

Framework for Clinical Evaluation of Devices for Adult Male Circumcision

February 2011

Executive Summary

Male circumcision has been shown to reduce the risk of HIV infection in men and is recommended by WHO and UNAIDS as a priority intervention in countries and settings with high incidence of HIV. Circumcision devices have the potential to accelerate delivery of male circumcision programmes in resource-limited settings by reducing the time to perform the operation and may in some circumstances be more acceptable to patients 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 countries in the African region where rapid expansion of male circumcision programmes for HIV prevention is most urgent.

Regulations regarding the development and evaluation of medical devices require limited clinical data on devices that are used as aids to surgery or remain external to the body. However, since male circumcision programmes for HIV prevention are public health interventions and involve large numbers of healthy men, more rigorous assessment of the clinical safety, efficacy, acceptability and cost-effectiveness of circumcision devices is required. The *Framework for Clinical Evaluation of Devices for Adult Male Circumcision* is aimed at (a) product developers seeking to develop new or modify existing male circumcision 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 required to oversee development, testing and evaluation of male circumcision devices, and (d) sponsors supporting expansion of programmes for male circumcision to prevent HIV infection.

The Framework covers the requirements for approval of devices in different regulatory environments relevant to development, manufacturing, testing and evaluation of male circumcision devices. A minimum series of steps and clinical studies are described to evaluate the acceptability, clinical performance and safety of a new male circumcision device

in the country and setting of intended final use. These studies include clinical studies in the country of origin, clinical studies in the countries or settings of intended final use (initial case series, comparative studies and acceptability studies) and field studies in settings of intended final use. The information generated from this progression of clinical and programmatic research will form the basis for recommendations on use of the device in adult male circumcision programmes in resource-limited settings.

Table of Contents

Chapter 1: Introduction	1
Male circumcision, HIV and other sexually transmitted infections	1
Expansion of male circumcision programmes	2
Male circumcision devices	3
Framework for evaluation of male circumcision devices	4
Objectives of this document	4
Target audience.....	4
Structure of document	4
Chapter 2: Prioritization of adult male circumcision devices for evaluation.....	7
Chapter 3: Regulatory issues in development, testing and registration of devices.....	11
Chapter 4: Clinical issues in development and evaluation of male circumcision devices.....	14
Clinical Studies in Country of Origin	14
Clinical Studies in Country of Intended Final Use	17
Case series	18
Comparative study.....	18
Acceptability studies	19
Field studies in country of intended final use	23
Chapter 5: Manufacturing and marketing of male circumcision devices	26
Intellectual Property	26
Public Sector Pricing	26
Manufacturer's Capability	26
Chapter 6: Monitoring use and safety of male circumcision devices.....	28
References.....	30
Appendix A: Selected male circumcision devices.....	32
Surgical methods.	32
Types of male circumcision methods devices based on list compiled by Walsh and Gola.	32
Appendix B: Medical device classifications (examples).....	36
Appendix C: Selected medical device regulations	37
USA Food and Drug Administration Guidelines	37
Medical device definition	37
Medical Device Classifications	37
Premarket Controls.....	39
Post marketing Controls	40
Medical Device Listing.....	40
Medical Device Reporting	40

EU Regulations	40
Medical device definition	41
Medical Device Classifications	41
Regulations in People’s Republic of China.....	43
Medical device definition:	44
Medical Device Classification:.....	44
International Organization of Standardization (ISO)	44
Global harmonization: The Global Harmonization Task Force	45
Appendix D: Operational definitions of adverse events	49

List of Tables

Table 1: Aspects of an ideal device and evaluation criteria for assessing male circumcision devices.....	9
Table 2: Data on circumcision device from country of origin	17
Table 3: Clinical studies in country of intended final use	21
Table 4: Field studies: pilot and cohort studies and post-marketing studies in country of intended final use.....	25

Abbreviations and Acronyms

CE	Conformité Européenne
CFR	Code of Federal Regulations
EU	European Union
FDA	US Food and Drug Administration
FHI	Family Health International
GHTF	Global Harmonization Task Force
GMP	Good Manufacturing Practices
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
HSV-2	Herpes Simplex Virus-2
IDE	Investigational Device Exemption
ISO	International Organization for Standardization
MDD	Medical Device Directive (European Union)
MDR	Medical Device Reporting
MHRA	Medicines and Healthcare Products Regulatory Agency
PMA	Pre-Market Approval
QSR	Quality System Regulation
SADC	Southern African Development Community
SFDA	State Food and Drug Administration (People's Republic of China)
UNAIDS	Joined United Nations Programme on HIV/AIDS
WHO	World Health Organization

Acknowledgements

This framework benefits from advice and from documentation provided by lead researchers in the field through their publications and publicly available documents, and discussions with Tim Hargreave, John Krieger, Philip Li and other urologists, on various issues relating to surgical techniques and research. Further, much of the information and impetus for this document was generated by the participants at a symposium, "Meeting the Demand for Male Circumcision," Convened by The Forum for Collaborative HIV Research, in Collaboration with The Bill and Melinda Gates Foundation, World Health Organization, and UNAIDS, March 2008, in Kampala, Uganda. The Framework was revised following a consultation to review manufacturing, clinical and regulatory requirements for male circumcision devices to support programme expansion in high HIV incidence settings in Africa, March 2009, in Nairobi, Kenya. The comments and insights of the participants at that consultation (Kawango Agot, Jackson Amone, Robert Bailey, Mark Barone, Kasonde Bowa, Peter Cherutitch, Emily Gumkowski, Timothy Hargreave, Mohammed Ibrahim, Fred Kambuni, Philip Li, Hilda Matumo, Walter Obiero, Christine Rousseau, Christopher Andrew Samkange, Kanwarjit KJ Singh, David Sokal, Christopher Charles Tapfumaneyi, Stephen Watya and J. Masasabi Wekesa) are gratefully acknowledged. Thanks are due to Agnes Chidanyika and Ariane van der Straten for compiling and updating the framework. Revisions and updates to the framework document were coordinated by Tim Farley.

The draft framework forms the basis for the clinical assessment of medical devices by WHO for use in male circumcision programmes for HIV prevention. It is currently being reviewed by representatives from national regulatory authorities and certified bodies responsible for authorizing marketing of devices in their countries.

Chapter 1: Introduction

The purpose of this document is to provide a framework for the clinical assessment of male circumcision devices for adult male circumcision in programs to expand male circumcision for HIV prevention. The document gives background on male circumcision and why it is recommended for HIV prevention. Next, it presents a review of the potential for male circumcision devices (once shown to be acceptable, safe and effective in the target population) to facilitate rapid expansion of adult male circumcision services in resource-limited settings. This is followed by a summary of different medical device regulatory systems with special reference to male circumcision devices in the country of origin, the country of use of the device, as well as considerations for sponsors of research and/or programmes.

The framework can guide discussion between product developers, clinicians involved with testing devices, programme managers, sponsors and donors who support expansion of adult male circumcision programmes, and regulators. This document was reviewed during a consultative meeting of interested parties from developed and developing countries in March, 2009 in Nairobi, Kenya. The final consensus recommendations are published so that a clear summary is available of the different steps required to include devices in national adult male circumcision programmes. A WHO Technical Expert Panel has been established to review new information that emerges on the new devices or devices used in new ways and make recommendations on the suitability of the device to move to the next level of assessment or to be used in male circumcision programmes for HIV prevention. These recommendations will be aimed at programme managers and public health officials responsible for implementing programmes.

Male circumcision, HIV and other sexually transmitted infections

In March 2007, WHO and UNAIDS issued recommendations for male circumcision to be considered as part of a comprehensive HIV prevention package following compelling evidence from three randomized controlled clinical trials.¹ The clinical trials conducted in Kenya, Uganda and South Africa 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 previous results from observational studies at the population and individual levels.

Male circumcision does not provide complete protection against infection with HIV or other STIs and is therefore being promoted as an additional 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 as 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, new results have been published from some of the above male circumcision trials, highlighting the additional role that adult male circumcision could play for the prevention of genital Herpes Simplex Virus-2 (HSV-2) and Human Papillomavirus (HPV) infection in men. One trial from Orange Farm, South Africa, demonstrated a 36% reduction in the prevalence of high risk-HPV in circumcised men.⁵ Another study from the Uganda circumcision trials, indicated that circumcised men had a 28 percent lower risk of HSV-2 acquisition and a 35 percent lower prevalence of high-risk HPV compared with uncircumcised men.⁶ These new results corroborate findings from previous observational studies, and contribute to the mounting evidence of the disease-prevention benefits of male circumcision as a public health intervention for preventing sexually transmitted infections (STIs) including HIV among men. Any direct effects of male circumcision on women's sexual health are less well documented, but include a potential lower incidence of HIV infection (observational study in Uganda⁷ and the multicountry Partners in Prevention study⁸), and a lower incidence of bacterial vaginosis and severe bacterial vaginosis, trichomonas infection and genital ulceration (randomized trial in Uganda⁹). Indirect benefits to women following lower incidence and prevalence of HIV infection and other STIs in men in the community are predicted from epidemiological models,¹⁰ but have yet to be demonstrated in community studies.

Expansion of male circumcision programmes

Thirteen countries have been identified as priority for the scale up of male circumcision services for HIV prevention because of high prevalence of HIV and low prevalence of male circumcision.¹¹ In the introduction and expansion of male circumcision programs, 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. The majority of male circumcision worldwide is performed for religious or cultural reasons, with smaller numbers performed for medical reasons. There is a wide range of religious and cultural practices surrounding male circumcision, and high rates of complications and pain associated with traditional practices when male circumcision is performed without local anaesthesia.¹² While this framework focuses on devices to be used to facilitate *medical* male circumcision through the formal health sector, considerations should be given for the development and evaluation of devices or surgical aids to make *traditional* circumcision safer, in areas where this practice is prevalent.

Mathematical models suggest that for a significant reduction in incidence and prevalence of HIV infection to occur, uptake of male circumcision will have to be as high as 50-80% and it could even take 10 years to see much of an effect on disease outcomes.¹³ While rapid expansion will have the greatest public health impact and provide the largest cost saving, as countries scale up, quality must be assured. Male circumcision procedures must be safe, performed under proper conditions and conform with all ethical and human rights guidelines and standards. Circumcision devices which make the procedure quicker, easier, more replicable and safer, and can be demonstrated to be cost-effective, may facilitate expansion of adult male circumcision programs for HIV prevention.

Male circumcision devices

Adult male circumcision is more complex to perform than early infant male circumcision. Experienced health workers can perform infant male circumcision very quickly and safely, especially with the aid of various devices that have been well studied, including in randomized controlled trials.¹⁴ 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 included in the *WHO/UNAIDS/Jhpiego Technical Manual for Male Circumcision under Local Anaesthesia*¹⁵ on the basis of the well-documented clinical experience in different regions of the world. In addition several other devices are used for infant male circumcision, but their safety and performance has 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 are thus technically more difficult, take longer to perform, and have higher complication rates than those seen with infant male circumcision.¹⁶

This Framework focuses on the evaluation of male circumcision devices to be used for post-puberty, in adolescent and adult male circumcision (referred to as “adult” circumcision) for which little clinical experience currently exists. A review of a selected number of devices in use is given in Appendix A. Chapters 2 and 3 consider various options towards identification of suitable male circumcision devices for adult and adolescent male circumcision and their clinical evaluation.

Since medical male circumcision for HIV prevention is a public health intervention performed on healthy men, introduction of male circumcision devices justifies scrutiny beyond that typically required by standard device regulations, specifically, the consideration of more stringent safety criteria. Conventional surgical approaches, as used in the randomized controlled trials, have low rates of complications (< 2%) when delivered by trained doctors

and surgeons in well-equipped and resourced settings. This document provides guidance and recommendations for the regulatory and clinical pathways of adult male circumcision device evaluation.

Framework for evaluation of male circumcision devices

Objectives of this document

The objective of this document is to provide a regulatory and clinical framework for the evaluation of devices for adult male circumcision. WHO and other health authorities wish to identify one or more devices that (a) would make the adult male circumcision procedure safer, easier, and quicker; (b) would have more rapid healing than current methods and/or might entail less risk of HIV transmission in the immediate post-operative period; (c) could be performed safely by health-care providers with a minimal level of training (mid-level providers) and (d) would be cost-effective compared to standard surgical methods for male circumcision scale up.

Target audience

This document is aimed at (a) product developers seeking to develop new or modify existing male circumcision 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 required to oversee development, testing and evaluation of male circumcision devices, and (d) sponsors supporting expansion of programmes for male circumcision to prevent HIV infection.

Structure of document

Chapter 2: Prioritization of adult male circumcision devices for evaluation. This chapter discusses the characteristics of ideal male circumcision devices for use on adult men in resource-limited settings, the criteria by which existing male circumcision devices would be selected for further evaluation and development of innovative devices to facilitate adult male circumcision.

Chapter 3: Regulatory issues in development, testing and registration of devices. This chapter reviews current regulations in developed and developing countries that are relevant to development, manufacturing, testing and evaluation of male circumcision devices.

Chapter 4: Clinical issues in development and evaluation of male circumcision devices. In addition to the regulatory requirements for device evaluation, a new male circumcision device must be evaluated for acceptability (by clients, providers, female partners and parents of male adolescents), clinical performance and safety in the country and setting of intended final use. This chapter proposes a minimum series of steps and clinical studies to be completed before a device could be assessed by WHO as a method for inclusion in the *Technical Manual on Male Circumcision under Local Anaesthesia* and recommended for use in an adult male circumcision programme in resource-limited settings.

Chapter 5: Manufacturing and marketing of male circumcision devices. This chapter summarises key elements of manufacturing and commercialisation of male circumcision devices that would lead to a sustained supply of high quality devices for use in adult male circumcision programmes in resource-limited settings, including issues related to intellectual property, preferential pricing in the public sector in developing countries, marketing and distribution of devices.

Chapter 6: Monitoring use and safety of male circumcision devices. As new devices are introduced into programmes for adult male circumcision for HIV prevention, mechanisms must be in place to monitor use of the devices, their acceptability by the patient, providers, female partner and parents (for male adolescents), record any complaints attributable to use of the device and ensure the necessary corrective actions are taken to minimize risks to patients. This chapter summarizes the minimum steps that must be taken to monitor programmes that include male circumcision devices, the training and reporting mechanisms and requirements, and special studies that may be necessary to assess safety and acceptability.

Appendices to the framework provide a summary of relevant information on circumcision devices and device regulations:

Appendix A: Selected male circumcision devices. This table presents a summary of different male circumcision methods and devices, any safety, acceptability issues and regulatory status within the United States FDA and European Union (EU), where known.

Appendix B: Medical device classifications (examples). This appendix provides examples of selected medical device classifications according to different regulatory authority jurisdictions to illustrate the types of devices in each class.

Appendix C: Selected medical device regulations in countries relevant to the development, assessment and marketing of male circumcision devices for HIV prevention. A summary of the USA FDA medical device regulations as well as

European Union, China, and selected countries from the Southern African Development Community (SADC) region (Kenya, Zambia, South Africa and Zimbabwe) are covered in this Appendix. A brief summary is given of the activities of the Global Harmonization Task Force whose objective is to promote harmonisation in the regulation of medical devices.

Appendix D: Operational definitions of adverse events reporting in clinical evaluation of male circumcision devices is included to facilitate uniform coding and reporting of complications associated with research on devices and surgical interventions. These tables provide a framework for use in clinical research and programme evaluation studies and are based on the three recently completed randomised controlled trials of adult male circumcision conducted in Africa.

Chapter 2: Prioritization of adult male circumcision devices for evaluation

Adult and adolescent male circumcision is most commonly performed using one of three surgical methods: dorsal slit, forceps guided method or the sleeve resection method. All these methods have been used in low resource settings according to preference or training and 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 (forceps guided method in Kenya³ and South Africa²; sleeve resection method in Uganda⁴). There are advantages and disadvantages of each approach. For example, the sleeve resection method produces a good cosmetic result but requires higher level surgical skill and may be longer to perform, while the forceps guided method may be the most suitable for training 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, though haemostasis can also be achieved with electrocautery where facilities and training permit.

Early infant male circumcision methods include the dorsal slit method and a range of crush or necrosing clamp devices. These devices have the advantage of cutting blood supply to the foreskin thereby resulting in minimal blood loss and reducing the need for suturing. The devices work in two main ways. One type crushes the foreskin tissue and is not left on the patient for a long period of time. In infants suturing is seldom required. Because only tissue is crushed, such devices may not always prevent bleeding when used in adults in whom there is a much greater blood supply to the foreskin. A second group is the ligature devices that do not require sutures. The ligature devices have smaller sizes compared to clamps and are typically worn for 3-7 days and then spontaneously detach.

In adult and adolescent circumcision important factors are devices that can be used by mid-level providers, require no suturing and allow shortened wound healing with a good cosmetic finish. Such devices are quite commonly used for male circumcision of young boys in the Asian region but there is little evidence of their satisfactory use in adult male circumcision. A number of existing male circumcision devices could be manufactured and studied for use in adults, but there are currently little or no high-quality published clinical data on the use of these devices in adults.

Only a limited number of clamps are currently on the market, and are primarily used for male circumcision in neonates and young boys. If a device is to be used in a different population

or age group, it is critical to carefully evaluate acceptability, safety and effectiveness (in removing the foreskin as opposed to effectiveness for HIV prevention). The experience reported in a study of the Tara KLamp device in Orange Farm, South Africa, underlines the importance of systematic and non-biased evaluation of any device before it is used in adult male circumcision programmes.¹⁷ Though the device has been successfully used in Asia and Europe in neonates and young boys, the device had a low acceptability among men in Orange Farm and the small-scale randomized trial comparing the device with conventional surgical approach was stopped because of high complication rates.

Considerations for improving or facilitating adult male circumcision devices include:

- a) Existing devices have the advantage of being currently available, and data should be accessible, though not always on the relevant age or population group (i.e. adolescent and adult males). Existing devices would provide the most rapid way to move into countries of intended use. Appendix A, summarizes over twenty male circumcision methods and devices, their intended use and regulatory status, where known.
- b) New devices would entail de novo development or the modification of existing devices. However these may be time consuming to develop and may entail unforeseen costs.
- c) Non-devices or aids to standard surgical methods include existing materials (such as haemostatic gauze and surgical glue) and new techniques to improve or facilitate surgical procedures. 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) circumcision providers (safety during handling, reproducibility and consistency of the final result, simplicity or ease of use, practicality and safety of cleaning and sterilization if device is intended for multiple uses); b) patients/clients (acceptability during the procedure and post-operatively, minimal pain, good cosmetic final result, rapid healing time, minimal complications), c) suppliers (safety features, costs, shelf life, sterilization) and d) policy makers (ease of training, ease of deployment and supply chain management, cost, cost-effectiveness and regulatory issues). Furthermore, when selecting devices for evaluation and assessment in countries wishing to expand adult male circumcision programmes for HIV prevention, the criteria below were proposed by Walsh and Gola (Table 1).¹⁸

Table 1: Aspects of an ideal device and evaluation criteria for assessing male circumcision devices

Aspects of an ideal device	Evaluation Criteria
1. Safety of device:	
<ul style="list-style-type: none"> • Safe to use • Should reduce the chance of injury to the glans (compared with standard surgical technique) • Consistent removal of an adequate amount of foreskin • Protects the urethra • Instructions for use of the device and its procedure should include a provision for how to deal with a short frenulum • Better haemostasis compared to standard surgical technique • Rapid uncomplicated post-operative recovery period 	<ul style="list-style-type: none"> • Equivalent to or safer than conventional surgical methods(similar or lower adverse event rates) • Data and Safety Monitoring Board independent from the producer or sponsor to review safety data during trials of the device • Good clinical profile of the device (published or unpublished data) among men or boys in the target age group or in other age groups • Whether and how the device ensures haemostasis and prevents blood loss • Whether the device protects the glans from any cutting or injury • Requires minimal post operative care • Minimizes cross-infection by preventing reuse of non-sterile material (ideally device should be disposable and auto-destruct, but if reusable device should be easily cleaned and sterilized) • Features to prevent reuse of single-use devices
2a. Patient/Client acceptability	
<ul style="list-style-type: none"> • to the patient • to the female partner • to caregivers of male adolescents 	<ul style="list-style-type: none"> • Quick resumption of daily activities • Minimal discomfort while device in situ • Minimal length of time device in situ • Acceptable cosmetic finish • Minimal or no requirement for post-operative visits
2b. Provider acceptability	
	<ul style="list-style-type: none"> • Ease of storage • Reliability of distribution systems • Ease of use and removal • Provides reproducible results
3. Ease of use	
<ul style="list-style-type: none"> • Device used easily by the provider • Shortened procedure • Training completed effectively and easily • Ease and practicality of removal 	<ul style="list-style-type: none"> • Skill required should be no more than required for conventional surgical procedure • Minimum kit requirements: kit should be simple with as few components as possible. • Procedure with device should need no more than local or topical anaesthesia. • Simple to manipulate and use, thus minimising opportunities for mistakes and injuries to the patient during the procedure • Does not require high level medical training or advanced surgical skills, but can be used by a suitably trained provider • Removal should be simple: consideration should be given to the safety and practicality of removal at other health facilities, including self-removal • Clear disposal instructions • Clear labelling to reduce chance of using wrong size device or other misuse of the device

Aspects of an ideal device

Evaluation Criteria

4. Low cost/affordable price

- More cost-effective than conventional surgical method
- Should not require expensive infrastructure
- Requires a minimal amount of other consumables
- Single use devices – features to prevent reuse
- Multiple use devices – easy to clean and sterilize, must withstand many reuses
- Reduced provider time for procedure
- Efficient packaging , shipping and storage system

5. Regulatory and marketing

- Regulatory status of the device in country of origin or manufacture
 - Current status of marketing and use of the device in the country of origin
 - Should be approved in country of origin, and high quality clinical data available
 - Preferably should be currently marketed in country of origin and used in the target age group relevant for the country of intended use
-

Chapter 3: Regulatory issues in development, testing and registration of devices

Regulations are developed and enforced to ensure the safety and effectiveness for a given procedure/purpose of medical devices. It is important to note that all devices carry some risk and can cause problems. Regulations consider the safety of a medical device throughout its life span, achieved through a risk assessment of each phase (from manufacture to use, removal and disposal) which estimates the hazard potential of the device for an adverse event or potential safety problems and harm.¹⁹

The regulation of medical devices varies greatly between countries. Obtaining regulatory approval for devices is much easier than for drugs, and in some developing countries, there is no specific mechanism for approval. In some countries devices can be imported without any regulatory review. As previously noted, it is worth re-emphasizing that because adult male circumcision is preventive and not curative, safety criteria when introducing adult male circumcision devices will have to be more stringent than the existing current regulatory rules for importation or approval for use of other medical devices in resource limited countries.

For illustrative purposes, a summary of the regulatory status for male circumcision devices is provided below for several countries, including the USA, Europe, China and a number of African countries from the SADC region. For more detailed regulations and the various classification systems, refer to Appendix B.

In the United States of America, the FDA divides medical devices into three classes: Class I, II, and III. Class I has the fewest restrictions while Class III is the most highly restricted. 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 510(k) submission generally without provision of clinical data (see Appendix C), though clinical data can be submitted if the manufacturer so desires. A number of different devices have been cleared to market in the USA in recent years including a newer clamp type device that is available in adult sizes, the SmartKlamp. The SmartKlamp could serve as a predicate device for other clamp type devices.

Manufacturers of medical devices must comply with premarket notification 510(k) requirements in accordance with 21 CFR 807 Subpart E along with the medical device general controls provisions of the Federal Food, Drug, and Cosmetic Act. The general controls provisions of the Act include requirements for establishment 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).

In the European Union, and per the European Union Medical Device Directive (MDD) 93/42/EEC, medical devices are divided into four classes: Class I, IIa, IIb and III. Like the USA system, the controls increase in each class with Class III being most stringent. In the European community, male circumcision devices would be considered Class IIa or Class IIb devices. Medical devices are required to meet the Essential Requirements of the MDD and comply with "Conformité Européenne" (CE) marking requirements of the MDD (see Appendix C for summary of regulations).

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 has three classes: Class I, II and III. 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 likely 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 and 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 devices regulations are not in full force yet, 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 (South Africa), Medicines Control Authority (Zimbabwe) and the Pharmacy and Poisons Board (Zambia).

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

- Device registration status in country of manufacture
- Manufacturing standards and marketing of device in country of manufacture
- Clinical profile of device (published or unpublished data)
- Known adverse events, warnings or "recalls" in countries where the device is marketed, and
- Systems that will need to be put in place by the country in order to monitor device during use in the country.

Special consideration should be made if a device appears promising, but is not registered in the country of origin or manufacture. 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 should be necessary for marketing and use, but not necessarily for research. Exceptions would be if there is no process or body for registration in the country of origin. While all case scenarios cannot be foreseen, it must be acknowledged that registration in the country of origin may be inadequate. All these cases would 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, which is not needed in the country of origin (for example change in device due to variation in the thickness of the foreskins in different geographical areas). These modified devices may thus not get registered in the country of origin. However, it would be appropriate to test and eventually register them in the country of intended use.

Other sources of reference are the International Organization of Standardization (ISO) and the Global Harmonization Task Force (GHTF) documents and resources. These are internationally set standards and regulations developed to facilitate technology transfer and minimize regulatory barriers between countries. The emphasis is on patient safety, effectiveness, performance and quality of devices as well as information exchange. Although countries maintain their own medical device regulatory systems and standards, reference and use of ISO and GHTF resources can benefit countries which are at early stages of medical device regulation development to learn from other established systems. More information on how these bodies work is found in Appendix C.

Chapter 4: Clinical issues in development and evaluation of male circumcision devices

While regulatory agencies in most countries may not require clinical data for approval of male circumcision devices, clinical data are necessary in order for WHO and national health authorities to assess the safety and cost-effectiveness of new male circumcision devices, develop guidelines and recommendations on their use, and propose their inclusion in programmes offering adult male circumcision for HIV prevention. Regulatory requirements to introduce new circumcision devices to the market or to make improvements to existing devices do not necessarily provide sufficient information as to whether the device would be acceptable to providers and clients, increase the rate at which circumcisions could be performed in country programmes, result in net cost savings and be a cost-effective addition to the method mix. Such additional information would be critical to making recommendations and policy decisions on the role of devices for expansion of circumcision services and sustaining those services in the long term.

In order to establish the clinical profile of a device, all relevant clinical data (published and unpublished) should be systematically compiled and assessed for quality. The following types of studies should be considered before WHO or other health authorities could assess and potentially recommend a circumcision device for general use in HIV prevention programmes in low-resource settings:

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

The rationale for and issues to be considered in designing and implementing these three types of studies are discussed below. The body of evidence and experience so generated would form the basis of guidelines and recommendations on the use of the device(s) in programmes in resource-limited settings that offer adult male circumcision for HIV prevention.

Clinical Studies in Country of Origin

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 and its potential benefits. A manufacturer may have already performed such a study, though data from

sources independent of the manufacturer would carry greater weight, unless high-quality and comprehensive data could be documented. A review of clinical adverse events and device-related incidents, together with the related actions taken by the manufacturer, should also be available. A new study will require a well-defined protocol for use of the device, selection of suitable patients (or exclusion of unsuitable patients), with well-documented outcomes including cases in whom the device procedures were started but not successfully completed. The types of patient should be relevant to those in whom the device is intended to be eventually used. The protocol should have defined stopping rules for serious Adverse Events. An initial study could be a case series using a staged recruitment with the first 5-10 cases followed through study completion before new patients are enrolled. For this type of study a small sample size of 25 to 100 cases would be adequate to provide the information on the performance of the device, whether the potential advantages over other methods were being realized. The primary endpoint would be safety – clinical adverse events and device-related incidents – recognizing that rare complications are not likely to be detected in such a limited study. The study would provide preliminary information of the acceptability of the device to patients and providers. Selected secondary endpoints such as technical difficulty and complications with the procedure, cosmetic results and healing process, should be documented by digital photos. Photographs should ideally have two views (top and bottom) and be reviewed by an independent (blinded) reviewer.

For devices that are aids to surgery and do not stay on the penis beyond the procedure study sizes at the lower end of the 25 – 100 range may be sufficient. Regulatory authorities might consider some devices that are just used during surgery to be Class I rather than Class II devices. Devices that remain on the penis 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 clinical 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,²⁰ 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. While it may be challenging to operationalize the healing process and the time to complete healing, it is important to develop objective criteria for these. 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.

Follow-up should be intensive and should preferably include a post-operative visit about two days after the procedure, and then at 1 week, 2 weeks, 3 weeks, etc., until wound healing is documented, and for a minimum of 6 weeks. For clamp-type devices which remain in place after the male circumcision procedure, a follow-up visit should be considered at about two days after removal of the clamp in addition to two days after the initial procedure. Such intensive follow-up is essential in the early phases of research but the frequency may be reduced as more experience with the healing and removal process is accumulated.

Ideally a second, larger study would compare the device with one or more of the current WHO-recommended male circumcision techniques, i.e. forceps guided, sleeve resection or the dorsal slit method. While a randomized controlled trial would be preferable, such a trial requires standardization of both study arms, in particular the traditional surgical arm. This may be problematic if surgeons already have a preference for, and extensive experience with, the device being studied. A non-comparative study, or comparison with a well-documented historical case series using a conventional surgical approach, could be considered depending on the nature of the device and location of the trial. The trial should be conducted to international standards and provided 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. Thus, 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 for the device.

Clinical parameters for study of a male circumcision device should have a clear definition of 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 a 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 the removal time (for devices that remain on the penis). Secondary endpoints are listed in Table 2 below. While the suggested sample sizes of 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. To enable comparison with other studies, the definitions of endpoints 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.^{2,16,21} A list of

types of adverse events defined in these studies is given in Appendix D: Operational definitions of adverse events.

Table 2: Data on circumcision device from country of origin

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

* would require documentation by photographs

Clinical Studies in Country of Intended Final Use

Following documentation on the clinical performance of the device in the country of origin or manufacture, it 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 and the ease of training should be documented. It is important to note that the patient population may be very different from the types of patient in the country of origin, particularly with respect to age, motivation, clinical indications for circumcision, and social environment. These could lead to unexpected and new difficulties with the device that investigators must be able to respond to. Concern for rapid progress through the different stages of clinical evaluation must be balanced by the importance of progression from assessment under well controlled conditions in the hands of experienced providers with backup in case of problems to the eventual target population and providers in resource-limited settings with little access to additional support. The types of study and key

elements are summarized in Table 3. 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 patient population. This would be determined in each country by the public health authorities on the basis of the available data.

Case series

The first study should be non-comparative in order to collect preliminary information on the ease of use and performance of the device in the new population and setting. There should be phased enrolment with completion of an initial small cohort of men to wound healing (or at least device removal) before enrolling the next cohort of men. As more experience accumulates with the device, enrolment of new patients while others are still under follow up would be acceptable, but ought to be sanctioned by an independent group of experts overseeing the study, such as a formal Data and Safety Monitoring Board (DSMB). It is important to collect systematic 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.

Starting with very stringent medical criteria would be preferable in the initial case series and small proof of concept studies. Patients with self-reported bleeding disorders or observed abnormalities of the penis should be excluded from the initial clinical studies and referred to hospitals or clinics for surgical male circumcision. Collection of information on refusals to participate in the study is important. Special consideration must be given on management of participants who do not return for post-operative visits, particularly with devices that require removal. All efforts should be made by investigators to follow every single participant enrolled in the study until planned completion of follow-up.

Care should be taken to ensure that patients 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 with HIV infection, even if not specifically intended for such groups. It is important at some 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 before including men with HIV infection or those of unknown HIV status in any research studies.

Comparative study

After successful completion of the first clinical studies, a formal trial comparing the device against one of the established methods of circumcision should be conducted by providers

experienced with both methods. Only surgeons who are competent and have successfully performed a minimum of five of each of the two procedures under study should be involved in such a comparative trial. While the incidence of adverse events and device-related incidents are important in the assessment of the devices, other outcomes should be considered primary endpoints and drive the sample size requirements. Studies involving about 100 men (range 50 to 300) 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. The exact choice of endpoint will be determined by the expected advantages of the new device over conventional surgery, but the total operation time is likely one key measure by which to compare the approaches. This should be “skin-to-skin” time measured from the first touch of the surgeon to the final wound closure, but excluding anaesthesia time.

Studies directly comparing adverse event (AE) rates between the new device and conventional surgery would require sample sizes of 800 – 1500 patients as the incidence of AEs in clinical environments with properly trained and equipped providers 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 circumcision. Yet the purpose of developing and assessing new devices is to allow providers not necessarily skilled in conventional surgery to perform circumcisions with a device, once shown safe and effective. The relevant testing pathway is to establish that the device performs well and presents several advantages in the hands of skilled providers and then proceed to clinical evaluation in populations of intended final use and providers with limited surgical skills.

In order to accumulate experience rapidly with the 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 patient population and larger range of providers involved in the formal assessment.

Acceptability studies

Aside from safety and performance of the device, an important consideration is the acceptability of the device (during the procedure itself, during healing period while the device remains *in situ*, and regarding cosmetic finish) for the patient, his female partner and caregivers (in case of adolescent boys), as well as the provider. This information could be collected on a subset of participants included in the clinical studies. An indirect measure of acceptability is the acceptance rate of volunteers approached to participate in the studies. Understanding reason(s) for refusal, comfort with the device while *in situ*, attitudes of family and/or partners and final cosmetic result will inform eventual decisions on programme design,

communications, and selection of suitable patient populations where the device could be used.

Table 3: Clinical studies in country of intended final use

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

*: Documented photographically

Field studies in country of intended final use

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

Table 4.

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

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

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

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

Post-marketing surveillance of medical devices is normally the responsibility of the manufacturer or distributor which must establish mechanisms to collate reports of adverse events and device-related incidents, and demonstrate that they have been considered and acted on if relevant. Since male circumcision is a public health intervention targeting large numbers of healthy men, monitoring of incidents and adverse events and a robust reporting system is critical for male circumcision programs whether or not devices are used, even if

such systems do not exist for other medical devices. Dedication of resources for gathering adverse events and developing an adequate reporting system should be a priority for countries considering scale up of male circumcision in general, and particularly where devices are to be used. At the same time it will be important to know the number of devices used, so that the incidence of adverse events can be computed. An additional risk with devices is that, once available in the country, they may be used outside the formal health sector by providers who have not received adequate training. Not only must such use be monitored where possible, but adverse events occurring outside the formal health sector should be included in the monitoring system.

Table 4: Field studies: pilot and cohort studies and post-marketing studies in country of intended final use

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

Chapter 5: Manufacturing and marketing of male circumcision devices

Considerations relevant to production and distribution of a device, in addition to regulatory issues, include intellectual property issues, public sector pricing, the capability of the manufacturer to produce and deliver the required quantities of product, while maintaining quality, and the ability of the manufacturer to meet the safety and clinical requirements for the device and make modifications to the product that might be suggested by users.

Because male circumcision programmes must be implemented carefully with an emphasis on education based around knowledge of HIV status, promotion of sexual and reproductive health, and minimizing risk compensation, marketing to the end user will likely be the responsibility of the local government and non-governmental organizations working within the context of a national circumcision programme. Direct marketing of circumcision devices to medical professionals or the public, if it occurs, should stress the importance of the minimum package of services that are considered an integral part of male circumcision for HIV prevention.¹

Intellectual Property

It is desirable that the manufacturer has patent protection for the device, otherwise a competitor could enter the marketplace and disrupt promotion and distribution. Since most male circumcision devices are relatively simple to manufacture and regulatory barriers are low, the lack of patent protection might make it difficult to obtain commitments with partners for distribution of the product and training of providers.

Public Sector Pricing

An agreement on preferential public sector pricing should be reached to ensure that the investment in research by WHO and other public or philanthropic sources is linked to a commitment by the 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.

Manufacturer's Capability

While the capability of the manufacturer to produce and deliver the required quantities of product should not be 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. Any purchasing or supply agreement with the

manufacturer should include requirements that the manufacturer give notification if production is interrupted and also include contingency plans if supply is permanently stopped. One consideration related to building a male circumcision programme around one or more devices is to ensure a suitably well resourced and reliable supply chain. Disruptions due to temporary stock outs could undermine the programme and have serious cost implications.

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

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

Chapter 6: Monitoring use and safety of male circumcision devices

Medical device regulations serve the purpose 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 determines the level of oversight required. All countries with medical device regulations follow a process for overseeing the manufacturer in order to maintain optimal safety and effectiveness of medical devices following approval for use. This oversight continues through out the life course of the device from manufacture, marketing and post market monitoring until disposal.

Monitoring of device-related incidents and AEs through a robust reporting system is critical for male circumcision devices even if a system may not exist for other medical devices in the country of use, as male circumcision for HIV prevention is a public health intervention that targets large numbers of healthy men. This system would be particularly important in early stages of testing during scale-up of device use. Dedication of resources to develop an adequate AE reporting system should be a priority for all countries considering scale up of male circumcision services. At the same time as gathering and analysing AEs related to devices, it will be important to know the denominator of the number of devices being used, to be able to estimate the incidence of device-related AEs.

There are several systems that can be put in place to monitor the safety of a device. In most low resource sub-Saharan African countries, manufacturers are required to carry out post surveillance studies as a condition of product approval and to re-affirm product safety when post market adverse event reports suggest that pre-market safety claims are inconsistent with actual use.

Post market device monitoring systems have three components:

1. Problem identification - Through identification of unanticipated health hazards information can be collated about potential risks of male circumcision devices. Possible sources of data and contact information should be gathered. All users of the male circumcision devices or facilities through which the device is provided should be registered into a surveillance system where they are required to report all complaints. All users of the devices should be included in the process for reporting complaints.
2. Problem assessment - All problems identified from the above system should be scientifically investigated. The available data should be analysed for public health significance and appropriate action should be taken.

3. Public health response - Government level monitoring is vital in ensuring public safety. When a trend in complaints is identified, the manufacturer must be proactive in taking corrective action, and if necessary, health care providers must be informed. If enforcement actions, such as product recall, need to occur as part of public health response, there needs to be a timely plan for information dissemination.

Any manufacturer of a male circumcision device will need to keep records of every complaint about their product. According to FDA definitions, a complaint is any communication of “deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a device after it is released for distribution.” For records to be tracked effectively, there must be a system in place so that the clinician’s complaint will reach the manufacturer. The information gathered during this process drives both safety and ergonomic improvements in device designs.

In the United States of America, when a clinician has a complaint, a form (supplied by the manufacturer, usually the sales representative) is filled out as much as possible. The form allows information to be recorded such as the nature of the complaint, the impact on the procedure as a result of the complaint, device information and patient information. The form is returned to the manufacturer with the used device, if applicable, including any tissue or other materials adherent to or blocked in the device if this has occurred. When these items arrive at the manufacturer, they are logged by an analyst into a tracking system for the company and, if necessary, the cause of the malfunction is investigated. Complaints are evaluated continuously and corrective action is based on severity, frequency and likelihood of a complaint to occur. Reporting to the government is also based on these criteria. The government periodically audits the manufacturer to make sure logging and follow up of complaints is maintained.

For such a system to be successful, the clinician must initiate the complaint. One approach to consider in low resource settings would be to include two standardized cards with each device, one completed by the device user and the other card given to the client, who should return it to the facility where the device was placed if he has any problems. If he returns to a different facility, then the provider at that site would send the complaint card to the original facility or a central facility. The clinician/site where the device is being used should be responsible for recording specific device incidents and AEs. Next, the collation and analysis of the information from individual sites/clinicians could be done by the male circumcision task force or other designated body in the country. The group responsible would send the collated information to the manufacturer and distributor, and then feed back any important information or responses from the manufacturer and distributor back to the purchasers and users of the device.

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 action.

References

1. WHO/UNAIDS. New Data on Male Circumcision and HIV Prevention: Policy and Programme Implications. Geneva, Switzerland: World Health Organization and Joint United Nations Programme on HIV/AIDS, 2007.
2. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: The ANRS 1265 Trial. *PLoS Medicine* 2005; **2**(11): e298.
3. Bailey RC, Moses S, Parker CB, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. *Lancet* 2007; **369**: 643-656.
4. Gray RH, Kigozi G, Serwadda D, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *Lancet* 2007; **369**: 657-666.
5. Auvert B, Sobngwi-Tambekou J, Cutler E, et al. Effect of male circumcision on the prevalence of high-risk human papillomavirus in young men: Results of a randomized controlled trial conducted in Orange Farm, South Africa. *J. Infect. Dis.* 2009; **199**: 14-19.
6. Tobian AAR, Charvat B, Ssempijja V, et al. Factors associated with the prevalence and incidence of herpes simplex virus type 2 infection among men in Rakai, Uganda. *JID* 2009; **199**.
7. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. *New England Journal of Medicine* 2000; **342**: 921-929.
8. Baeten JM, Donnell D, Kapiga SH, et al. Male circumcision and risk of male-to-female HIV-1 transmission: a multinational prospective study in African HIV-1-serodiscordant couples. *AIDS* 2010; **24**(5): 737-744.
9. Gray RH, Kigozi G, Serwadda D, et al. The effects of male circumcision on female partners' genital tract symptoms and vaginal infections in a randomized trial in Rakai, Uganda. *AJOG* 2009; **200**: 42.e.1-42.e.7.
10. UNAIDS/WHO/SACEMA Expert Group on Modelling the Impact and Cost of Male Circumcision for HIV Prevention. Male circumcision for HIV prevention in high HIV prevalence settings: What can mathematical modelling contribute to informed decision making? *PLoS Medicine* 2009; **6**(9): e1000109.
11. WHO/UNAIDS. Progress in male circumcision scale-up: country implementation and research update. Geneva, Switzerland: World Health Organization and Joint United Nations Programme on HIV/AIDS, 2010.
12. Bailey RC, Egesah O, Rosenberg S. Male circumcision for HIV prevention: a prospective study of complications in clinical and traditional settings in Bungoma, Kenya. *Bull World Health Organ* 2008; **86**(9): 669-677.
13. Nagelkerke N, Moses S, de Vlas S, Bailey R. Modelling the public health impact of male circumcision for HIV prevention in high prevalence areas in Africa. *BMC Infectious Diseases* 2007; **7**(1): 16.

14. Alanis MC, Lucidi RS. Neonatal circumcision: a review of the world's oldest and most controversial operation. *Obstet Gynecol Surv* 2004; **59**(5): 379-395.
15. WHO/UNAIDS/Jhpiego. Technical Manual for Male Circumcision under Local Anaesthesia. Geneva, Switzerland: World Health Organization, 2010.
16. Krieger JN, Bailey RC, Opeya JC, et al. Adult male circumcision outcomes: Experience in a developing country setting. *Urologia Internationalis* 2007; **78**(3): 235-240.
17. Lagarde E, Taljaard D, Puren A, Auvert B. High rate of adverse events following circumcision of young male adults with the Tara KLamp technique: A randomized trial conducted in South Africa. *S Afr Med J* 2009; **99**(3): 163-169.
18. Walsh T, Gola G. Presentation at workshop: "Meeting the Demand for Male Circumcision". Kampala, Uganda: The Forum for Collaborative HIV Research, The Bill and Melinda Gates Foundation, World Health Organization and UNAIDS, 2008.
19. World Health Organization. Medical device regulations: Global overview and guiding principles. Geneva, Switzerland: World Health Organization, 2003.
20. Wawer MJ, Makumbi F, Kigozi G, et al. Circumcision in HIV-infected men and its effect on HIV transmission to female partners in Rakai, Uganda: a randomised controlled trial. *Lancet* 2009; **374**(9685): 229-237.
21. Kigozi G, Gray RH, Wawer MJ, et al. The safety of adult male circumcision in HIV-infected and uninfected men in Rakai, Uganda. *PLoS Medicine* 2008; **5**(6): e116.

Appendix A: Selected male circumcision devices

Surgical methods.

Method ¹⁵	Summary	Intended use	Issues/comments
1 Forceps Guided	Metal (reusable). forceps clamped in front of the glans and scalpel run across the face of the forceps Requires suturing	Older children and adults	Possible to capture glans in the forceps - may cut head of penis. Amount of foreskin removed not standardized & may vary from surgeon to surgeon May be more suitable for training mid-level providers than other surgical approaches
2 Sleeve Resection	Strip of skin cut around the shaft Requires suturing	Adults	Glans not protected. Good cosmetic result, more foreskin removed. Requires more surgical skills. Result very dependent on the skill of the provider
3 Dorsal slit	A slit is made before a strip of the foreskin is cut around. Requires suturing in adults	Neonates to adults	Requires more surgical skill

Types of male circumcision methods devices based on list compiled by Walsh and Gola.

Device ¹⁸	Method	Summary of mechanism	Intended use	Issues/comments	Regulatory status
1 AccuCirc Circumcision clamp/cutter	Crush	Grasp, crush and cut foreskin Identical* to Gomco clamp	Full term, new born infants (up to 10 days)	Bleeding may occur. Manufacturer recommends management with surgical technique.	FDA class II 510 (k): K061539 Code: HFX (Circumcision Clamp)

Device ¹⁸	Method	Summary of mechanism	Intended use	Issues/comments	Regulatory status
2	Ali's Klamp	Ligature	Single use, disposable plastic device consisting of a tube and pinching ring. Clamps and crushes the foreskin. Penis and glans protected by tube. Five different sizes, with measuring device with each clamp. Clamp is left to necrose skin for several days Similar action to the SmartKlamp,	Infants to Children up to age 15 years. Two larger sizes being developed for adults	CE Certificate from Turkey.
3	Circumcision Bell	Crush			FDA 510 (k): Exempt Code: FHG
4	Fine Surgical Circumcision Clamp	Crush	Compress the foreskin during male circumcision of an infant or child Identical* to Gomco clamp Similar to Centurion CirClamp K890897 .	Infant or child. Larger size will be available.	Sold non-sterile FDA 510 (k): K040052 Code: HFX
5	GMD Universal Circumcision Clamp, Model 200	Crush	Circumferential excision of the foreskin at or near the level of coronal sulcus, with minimal amount of preputial skin remaining. Identical* to Gomco clamp	Infant or child. Same intended use as K926535 GOMCO Clamp	Same complications as K926535 GOMCO Clamp FDA 510 (k): K063429 Code: HFX
6	Gomco Clamp	Crush	Circumferential excision of the foreskin at or near the level of coronal sulcus, with minimal amount of preputial skin remaining.	Infants and Children	Common issues are related to technique (assessing how much foreskin to remove) haemorrhage, urethral damage. FDA 510 (k): K926535 Code: HFX
7	Ismail Clamp	Ligature	Same principle as the Tara Klamp.	Children	Potential risk of being re-used since removal does not damage device.
8	Kirve Klamp	Ligature	Same principle as the Smart Klamp.	Infant to young adult	Clamp left for 3-5 days

	Device ¹⁸	Method	Summary of mechanism	Intended use	Issues/comments	Regulatory status
9	Mogen Clamp	Crush	Locks in front of the glans then foreskin cut with scalpel. Reusable	Infants	Will only open to 3mm thereby minimizing risk of trapping the glans.	FDA 510 (k): K926471 Code: HFX
10	One/Circ Circumcision clamp	Crush	US based company (BIONIX DEVELOPMENT CORP)			FDA 510 (k): K900370 Code: HFX
11	Plastibell	Ligature	Plastic (disposable). Plastic ring with groove and a suture tied round the groove in the bell.	Up to 12 years of age. Europe has adult sizes.	Remains in place for 7-10 days. If size too small, can dig into the glans and cause problems. Bleeding.	Used in USA and Europe
12	Shenghuan Disposable Minimally Invasive Circumcision Anastomosis Device "Shang ring"	Ligature	Two nested plastic rings with silicon gasket in between. Single use, disposable.	Children to Adults	Device kept on for 7 days	SFDA
13	Shield & Knife (Scalpel)	Crush	<u>Metal shield (reusable)</u> . Traditionally used in Jewish male circumcision. Shield protects the glans	Infants	Depends on skill of the provider	FDA 510 (k): Exempt Code: FHJ (Circumcision Shield)
14	Smart Klamp	Ligature	Traps the foreskin between an outer ring and inner tube cutting the blood supply to the foreskin.	Infant to young Adult	Glans is protected. Device left in place for 5 days	FDA 510(k): K032091 Code: HFX
15	Sunathrone Clamp	Ligature	Same functionality as the Smart Klamp.	Infant to Adult	Clamp left for 8-12 days,	manufacturing not ISO 13485 certified.
16	Surgical Design Circumcision Clamp	Crush	Identical* to GOMCO clamp	Same use as Centurion CirClamp K890897 . Infant/child. Larger size will be available		FDA 510 (k): K043533 Code: HFX

	Device¹⁸	Method	Summary of mechanism	Intended use	Issues/comments	Regulatory status
17	T.S. Medical Circumcision Clamp	Crush	identical* to Mogen clamp	Mogen style and similar to K935491 Infant.		FDA 510 (k): K033403 Code: HFX
18	Tara KLamp	Ligature	Plastic (disposable). Plastic arms lock into place to force 2 surfaces into tight contact with the foreskin trapped between them. Remains in place for 7-10 days,	Infant to Adult	Compared to forceps-guided surgical method, higher reported AEs in adults; delayed wound healing, more infection, pain, low acceptability, cosmetic problems ¹⁷ More bulky than other clamps with similar method.	
19	Zhenxi Circ Ring	Ligature	Circumcision ring and a spandex rubber string. Plastic clamping ring is fitted over a sleeve. Elastic cord wound tightly round the foreskin cutting off blood supply. Single use 6 sizes for infants and 6 sizes for adults	Infants and Adult	Ligature left on for ~2 days	

* "identical to" under "summary of device" means that the device is equivalent to, as stated in the 510k application.

Appendix B: Medical device classifications (examples)

Medical Device	USA	EU	Canada	Japan	Australia	China
Hand-held surgical instruments (scalpel, forceps)	Class I	Class I	Class II		Class I	
Male circumcision devices (e.g. Gomco clamp, Mogen clamp)	Class II					
Male condoms	Class II	Class IIb	Class II		Class IIb	
Female condoms	Class III		Class III		Class IIb	
Diaphragms	Class II	Class IIb			Class IIb	
Intrauterine device and inserter	Class III	Class III	Class III		Class III	
Absorbable Sutures	Class II	Class III	Class III		Class III	
Urethral stent	Class III	Class IIb			Class IIb	
Replacement heart valves	Class III	Class III	Class IV		Class III	
Silicone breast implants	Class III	Class III	Class IV		Class III	

Appendix C: Selected medical device regulations

USA Food and Drug Administration Guidelines

The Food and Drug Administration is a government body with legal powers and is responsible for enforcing regulations on drugs and medical devices. The information below was obtained from the FDA website¹.

Medical device definition

The FDA defines medical devices as follows:

"an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is: recognized in the official National Formulary or the United States Pharmacopoeia or any supplement to them, intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in man or other animals or intended to affect the structure or any function of the body of man or other animals and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

In the USA, medical devices are subject to General Controls, premarket and post market regulatory controls. The FDA has 3 regulatory classifications (Class I, Class II, and Class III) of medical devices which are risk based and dependent on intended use and indication for use. The risk is for both to the patient and to the user. As the classification level of the medical device increases, so does the risk to the patient and the regulatory control required. General Controls are the baseline requirements and apply to Class I, II and III.

Medical Device Classifications

The regulatory classes as well as regulations for the devices are found in Title 21 Code of Federal Regulations (CFR) Parts 800 - 1299. Classification is based on the level of regulation or control necessary to assure safety and effectiveness of the device. New

¹ Food and Drug Administration Device Advice: Device Regulation and Guidance

(<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm>)

devices are compared to legally marketed devices with the same intended use and technological characteristics, often referred to as "predicate" device, to determine the device classification. Male circumcision devices are classed under Class II.

Class I - General Controls.

This is the lowest level of regulation with devices that present minimal potential of harm. These are typically simple in design, manufacture and have a safe history of use. Class I device require General Controls:

- Registration of manufacturers, distributors, repackagers, relabelers and foreign firms.
- Medical device listing of devices to be marketed.
- Premarket Notification 510 (k) submission and subsequent clearance by FDA before marketing the device.
- Manufacturing devices in accordance with the Quality System Regulations (QSR) and Good Manufacturing Practices (GMP).
- Labelling devices in accordance with labelling regulations in Title 21 CFR Part 801 or 809. There are prohibitions against misbranding and adulteration.

Most are exempt from the premarket notification 510 (k).

Class II - General Controls plus Special Controls

Required to comply with General Controls as given in Class I above in addition to Special Controls:

- Include special labelling requirements.
- Mandatory and voluntary performance standards.
- Post market surveillance.
- FDA medical device specific guidance.

Usually not exempt from the premarket notification or the QSR. Typically require submission and FDA review of a 510 (k) clearance. No clinical trials required.

Class III - General Controls and Premarket Approval (PMA).

This is the most stringent regulatory category for device which usually requires a complex process involving clinical trials. This class is for devices that support or sustain human life, of importance in preventing impairment of human health, or present a potential unreasonable risk of illness or injury. Premarket approval is the required process although some Class III devices do not require an approved premarket approval application for marketing. If the new device is equivalent to devices legally marketed before May 28, 1976 it can be marketed through the premarket notification 510 (k).

Premarket Controls

The premarket controls are device and classification specific. The controls can include: clearance to market by submitting a Premarket Notification, also known as a 510 (k) or obtaining an approval to market through a Premarket Approval (PMA).

Premarket Notification 510 (k) requires descriptive data and when necessary, performance data must be submitted to establish that the device is substantially equivalent (SE) to the predicate device. Data are required to show comparability of new device to the predicate device. Substantial equivalence is assessed by: device has same intended use as predicate device, has same technological characteristics, or if it has different technological characteristics they do not raise new questions of safety and effectiveness. The process for a Premarket notification (510k) takes 20 days - 3 months.

A Premarket Approval (PMA) application however, 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. The data should include safety and effectiveness data, adverse reactions and complications, device failures and patient complaints. The PMA process takes 6 months and is required for all devices that present significant risk to the patient. Most Class III devices require a PMA.

Good Manufacturing Practices (GMP) are also referred to as Quality System Regulations. The QSR is similar to ISO 9001: 1994. FDA may audit manufacturing facility for GMP compliance every 2 years depending on results of prior audits, device risks, recall of devices and FDA initiatives. The regulation covers:

- Quality management and organization,
- Device design,
- Buildings,
- Equipment,
- Purchase and handling of components,
- Production and process controls,
- Packaging and labelling control,
- Device evaluation,
- Distribution,
- Installation,
- Complaint handling,
- Servicing and
- Records.

Post marketing Controls

Post marketing controls include Medical Device Listing, Medical Device Reporting (MDR), Establishment Registration and Quality System Compliance Inspection.

Medical Device Listing

Manufacturers are required to list the devices they have in commercial distribution. The listing should be updated if there are any changes for example new devices entered into commercial distribution, discontinuation of a device, restarting marketing for a discontinued device. The process of device listing should be completed within 30 days of entering a device into commercial distribution.

Medical Device Reporting

The MDR regulation provides a mechanism for FDA and manufacturers to identify and monitor significant adverse events involving medical devices. The goals of the regulation are to detect and correct problems in a timely manner. Manufacturers and “user facilities” are required to report malfunctions, deaths, and serious injuries due to a medical device. Events that require remedial action should be reported to prevent an unreasonable risk of substantial harm to the public health.

Steps for device registration with the FDA:

1. Premarket Notification 510 (k), unless exempt or Premarket Approval (PMA).
2. Establishment registration on form FDA 2891.
3. Medical Device Listing on form FDA 2892.
4. Quality System Regulation (QSR).
5. Labelling requirements.
6. Medical Device Reporting (MDR)

EU Regulations

Although each country has Notified Bodies which have been accredited to review and ensure medical devices are safe and effective, they all follow the EU Medical Device Directives. The directives are aimed at bringing about a single market with harmonized and statutorily based controls to regulate the safety and marketing of medical devices throughout the EU. The Notified Bodies are not government bodies but are commercial institutions which do not have legal powers but have authority to enforce regulations. For example in the UK, the Medicines and Healthcare products Regulatory Agency, (MHRA) is the government appointed body that regulates medical devices. Regulations specifically ensure

that medical devices meet essential requirements with regard to performance and safety; and manufacturers, distributors, professional users, conformity assessment bodies and authorities perform specified duties in order to protect patients and third parties from hazards and deception. The EU requires all manufacturers of devices sold in the EU to report any serious incidents involving devices.

All products covered by the EU are required to have a mandatory "Conformité Européenne" (CE) marking which means the manufacturer satisfies the requirements essential for product to be considered safe for intended purpose. Sale of any devices without a CE marking is prohibited in the EU. Before CE marking Essential Requirements must be complied with. These usually include quality systems, third party testing and product approval.

Medical device definition

The EU defines medical devices as follows:

"Any instrument, apparatus, appliance, software, material or other article whether used alone or in combination including the software intended by its manufacturer to be used specifically for diagnostic or other therapeutic purposes and necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception

and which does not achieve its principal intended action in or on human body by pharmacological immunological or metabolic means which maybe assisted in its function by other means".

Medical Device Classifications

Devices are divided into following classes: Class I, IIa, IIb, and III. The classification considers potential hazards related to the use and possible failure of the device taking into account the technology used and health policy implications. Rules for the classifications are derived from assessments of: duration of contact with patient, 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.

Class I

Medical devices in this category are those that pose low risk to the patient and can be self certified by the manufacturer (except for sterile products and measuring devices). This Class is subject only to safety requirements. Medical devices in Class I generally do not enter into contact or interact with the body.

Steps for Class I devices:

1. Choose Conformity Assessment Route.
2. Compile Technical File.
3. Declaration of Conformity.
4. Appoint an Authorized Representative (Register with the Competent Authority).
5. Vigilance and Post Market Surveillance (Affix CE marking and market the device).

Class IIa

Devices are of medium risk to patients and require assessment according to quality systems ISO 13485 standards. A conformity assessment procedure has to be carried out by a Notified Body to confirm that the device meets the Essential Requirements. The devices are invasive in nature but method of invasion limited to natural body orifices.

Steps for Class IIa devices:

1. Choose Conformity Assessment Route.
2. Compile Technical File.
3. Obtain certification from a Notified Body.
4. Declaration of Conformity.
5. Appoint an Authorized Representative (Hold the Technical Files for inspection by the Competent Authority).
6. Vigilance and Post Market Surveillance (affix CE marking and market the products).

Class IIb

Class IIb devices are medium risk and require assessment according to ISO 13485 standards and like Class IIa, a conformity assessment procedure has to be carried out by a Notified Body to confirm that the device meets the Essential Requirements. The main difference is Class IIb devices are either partially or totally implantable within the human body and may modify the biological or chemical composition of body fluids.

Steps for Class IIb devices:

1. Choose Conformity Assessment Route.
2. Compile Technical File.
3. Obtain certification from a Notified Body.
4. Declaration of Conformity.
5. Appoint an Authorized Representative (Hold the Technical Files for inspection by the Competent Authority).
6. Vigilance and Post Market Surveillance (affix CE marking and market the products).

Class III

This class is of high risk devices and require design/clinical trial reviews, product certification and an assessed quality system. These devices affect the functioning of vital organs and or of life support systems.

Steps for Class III devices:

1. Choose Conformity Assessment Route.
2. Compile Technical File.
3. Obtain certification from a Notified Body.
4. Declaration of Conformity.
5. Appoint an Authorized Representative (Hold the Technical Files for inspection by the Competent Authority).
6. Vigilance and Post Market Surveillance (affix CE marking and market the products).

All third party product and system certification is done by a European Notified Body.

Regulations in People's Republic of China

In the People's Republic of China regulation is either done at provincial level by the provincial government or by the State Food and Drug Administration (SFDA) at national level. Information on the SFDA is found on the SFDA website²

² <http://www.sfda.gov.cn> (<http://eng.sfda.gov.cn/eng/>)

Medical device definition:

The SFDA defines medical devices as instruments, equipment, tools, materials and other objects, including the software attached to them, that are designed to be used either independently or in combination on human body. These devices are used for:

1. Prevention, diagnosis, treatment, monitoring or remission of diseases;
2. Diagnosis, treatment, monitoring, remission or compensation of injury or physical disability;
3. Research, replacement or adjustment of anatomical or physiological process;
4. Control of pregnancy.

Medical Device Classification:

The SFDA has three classification levels: Class I, II and III.

Class I - low risk devices which are regulated by the provincial government. The process from dossier application to final approval takes 5-6 months.

Class II - moderate risk which are also regulated by the provincial government. Process to approval takes 7-8 months without clinical trials.

Class III - high risk devices which are regulated at national level by the SFDA. These take 12-14 months to be approved with clinical trials.

The process to approval in China starts with Dossier preparation and specification drafting which is then followed by sample testing. After filing to the SFDA, there is an evaluation review of the manufacturing centre followed by clinical trials. SFDA final approval is given depending on the clinical trial results.

International Organization of Standardization (ISO)

The International Organization for Standardization is a non profit organization which started operating in 1947 as an international standard setting body. ISO has very strong links with governments and is made up of representatives or experts from 157 countries. The experts who form technical committees are taken from industrial, technical and business sectors and participate as national delegates. The technical committees develop standards according to the needs of the manufacturing, business and consumer industry. Although ISO sets industrial and commercial standards, the body does not regulate or legislate. The main aim of ISO is to equalize and standardize procedures across different countries and regulatory systems. Many countries have their own national regulations and guidelines. The use of

ISO standards necessitates operation at an international level, promoting trade and technology transfer.

The international standards are set to ensure quality, safety, reliability, efficiency and environmental friendliness of products and services. Standards enable the manufacturing industry to develop products and services that meet international specifications and thus, wider international acceptance, thereby facilitating innovation and trade between countries. Standards are made specific to a particular product, material or service. Medical devices are covered in ISO 13485: 2003 which lay out quality management systems for medical devices.

Global harmonization: The Global Harmonization Task Force

In order to achieve uniformity in the classification and regulation of medical devices across the world, a Global Harmonization Task Force (GHTF) was formed in 1992. The GHTF was founded by governments and industry representatives of Australia, Canada, Japan, the European Union and the United States of America. The goal of the GHTF is to promote the safety, effectiveness / performance and quality of medical devices; encourage technological innovation; foster international trade; and serve as an information exchange forum through which countries with medical device regulatory systems under development can benefit from the experience of those with established systems. This should benefit patient safety and minimize regulatory barriers around the world. The GHTF proposes a risk-based device classification system, a definition of all terms, and requires manufacturers or vendors to report all device related events that have resulted or could result in serious injury or death. The Task Force is organized into five study groups:

Study Group 1: Pre-market Evaluation

The purpose of this group is to compare the medical device regulatory systems around the world and compile elements that could be suitable for harmonization and those that might obstruct harmonization of regulations. The group is also responsible for developing a standardized format of pre-market submissions and product labelling requirements. See Figure 1 below of work programme.

Study Group 2: Post market surveillance/Vigilance

For countries with developed medical device regulatory systems, this group reviews their current adverse event reporting, post-market surveillance and other vigilance systems in the aim to standardize all post market reporting.

Study Group 3: Quality Systems

This group examines the existing quality systems in countries to develop standardized quality systems.

Study Group 4: Auditing

Tasked with examining auditing practices in different countries, this group will develop harmonized medical device auditing processes.

See Figure 2 for the work programme of Groups 1-4.

Study Group 5: Clinical Safety / Performance

This group looks at promoting the use of evidence of clinical safety and performance of medical devices. The group also reviews terminology and standardizes definitions of terms to assist with the reporting and formatting of clinical data.

FIGURE 1: OVERVIEW OF STUDY GROUP 1 WORK PROGRAMME

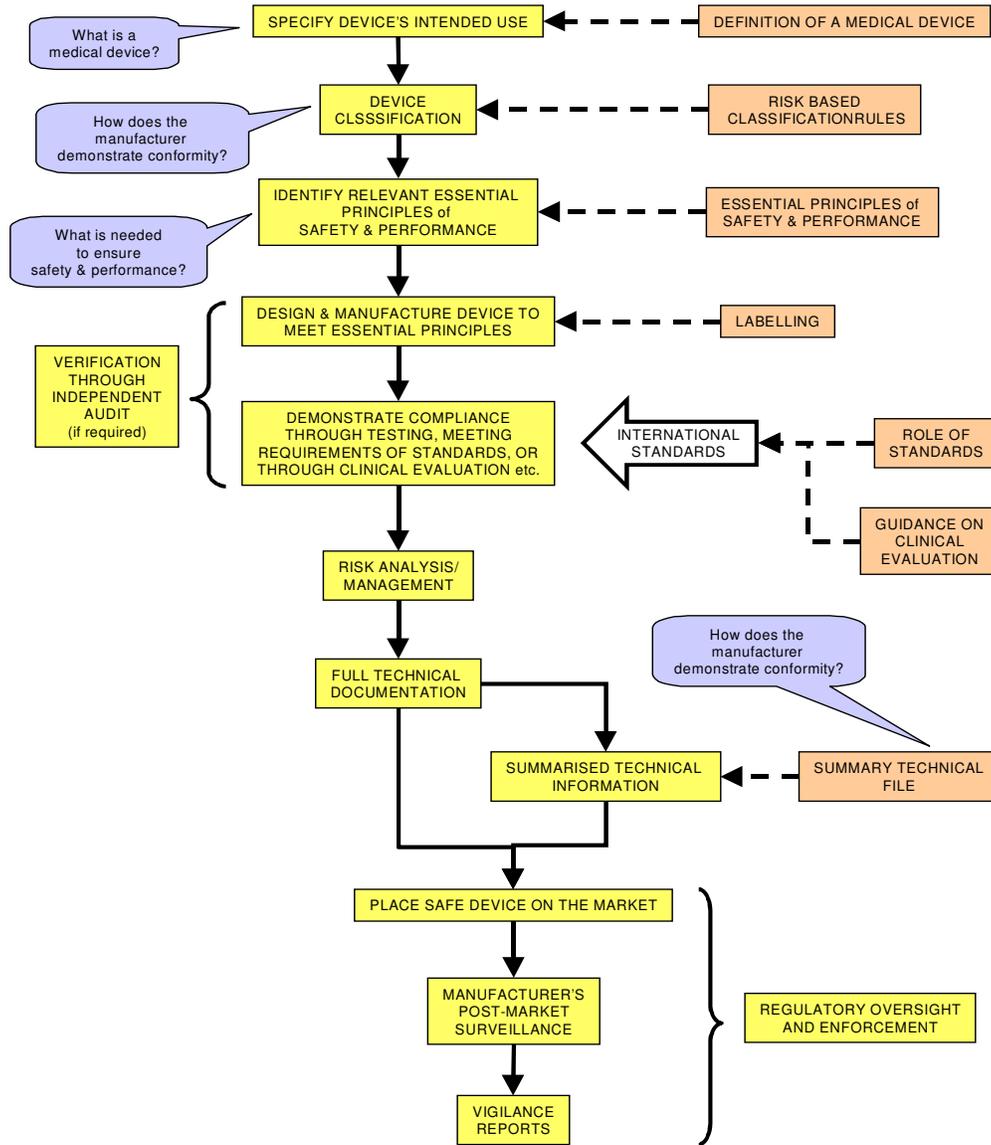
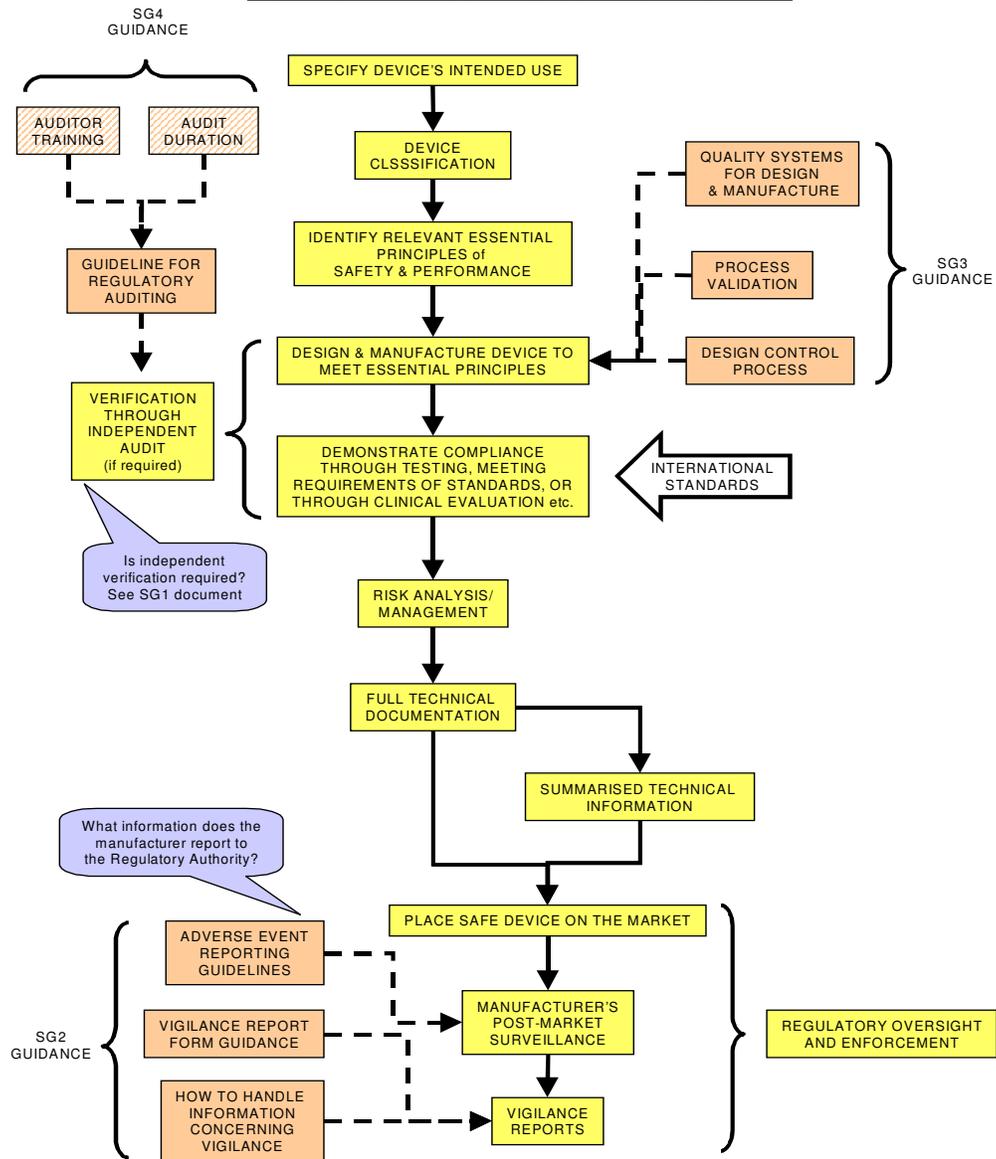


FIGURE 2: OVERVIEW OF STUDY GROUPS 2, 3 & 4 WORK PROGRAMMES



Appendix D: Operational definitions of adverse events

Standardization of Adverse Event reporting in clinical evaluation of male circumcision devices – operational definitions of Adverse Events during clinical studies ³

Adverse Event	Description	Severity	Code
A. During Surgery			
Pain	Minor, not requiring additional anaesthesia	Mild	APS1
	Moderate/severe controlled with additional anaesthesia*	Moderate	APS2
	Severe, not controlled by additional anaesthesia	Severe	APS3
Excessive bleeding	More bleeding than usual, but easily controlled	Mild	ABL1
	Bleeding that requires pressure dressing to control	Moderate	ABL2
	Blood transfusion or transfer to another facility for management required	Severe	ABL3
Anaesthetic-related event	Palpitations, vaso-vagal reaction or emesis	Mild	AAN1
	Reaction to anesthetic requiring medical treatment in study clinic but not transfer to another facility	Moderate	AAN2
	Anaphylaxis or any reaction requiring transfer to another facility	Severe	AAN3
Excessive skin removed	Adds time or material needs to the procedure, but does not result in any discernable adverse condition	Mild	AES1
	Skin is tight, but additional operative work not necessary	Moderate	AES2
	Requires re-operation or transfer to another facility to correct the problem	Severe	AES3
Damage to the penis	Mild bruising or abrasion, not requiring treatment	Mild	ADP1
	Bruise or abrasion to the glans or shaft of the penis requiring pressure dressing or additional surgery to control	Moderate	ADP2
	Portion or all of the glans or shaft of the penis severed or burned by electrocautery	Severe	ADP3

³ compiled by David Sokal based on the reporting procedures on the 3 male circumcision RCT

Adverse Event	Description	Severity	Code
B. First Month Post-Surgery			
Pain	Symptoms of pain requiring bed rest for less than half the day	Mild	BPA1
	Pain requiring bed rest for more than half day	Moderate	BPA2
	Excruciating pain requiring total bed rest	Severe	BPA3
Excessive bleeding	Dressing or other materials (for example underwear) spotted but dry	Mild	BBA1
	Dressing or other materials wet with clotted blood requiring change of dressing	Moderate	BBA2
	Dressing or other materials soaked with blood with obvious active bleeding requiring surgical exploration or transfusion	Severe	BBA3
Excessive skin removed	Client concerned but no discomfort on erection	Mild	BES1
	Causes slight discomfort on erection but surgical correction not necessary.	Moderate	BES2
	Interferes with life and surgical correction necessary	Severe	BES3
Insufficient skin removed	Prepuce partially covers the glans only when extended	Mild	BIS1
	Prepuce still partially covers the glans and re-operation is required to correct	Moderate	BIS2
Swelling or haematoma	More swelling than usual, but no treatment needed	Mild	BSH1
	swelling requiring surgical exploration but no evidence of active bleeding	Moderate	BSH2
	Rapidly expanding haematoma suggesting active bleeding requiring surgical exploration or referral	Severe	BSH3
Damage to the penis	Mild bruising or abrasion, not requiring treatment	Mild	BDP1
	Bruise or abrasion to the glans or shaft of the penis requiring pressure dressing or additional surgery to control	Moderate	BDP2
	Portion or all of the glans or shaft of the penis severed	Severe	BDP3
Infection	Pain and erythema with no obvious swelling	Mild	BIN1
	Painful swelling with erythema or elevated temperature or purulent wound discharge	Moderate	BIN2
	Cellulitis or wound necrosis	Severe	BIN3
Delayed wound healing	Healing takes longer than usual, but no extra treatment necessary	Mild	BDW1
	Additional non-operative treatment required	Moderate	BDW2
	Requires re-operation to correct	Severe	BDW3

Adverse Event	Description	Severity	Code
B. First Month Post-Surgery			
Appearance	Client concerned, but no discernable deformity	Mild	BAP1
	Minimal deformity does not require re-operation	Moderate	BAP2
	Significant deformity requires re-operation to correct	Severe	BAP3
Problems with voiding	Transient complaint that resolves without treatment	Mild	BVO1
	Requires a special return to the clinic, but no additional treatment required	Moderate	BVO2
	Requires referral to another facility for management	Severe	BVO3
Wound dehiscence	Wound disruption involving no more than one principal suture.	Mild	BWD1
	Wound disruption and involving two or more principal sutures. No surgical intervention required.	Moderate	BWD2
	Significant wound disruption requiring surgical correction	Severe	BWD3

Adverse Event	Description	Severity	Code
C. One Month or More Post-Surgery			
Infection**	Pain and erythema no obvious swelling	Mild	CIN1
	Painful swelling/purulent wound discharge	Moderate	CIN2
	Cellulitis or wound necrosis	Severe	CIN3
Delayed wound healing	Healing takes longer than usual, but no extra treatment necessary	Mild	CDW1
	Additional non-operative treatment required	Moderate	CDW2
	Requires re-operation to correct	Severe	CDW3
Appearance	Client concerned, but no discernable deformity	Mild	CAP1
	Significant scarring or other cosmetic problem, but does not require re-operation	Moderate	CAP2
	Requires re-operation to correct	Severe	CAP3
Excessive skin removed	Client concerned, but there is no-deformity on erection	Mild	CES1
	Causes slight discomfort on erection but surgical correction not necessary	Moderate	CES2
	Interferes with sexual life and surgical correction is necessary	Severe	CES3
Insufficient skin removed	Prepuce partially covers the glans only when extended	Mild	CIS1
	Prepuce still partially covers the glans and re-operation is required to correct	Moderate	CIS2
Torsion of penis	Torsion is observable, but does not cause pain or discomfort.	Mild	CTP1
	Causes mild pain or discomfort on erection, but additional operative work not necessary	Moderate	CTP2
	Requires re-operation or transfer to another facility to correct the problem	Severe	CTP3
Erectile dysfunction	Client reports occasional inability to have an erection	Mild	CED1
	Client reports frequent inability to have an erection	Moderate	CED2
	Client reports complete or near complete inability to have erections	Severe	CED3
Psycho-behavioural problems	Client reports mild sexual dissatisfaction attributed to male circumcision, but no significant psycho-behavioural consequences	Mild	CPB1
	Client reports significant sexual dissatisfaction attributed to male circumcision, but no significant psycho-behavioural consequences	Moderate	CPB2
	Significant depression or other psychological problems attributed by the participant to the male circumcision	Severe	CPB3

Adverse Event	Description	Severity	Code
C. One Month or More Post-Surgery			
Other AEs	Other AEs are described below***		

Comments:

* Additional anaesthesia implies a volume of local anaesthetic in excess of initial amount drawn up in the syringe and calculated to be sufficient for patient's weight before surgery.

** Infection is indicated by swelling, erythema, pain, elevated temperature (locally or systemically, or purulent discharge)

*** Other AEs

All other SAEs resulting in hospitalization or death should be reported to the local Institutional Review Board (IRB) and the Data and Safety Monitoring Board (DSMB) according to standard rules and procedures, usually within 10 days of notification of the event to the local Principal Investigator.

1. Genitourinary adverse events other than those listed in the above tables will be reported as cumulative aggregate events to the DSMB and IRBs at the agreed periodic reporting interval.