery.

Throughout pilot implementation (as in routine service delivery), monitoring the incidence and severity of adverse events, using standardized definitions, is important to: ensure quality, guide quality improvement actions including training and supervision, and enhance the acceptability of the programme.

**Table 6. Potential pilot implementation studies**

TYPE OF STUDY	NUMBER OF CLIENTS (RANGE)	OBJECTIVES/END-POINTS	NOTES AND COMMENTS
Preparatory			Key stakeholder consultations and agreement on conditions for use in pilot study (which providers, which settings), regulatory issues
Phase 1	Typically 100 (50–200)	<p><b>Training</b> for providers (if training is included as part of the pilot implementation study), evaluation of training (e.g. ease of training, training and supervision requirements, practicality of training)</p> <p><b>Acceptability</b> for providers (e.g. comfortable using and promoting device) and for clients (e.g. pain and comfort with procedure, support of family, partners and friends), potential advantages and disadvantages</p> <p><b>Safety</b> in specific country context and setting (types of providers, clients and settings).</p> <p><b>Feasibility</b> in various settings where service delivery is expected to occur</p>	<p>Conduct training and determine training requirements.</p> <p>Use the same eligibility criteria for client selection as in the clinical trials and field studies (e.g. age, exclusion of medical or device-specific contraindications).</p> <p>Define the evaluation plan and assessment criteria in advance, with review by those independent of the programme managers and device promoters</p> <p>Monitor adverse events systematically using standardized definitions</p>
Phase 2	Typically 500 (250–1000)	Acceptability, safety, feasibility; cost, training, logistics in settings where service will be routinely provided	Issues to be addressed in second phase pilot implementation will be driven by experiences and outcomes of first phase.

#### 4.8.3 Sequencing pilot implementation studies with evolving global recommendations

As discussed above, key stakeholder inputs should be obtained to inform the country's approach to product introduction and the formative research agenda. Any studies implemented in advance of global recommendations will need to be reviewed and approved by the national research ethics review process. If international organizations are involved, their review and approval may be necessary. Once a new innovation or device has been prequalified by WHO and a national public health programme recommends or approves use in the country, ethical review is required only for specific research studies implemented in parallel with the programme.

## 4.9 SURVEILLANCE AND REPORTING OF ADVERSE EVENTS AS PROGRAMMES ARE SCALED UP

Male circumcision is a public health intervention involving large numbers of healthy men. Therefore, it is crucial that male circumcision programmes dedicate resources to monitoring incidents and adverse events and establish a robust reporting system, whether or not devices are used. Since the number of clients receiving the new device in the comparative trials and field studies is limited, it is important to ensure careful surveillance for adverse events as the device is introduced into programmes and programmes are expanded. Monitoring and evaluation is considered to be a routine part of programme implementation and thus does not in general require approval by a research ethics review committee.

Since the large majority of male circumcision procedures will be performed within specially designed programmes, it is possible to keep basic statistics on the number of procedures performed, the characteristics of the clients, and the flow of clients through the various elements of the minimum service package (HIV testing and counselling, sexual health counselling, condom promotion, STI management). Such statistics should be readily available from routinely collected programme monitoring information. With good-quality information on the number of procedures performed, the overall incidence of complications and adverse events can be calculated and disaggregated according to client, provider or facility characteristics. Regular review of such statistics is an important element of programme management and quality improvement.

Knowledge of the incidence of adverse events and programme quality is important when communicating with the public and the media about the programme and putting in context reports of individual complications or adverse events that may be reported by the media. If not adequately addressed, such reports have the potential to undermine public confidence in the male circumcision programme and thus prevent the programme from reaching its public health objectives. One difficulty with monitoring safety and use of devices is that, once available in the country, devices may be used outside the formal health sector by providers who have not received adequate training. Adverse events occurring with such use should be included in the monitoring system, but these events can be difficult to capture.

The WHO Technical Advisory Group on Innovations in Male Circumcision recommended active follow-up of the first 1000 clients when a new device is introduced into a programme or as a new programme is implemented. This active follow-up should take place in the context of routine service delivery and not as an aspect of other studies such as the pilot implementation studies described above. The purpose is to capture, among these 1000 clients, all complications and adverse events and ensure that their incidence is within acceptable limits. If so, then it would be appropriate to switch to on-going passive surveillance for severe and moderate adverse events, but the passive surveillance system must be credible and functional. Definition and recording of adverse events should be, as much as possible, standardized to facilitate compilation, comparison and analysis of adverse event data across different settings.

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## 5. ENSURING QUALITY AND SAFETY OF MALE CIRCUMCISION DEVICES: THE WHO PREQUALIFICATION PROCESS

In addition to clinical evidence that the new device is safe and effective, several criteria related to device specification and quality manufacturing must be satisfied before it can be considered for use in public health programmes of male circumcision for HIV prevention. Through a technical file (dossier) review, the WHO Prequalification of Male Circumcision Devices Programme (24) assesses the technical characteristics of the device, its conformity with the Global Harmonization Task Force *Essential Principles of safety and performance of medical devices (GHTF/SG1/N41R9:2005)* (see <http://www.ghtf.org/documents/sg1/sg1n41r92005.pdf>) and the manufacturer's capacity to produce and supply adequate quantities of devices meeting minimum quality standards. The product dossier shows that the device meets essential safety and performance criteria to demonstrate that the product is suitable for its intended use.

Inspection of the manufacturing site(s) assesses compliance with the quality management standard *ISO 13485:2003 Medical devices — Quality management systems — Requirements for regulatory purposes* and other relevant standards, such as the Global Harmonization Task Force guidelines, and end-user issues such as the suitability of instructions for use and the stability of the product in difficult environmental conditions. The site of the legal manufacturer is inspected, and this may include inspection of the site of key suppliers of raw materials or components of the product. The inspection is carried out by WHO staff and external experts (qualified auditors and subject matter experts) appointed by WHO and may involve representatives of national regulatory authorities. All external experts are required to declare any potential conflicts of interest and to be bound by confidentiality agreements in order to protect technical and proprietary information.

Clinical evidence may not be required to obtain national registration of a male circumcision device, but clinical evidence to demonstrate safety and suitability of a device for use in public health male HIV prevention programmes is considered a critical component of the evaluation of male circumcision devices. This evidence should be generated in accordance with the current *Framework for clinical evaluation of devices for male circumcision* and should demonstrate safety in the intended client population in resource-limited settings when delivered by suitably trained mid-level health-care providers. The clinical evidence is reviewed by the WHO Technical Advisory Group on Innovations in Male Circumcision, which includes clinicians and public health and technical experts who have directly relevant experience with and expertise on male circumcision in resource-limited settings.

Once the assessment of a product is complete and the overall findings demonstrate that the product meets the WHO prequalification requirements, the product, as manufactured at the specific site(s), will be included in the list of prequalified male circumcision devices that is published on the WHO web site. These products are eligible to participate in UN agency procurement processes. National government procurement agencies may choose to buy only devices that have been prequalified by WHO. Use of prequalified devices may also be required by other global procurement agencies or agencies supporting international public health partners—for example, the Global Fund to Fight AIDS, TB and Malaria (GFATM), the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and the United Kingdom Department for International Development.

One of the manufacturer's responsibilities is to ensure transparency by providing the most up-to-date information (both positive and negative) on the use of the device. The purchasers of the devices, the end-users (and the public) should be actively informed about recalls, negative data and the reported incidence of AEs as well as steps that the manufacturer has taken to remedy any problems that have arisen. If there are any serious issues or problems with the device, the manufacturer or distributor should promptly notify purchasers of the device.

Commonly, medical devices go through various versions, both during development and initial testing and once marketed, as the users and manufacturer identify problems and/or potential improvements. On one hand, this can be disruptive, because new versions may require additional assessments and regulatory approvals, interruption in supply, additional cost and retraining. On the other hand, changes can improve the usefulness, efficiency, safety and acceptability of the device. To the extent possible, the manufacturer's willingness to modify the device in response to feedback should receive support. To facilitate this exchange of information, two-way communication should be encouraged—from countries of use to the manufacturer and distributor regarding use of the device, possible improvements and modifications needed and then from the manufacturer back to the end-users.

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## **6. MARKETING, PRICING, SUPPLY AND POST MARKET SURVEILLANCE**

### **6.1 DIRECT MARKETING OF DEVICES**

Public health programmes for HIV prevention must provide education based on knowledge of HIV status, promote sexual and reproductive health, and minimize risky sexual behaviours. The majority of male circumcision devices are expected to be used within organizations working under the guidance and oversight of a national programme. If direct marketing of male circumcision devices to medical professionals occurs, it is critical to stress the importance of the minimum package of services that are considered an integral part of male circumcision for HIV prevention (1).

### **6.2 PUBLIC-SECTOR PRICING**

An agreement on preferential public-sector pricing should be reached to ensure that the investment in research by public and philanthropic sources is linked to a commitment by a manufacturer to provide affordable and low-cost supplies of the device to public-sector purchasers. The cost to the end-user—whether it will be free of charge or involve cost recovery—will be determined at the country level according to national policies, sources of funds and priorities. The majority of funds to purchase devices for public health HIV prevention programmes in the short term will likely come from bilateral, multilateral or philanthropic sources, and it is difficult to justify excessive payments for devices and profits for manufacturers in the face of competition for resources for other HIV prevention interventions, for treatment of persons living with HIV and for other high-priority diseases.

### **6.3 MANUFACTURER'S CAPABILITY**

The capability of the manufacturer to produce and deliver the required quantities of product is a major issue. The stability and financial resources of the manufacturer are of concern, since it would take time to find an alternate manufacturer of a device if the manufacturer were to cease to trade. Patents are also a consideration. Any purchasing or supply agreement with the manufacturer should include requirements that the manufacturer give notification if production is interrupted and also contingency plans if supply is interrupted for an extended period or permanently stopped. If a programme of male circumcision for HIV prevention will use one or more devices, it is essential to ensure a suitably resourced and reliable supply chain. Temporary stock-outs could undermine the programme and substantially raise costs.

## 6.4 POST-MARKET SURVEILLANCE

Medical device regulation seeks to promote and protect the public health through oversight of the safety and effectiveness of medical devices available to the public. The complexity and risk profile of a device determine the level of oversight required. All countries with effective medical device regulations follow a process for overseeing manufacturers in order to maintain optimal safety and effectiveness of medical devices following approval for use. This oversight continues throughout the life course of the device from manufacture through marketing and use until final disposal. Manufacturers must demonstrate that they have a functioning system to collate information on problems and complications with their devices and act on this information as necessary to ensure product safety.

Monitoring adverse events and device-related incidents through a robust reporting system is crucial. The main burden of recording and reporting on adverse events will lie with the male circumcision programme, which must develop efficient and robust reporting systems (see Chapter 4). However, there needs also to be a mechanism for monitoring the performance of male circumcision devices and ensuring that information flows back to the manufacturer or distributor if any adverse events attributable to the device occur. These reports must be collated, analysed and acted on if necessary. Examples include device malfunctions, potential contamination of a sterile package and problems with packaging or adherence to the instructions for use. The process starts with problem identification by the health-care provider using the device and who, therefore, must be alert to the importance of recording and reporting device-related issues and adverse events. This information should be collated and analysed by programme managers as part of the routine monitoring process, and key information fed back to the distributor and manufacturer in a timely manner.

Manufacturers must keep records of all complaints about and complications associated with their product (see ISO 13485). Complaints and problems must be evaluated continuously, and corrective action taken as required. Working collaboratively with end-users in a culture that encourages cooperation will ensure that any incidents with devices, whether user- or device-related, are reported promptly and accurately. This will allow documentation and analysis of the incidents and stimulate appropriate corrective action.

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