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Innovative Methods of Male Circumcision for HIV Prevention—Getting the Right Evidence

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Abstract: World Health Organization recommends that countries with hyperendemic and generalized HIV epidemics implement voluntary medical male circumcision programs for HIV prevention. Innovative methods of male circumcision including devices have the potential to simplify the procedure, reduce time and cost, increase client acceptability, enhance safety, and expand the numbers of providers who may perform circumcision. We describe work led by World Health Organization and supported by global partners to define a pathway for the evaluation of efficacy and safety of male circumcision devices, to set priority criteria, and to establish a process to guide the use of devices in publicly funded voluntary medical male circumcision programs for HIV prevention. A device classification scheme, an expert Technical Advisory Group on Innovations in Male Circumcision, and a formal prequalification program have also guided considerations on safe use of devices. A rigorous approach was deemed appropriate given the intervention is for use among healthy men for public health purposes. The pathway and processes led to coordinated research, better standardization in research outcomes, and guidance that informed the research, introduction and implementation phases. The lessons learnt from this case study can inform evaluation and use of future public health innovations.

Key Words: male circumcision, medical devices, innovation research, implementation, prequalification, ShangRing, PrePex

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INTRODUCTION

Based on compelling evidence,^{1–5} World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS recommended in 2007 that countries with hyperendemic and generalized HIV epidemics implement voluntary medical male circumcision (VMMC) programs for HIV prevention.⁶ Modelling studies estimated that rapid scale up of VMMC would result in reduction of HIV incidence and be cost saving.⁷ Given the considerable requirements to implement and sustain this programme, simpler male circumcision methods that minimize surgical skills and requirements were and continue to be urgently needed. This article reviews work led by WHO and supported by global partners to define a pathway for the evaluation of efficacy and safety of innovative circumcision methods including devices, to set priority criteria, and to establish a process, including through the WHO Technical Advisory Group on Innovations in Male Circumcision (MC TAG), to guide the use of devices in publicly funded VMMC programs for HIV prevention. Lessons from this case study can be applied to future innovations that seek to address urgent public health needs.

Device Landscape and Approaches to Fill Evidence Gaps

In 2008, potential technical innovations identified to simplify the male circumcision procedure included devices and innovations for anesthesia, hemostasis, and wound closure. Devices were assessed as the most promising approach to accelerate intervention delivery. The first systematic review on male circumcision devices⁸ found more than 20 commercially available products. Because few data, other than the claims by the inventors or manufacturers, were available on their clinical performance and safety for use in adult males, the MC TAG was established to advise on the minimum evidence needed and to review which devices could be considered for adult VMMC for HIV prevention in the priority African countries.

Given that low-resource countries have limited capacity to evaluate medical devices, WHO established in 2011 the Prequalification of Male Circumcision Devices Programme.⁹ WHO prequalification is a mechanism for guiding procurement decisions of Governments, United Nations, and other funding agencies. Through an objective and comprehensive assessment of a product dossier and inspection of the manufacturing site(s), the Programme ascertains whether a device has met international standards on design, testing, and adequacy of the quality management system. This body of information, together with

evidence on clinical safety, performance and acceptability reviewed by the MC TAG, results in the decision to list a product as “prequalified.” These products are then considered suitable for public sector procurement. Prequalification does not imply approval or recommendation by WHO to use a specific device. Approval for device importation and use remains the prerogative and responsibility of national regulatory authorities and ministries of health. Information about the prequalification process and an up-to-date list of prequalified devices can be found on the WHO website.¹⁰ Prequalification is time-limited, regularly reassessed, and may be retracted if the manufacturer does not adhere to postmarketing surveillance requirements, maintain manufacturing quality controls, or if new concerns about safety arise.

Which Evidence: WHO Clinical Evaluation Pathway

The MC TAG decisions on the evidence required were based on the following points:

- The risk–benefit balance of a prevention product is different than that for a therapeutic one. Male circumcision methods, including innovative devices, will be used on large numbers of healthy young men for the purpose of prevention.
- The assessment of efficacy, safety, clinical performance, and acceptability should be balanced with the importance of timeliness and practicality given the desired pace of scaling up VMMC as an effective HIV prevention intervention.
- Circumcision devices must be objectively evaluated before they are used in public health VMMC programs with evidence from at least 2 randomized controlled comparisons and 2 field research studies in at least 2 different settings or countries.

Evaluation issues center on clinical performance, efficacy, safety, ease of use, acceptability, and feasibility, including cost. Specific criteria to evaluate these aspects of an innovative device method include:

- Perspectives of clients (eg, pain control, healing and associated abstinence time, interference with normal activities)
- Perspectives of providers (eg, ease of use, procedure time, reproducibility, safety)
- Safety (eg, hemostasis, protection of glans, adverse events, minimizing risk of cross infection, including through single-use devices)
- Program considerations (eg, cost, training needs, supply management).

A preliminary evaluation pathway was developed in 2009 by experts in medical device regulation, research, public health program delivery, and clinicians with experience in resource-limited settings. The MC TAG members further advised, developed, and adopted in 2012 the *Framework for Clinical Evaluation of Devices for Male Circumcision*.¹¹ The *Framework* serves as the basis for a uniform approach to research and assessment of circumcision devices and other innovations and describes steps to progress from an initial series of studies to phased implementation in specific national

contexts. Because the purpose of using a device for VMMC was to develop a standardized method that simplified the procedure and reduced riskier steps, such as injected anesthesia, incision, and sutures, studies with diverse health care cadres in more than 1 geographic location were deemed necessary.

The first step on the pathway is to establish the clinical profile through review of available clinical data and experience in the country of origin or manufacture and assess its relevance to the population and setting of intended final use. If deemed promising, the device should be evaluated in a series of studies in countries or settings of intended final use, including case series, randomized comparative studies by skilled surgeons, studies on acceptability by providers and clients, and field studies involving trained mid-level clinical providers to demonstrate their potential to perform circumcision safely (Table 1). In addition to the clinical studies, phased implementation is advised beginning with country-led pilots and adverse event surveillance that would inform progressive expansion (Table 2).¹²

Although 2 comparative and 2 field studies are required for prequalification (see below), the total number of clients in these studies (minimum 1200) gives limited statistical power to show rare but potentially serious adverse events. Following the initial studies that inform prequalification of a device, active adverse event surveillance should document outcomes among at least the first 1000 clients within each country. If the complication rates are within acceptable limits, broader scale-up with passive surveillance should continue, documenting adverse events among clients who return.

The MC TAG advised that initial studies be conducted on men aged 18 years and older in accordance with local regulations on age of research participants. Once safety and acceptability had been established in adult populations, bridging studies involving at least 200 clients were necessary to demonstrate clinical safety in younger age groups.

Classification of Devices

To provide a framework for considering issues and potential risks with different types of circumcision devices, the MC TAG developed a classification system for male circumcision devices according to the time that a device remains on the body and the mechanism of action (Table 3). This comprehensive classification covers male circumcision devices relevant for infants, adolescents, and adults. Three device categories by mechanism of action are (1) clamp, (2) elastic collar compression, and (3) ligature compression. Clamp devices deliver a rapid, tight compression of the foreskin sufficient to achieve hemostasis and prevent tissue slippage such that the foreskin can be removed at the time of device application; injected local anesthesia is required. Part or all of device is left in situ, usually up to 1 week. The elastic collar compression-type device provides slow compression between an elastic ring and a hard inner ring sufficient to cause ischemic necrosis of the foreskin over a period of 1 week while the device remains in place. Ligature compression devices are similar except that a nonrigid ligature holds the foreskin in place against an inner hard ring. These different mechanisms of action have unique risks that inform monitoring.

TABLE 1. Research Pathway for Clinical Evaluation of Innovative Male Circumcision Methods: Clinical and Field Studies in Country or Setting of Intended Final Use

Type of Study	Sample Size (Range)*	End-Points	Notes and Comments
Case series (noncomparative study)	~50 (25–100)	Primary end-points Clinical AEs Device-related incidents Secondary end-points Technical difficulty and complications during procedure and removal processes† Pain assessment at key time points Client satisfaction Cosmetic results† Healing process† Time to complete healing	Conducted with appropriate attention to data quality and integrity and independence from the manufacturer or developer Stopping rules defined for serious AEs, including independent review by, for example, independent Data Monitoring Committee Phased recruitment Followed up closely for a minimum of 6 wks and then weekly to complete healing (epithelium covering entire wound) Documented ease of training new providers and time required to achieve adequate competence with the new device and procedure Collated reasons to decline participation as indirect measure of acceptability
Comparative trial	~100 (50–300)	Primary end-point Operative and removal times Secondary end-points Technical difficulty and complications during placement and removal† Pain assessment at key time points Clinical AEs Device-related incidents Client satisfaction Cosmetic results† Healing process† Time to complete healing	Randomized controlled trial comparing new device with a standard surgical procedure as defined in WHO Manual for Male Circumcision Under Local Anaesthesia or other well-standardized and documented circumcision method Could consider unbalanced randomization (eg, 2:1) to accumulate more data on new device Superiority or noninferiority trial Define stopping rules for serious AEs and device-related incidents, including review by an independent Data Monitoring Committee Consider accumulating data and experience from more than 1 site in a series of coordinated single-site trials with standardized definitions and procedures Use appropriate methods to measure procedure and removal times; document ease and duration of training; follow-up for a minimum of 6 wks after device removal, but follow-up can be less intensive than in previous study because more clinical experience is available Collate data on reasons to decline participation as indirect measure of acceptability
Acceptability substudies	—	Assess acceptability During procedure to place device While device in situ, including during (nocturnal) erections During removal Cosmetic finish	Incorporate assessment of acceptability into all clinical research in country of intended final use; could be based on subgroups of men involved in the case series and/or the comparative trials Assess acceptability to partners of clients and to parents of any minors undergoing circumcision
Pilot field study	100 (50–200)	Primary end-points Provider training needs Provider acceptability Secondary end-points AEs and device-related incidents among all men in whom the device procedure was planned or started, even if subsequently abandoned Procedure and removal times	To determine training and support needs, train at least 10 providers Ensure good data quality and integrity, including recording outcomes on all procedure starts Collate data on reasons for declining participation in the study, as an indirect measure of acceptability This maybe a run-in phase to the cohort field study

(continued on next page)

TABLE 1. (Continued) Research Pathway for Clinical Evaluation of Innovative Male Circumcision Methods: Clinical and Field Studies in Country or Setting of Intended Final Use

Type of Study	Sample Size (Range)*	End-Points	Notes and Comments
Cohort field study	~500 (250–1000)	Primary end-points Procedure and removal times Secondary end-points Training needs of providers Safety of procedure and removal Clinical AEs and device-related incidents among all men in whom the device procedure was planned or started, even if subsequently abandoned Practicality of device use (ie, need to return to clinic for removal)	Systematic review of clinical AEs and device-related incidents after every 100 procedure starts; interval between reviews can be increased as experience with method grows Ensure mechanisms in place to capture information on all AEs, even if men are not followed systematically to complete wound healing Monitoring outcomes, especially AEs and losses to follow-up, is important Collate data to compare costs of: The device Training to use device compared with cost of training in standard surgical method Provider's time Staff time for follow-up visits Equipment and supplies needed for placement and removal Collate data on reasons for declining participation in the study, as indirect measure of acceptability Include assessments of acceptability among subset of clients, their partners and, for adolescents, their parents, with respect to device placement, wearing the device, and device removal

*Number of clients circumcised with the new device.

†Requires documentation by photographs.

AE, adverse event.

Getting the Evidence: Application of the Framework

Two innovative devices that are currently prequalified, the PrePex and ShangRing, are used as examples of the application of the *Framework*. The PrePex is considered simpler than surgery as no local injectable anesthesia or suturing are needed as the foreskin is removed at a second visit after 1 week. The recommended studies were conducted in 3 countries with support from ministries of health, President's Emergency Plan for AIDS Relief, the Bill & Melinda Gates Foundation, and the United Nations Population Fund. The first-in-human study involving 55 men was conducted in Rwanda in 2010.¹³ A randomized comparison between the device and surgery in 217 men demonstrated that the device resulted in successful circumcision but could not be placed on about 10% of men because of phimosis or narrow foreskin opening.¹⁴ A subsequent pilot study with mid-level providers in 49 men¹⁵ and a field study in 590 men¹⁶ demonstrated safety and acceptability. These data were reviewed in 2012 by the MC TAG, which advised collection of further evidence in a different country and setting.¹⁷

In January 2013, results from 3 studies in Zimbabwe were reviewed¹⁸—an initial study with 53 men, a randomized controlled trial in 240 men, a field study using mid-level providers in 642 men, and 2 field studies from Uganda

involving a total of 921 men.^{19,20} In total, more than 2500 men aged 18 years and older were enrolled in these studies. Approximately 7% of men could not have the PrePex device placed for various anatomical and technical reasons. Adverse events occurred in 1.7% of men, most of which were mild or moderate. Serious adverse events occurred in 0.4% of men and more than half were because of device displacement or removal (including self-removal). These displacements resulted in pain, swelling, and occasional blistering of the partially necrotic foreskin, requiring rapid intervention by a skilled surgeon to prevent severe local or systemic infection and/or permanent sequelae. MC TAG concluded that the device was efficacious and safe among healthy men aged 18 years and older when used by trained mid-level providers in public health programs. It advised that skilled surgical backup be available within 6–12 hours to manage complications, particularly displacements, and that conventional surgical circumcision needed to be available to the 10%–15% of adult men who could not be circumcised by PrePex.

Other components of the WHO prequalification process (review of product dossiers, assessment of manufacturing quality management systems) were undertaken in parallel with the clinical evaluation. PrePex was prequalified by WHO in 2013 for use in men aged 18 years and older, allowing its use within national programs. Most national programs, supported by key global partners, have

TABLE 2. Pilot Implementation Studies: One Step in Introducing a New Male Circumcision Method

Type of Study	No. Clients (Range)	Objectives/End-Points	Notes and Comments
Preparatory	—	—	Undertake key stakeholder consultations and agreement on conditions for use in pilot study (which providers, which settings), regulatory issues Conduct training and determine training requirements
Phase 1	Typically 100 (50–200)	Training for providers (if training is included as part of the pilot implementation study), evaluation of training (eg, ease of training, training and supervision requirements, practicality of training) Acceptability for providers (eg, comfortable using and promoting device) and for clients (eg, pain and comfort with procedure, support of family, partners and friends), potential advantages and disadvantages Safety in specific country context and setting (types of providers, clients, and settings) Feasibility in various settings where service delivery is expected to occur	Use the same eligibility criteria for client selection as in the clinical trials and field studies (eg, age, exclusion of medical or device-specific contraindications) Define the evaluation plan and assessment criteria in advance, with review by those independent of the program managers and device promoters Monitor adverse events systematically using standardized definitions
Phase 2	Typically 500 (250–1000)	Acceptability, safety, feasibility, cost, training, logistics in settings where service will be routinely provided	Issues to be addressed in second phase pilot implementation will be driven by experiences and outcomes of first phase

undertaken the phased approach to implement this new method.

The ShangRing does not require suturing but requires injected local anesthesia and a return visit after 1 week for device removal. The foreskin is removed at the time of placement. The device had been initially assessed in multiple research studies in China.²¹ For the review of ShangRing use

in African settings, evidence from men aged 18 years and older was available from Kenya, Zambia, and Uganda. It consisted of an initial case series (40 men),²² a study of spontaneous detachment (50 men),²³ a randomized comparison with surgery (400 men, 200 allocated to ShangRing),²⁴ and 3 field studies (total 1764 men).^{25,26} Approximately 1% of men were ineligible for the ShangRing because of foreskin abnormalities. During device placement, 0.4% men (7) required rapid intervention with surgical circumcision as the excision had occurred but the foreskin slipped from the device and required suturing. No serious adverse events occurred; 20 men (1.0%) experienced moderate adverse events from a total of 1983 successful device placements. All adverse events were managed with minor interventions and resolved without long-term sequelae. Rates were similar to those observed with conventional surgical circumcision. The MC TAG concluded that the ShangRing was efficacious and safe for use in healthy men aged 18 years and older when performed by trained providers in public health programs and that skilled surgical backup needed to be available to convert device placement failures to a conventional procedure.²⁷

In September 2014, additional evidence which met the *Framework's* minimum data requirements on the clinical profile of the ShangRing from studies in Kenya and Uganda in 357 adolescents aged 13–17 years was reviewed and showed the device to be safe and acceptable in this age group.^{28,29} In June 2015, the ShangRing manufacturer satisfactorily met the necessary prequalification requirements and the device was prequalified for males 13 years and older.

In a bridging study among adolescents aged 13–17 years in Zimbabwe, PrePex could not be placed in 36% because of a narrow foreskin opening or adhesions between glans and foreskin. However, the device was safe and acceptable in the 402 successful placements.³⁰

Because of limited numbers of device (PrePex and ShangRing) placements in those 13–17 years, MC TAG advised active surveillance of 2000 adolescents from at least 3 countries for each specific device. This surveillance will provide further evidence on safety and use.

The MC TAG also reviewed data on more than 24,000 PrePex device placements from 14 pilot implementation studies in 10 countries [Botswana, Kenya, Lesotho, Malawi, Mozambique, South Africa (3), Uganda (3), United Republic of Tanzania, Zambia, Zimbabwe], 6 active surveillance studies [Botswana, Rwanda, South Africa, Uganda (2), Zimbabwe], and passive surveillance in Rwanda and Zimbabwe. Safety in the hands of mid-level providers was consistent with earlier reports and displacements occurred at a similar rate; all were successfully managed by prompt referral to skilled surgery. A small number of tetanus cases after both conventional surgical and PrePex circumcision were reported from routine surveillance of VMMC programs. In response, an expert consultation was convened by WHO²⁷ to further review and advise on tetanus risk and mitigation with surgery and device use. Overall, the monitoring during phased implementation provided further evidence to guide use and safety.

TABLE 3. Categories of Medical Male Circumcision Devices With Examples

Age Group	When Used*	Mechanism of Action†	Reuse	Example Products
Infant	Surgical assist	Vice clamp	Reusable	Gomco clamp, Mogen clamp
		All-in-one clamp and cut	Single use	AccuCirc
Adult and adolescent	Surgical assist	Ligature	Single use	Plastibell
		Vice clamp	Reusable	Gomco clamp
		Vice clamp	Single use	UniCirc, CircumQ
	In situ	Cutting and suturing guide	Single use	SimpleCirc
		Vice clamp	Single use	TaraKLamp, Alisklamp, RapideClamp, Ismail Clamp, SmartKlamp, CircumStar
		Collar clamp	Single use	ShangRing, Kirve Klamp, Sunathrone clamp
		Elastic collar compression	Single use	PrePex

*Surgical assist devices are used with standard surgical instruments, such as scalpel and artery forceps; in situ devices remain on the penis after placement, usually up to 1 week.

†Vice clamp devices compress foreskin between 2 hard rings and tend to be bulky because of lever or screw mechanism necessary to crush foreskin, particularly in adults; “all-in-one clamp and cut” stand-alone devices require no other surgical instruments; ligature devices comprise a rigid inner ring placed under the foreskin with a nonrigid ligature tightened to exert crushing force on foreskin; collar clamp devices compress foreskin between an inner rigid ring and an outer rigid collar, tightened with a latch or ratchet mechanism; elastic collar compression devices comprise a rigid inner ring with an elastic outer ring, which exerts slow compression that is sufficient to cause ischemic necrosis of the foreskin.

DISCUSSION

The *Framework for Clinical Evaluation of Devices for Male Circumcision* has been instrumental in facilitating uniform and relevant research to evaluate an innovative method. The clear research pathway, objective evaluation criteria, and a rational sequence for phased implementation are likely relevant to other public health innovations. Although the process from innovation to research and expanded use seems long and cumbersome (Fig. 1), all the steps, without shortcuts, remain necessary to ensure safety, acceptability, and suitability for use in public health programs. In addition for prequalification, manufacturing procedures and documentation considered adequate to support quality large-scale production take time to develop, implement, and test. Although the clinical requirements defined in the *Framework* are substantially more stringent than those normally required by national regulatory authorities for circumcision devices, they are appropriate given the risk–benefit balance of a medical device used for prevention purposes.

A number of advantages and lessons emerged through this process (Table 4). First, countries and funders have unbiased information on circumcision devices suitable for use within publicly funded VMMC programs. The prequalification process does not replace national regulatory authority responsibilities to authorize and oversee marketing of medical devices but provides them with additional information on which to base decisions. Second,

from the perspective of the device manufacturer and stakeholders providing technical or funding support, a clear evaluation pathway provides clarity on the assessments and evidence needed. Third, the process of developing the *Framework*, evaluation of devices, convening of the MC TAG, and prequalification activities required input from multiple stakeholders in the form of personnel time and financial resources. The support that came primarily from Bill & Melinda Gates Foundation and President’s Emergency Plan for AIDS Relief was considerable and likely exceeded the manufacturers’ contributions to development costs of the devices. This external support reinforces the need for fair public sector pricing of devices (Table 5).

Initial device studies were undertaken on adult men. Countries and implementing partners have queried the safety and effectiveness of specific devices for adolescents and infants. Safe methods for these age groups are becoming increasingly important as countries consider how to sustain high prevalence of VMMC and reduced risk of HIV infection once 80% of men aged 15–49 years are reached. The pathway described in the *Framework* also applies to the assessment of novel infant and adolescent male circumcision devices.

The processes described to evaluate safety with innovative methods are relevant for other global public health interventions supported through limited international and



FIGURE 1. Timeline for WHO technical reviews and prequalification process on male circumcision devices.

TABLE 4. Advantages and Lessons Learned on Development and Implementation of Evaluation Criteria for Male Circumcision Devices

Advantages	Lessons Learned
Defines development and assessment pathway	Global partner collaboration and coordination is key
Greater uniformity in data obtained, including outcome and adverse event definitions	Stakeholder agreement of prequalification as a requirement for procurement needed to ensure manufacturer compliance with evaluation pathway
Objective review of clinical data	Longer than expected timelines for clinical studies
Collaboration among stakeholders including donors and ministries of health leading to consensus and coordination of research activities to increase efficiencies	Prequalification process requires significant staff and financial resource investments; donor funding support needed
Formal prequalification process adds assessment of other aspects of a device product, further assuring quality	Completing the prequalification process can take many months before the manufacturer satisfactorily meets requirements by submitting complete documentation, responding to requests for clarification, and implementing suggested corrective actions following site inspections
Rational sequence for phased implementation that expands beyond clinical aspects to include program and policy considerations	Phased implementation critical to engage stakeholders, enhance acceptability of new method, and learn from pilots to refine service delivery in specific contexts
Detection of rare but important adverse events	Postmarketing surveillance with reviews at global level permits identification of rare events that may not be apparent at national level

TABLE 5. Roles of Principal Collaborating Partners

Partner	Role
WHO	Defined a clear evaluation pathway, balancing the need for quality safety data with timeliness of expanding VMMC coverage Established MC TAG and acted as secretariat for MC TAG Developed rigorous, transparent process to assure independent and objective evaluation of safety, efficacy, and acceptability data by MC TAG Established Prequalification Programme to assure quality medical devices for use in public health programs Collaborated with researchers to share unpublished data for review Conducted postmarketing surveillance to identify rare but serious adverse events
Bill & Melinda Gates Foundation	Funded landscape assessment of safety and suitability of available devices for use in VMMC programs Funded WHO for staffing and operating costs, MC TAG secretariat, and TAG meetings Supported research on PrePex, ShangRing, and AccuCirc devices
President's Emergency Plan for AIDS Relief	Supported pilot implementation studies of PrePex Supported WHO to convene meetings, develop guidance, and provide technical support to countries

domestic financial resources. Lessons that have been learned to date and that will continue to accrue should be used to inform introduction and broad implementation of other public health interventions.

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