Adult Male Circumcision Devices

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The Challenge

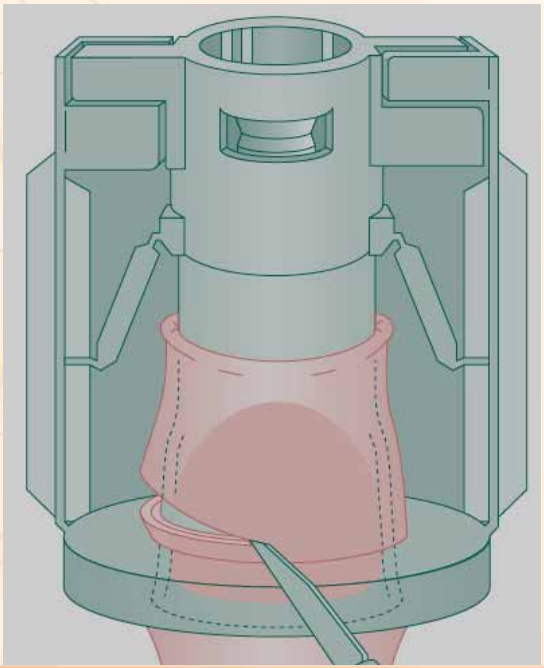
- **Male circumcision devices have potential to accelerate programme scale up**
  - Potentially faster, simpler procedure requiring fewer instruments
  - May require less highly-trained providers
  - May be more acceptable
- **Several devices used and well-documented in infants and boys, but safety, effectiveness, acceptability among adults in Africa not known**

The Tara KLamp Device

http://www.taraklamp.com/

Taramedic Corporation, Kuala Lumpur, Malaysia

- **Developed by Gurcharan Singh in Malaysia**
- **Successfully used in Malaysia for circumcision of boys, including in public sector hospitals and circumcision campaigns**
- **Promoted by developer in Lesotho and South Africa as an improvement on existing traditional methods**



Tara KLamp Clinical Data

- **Schmitz et al, Tropical Doctor 2001**
  - 64 boys ages 7 - 12 years in Kuala Lumpur circumcised on same day
  - Median operating time 10 minutes
  - One procedure reverted to surgical circumcision
  - After 4 days the external clamping mechanism removed (1 case mild bleeding)
  - Inner tube allowed to fall off spontaneously (majority within 3 days)
  - One case of wound dehiscence
  - In 3 boys residual foreskin considered "too long" → importance of marking desired position of device

Tara KLamp Clinical Data

- **Schmitz et al, BJU International 2001**
  - 143 boys ages 2 – 5 years in Rotterdam, NL using Tara KLamp
  - 160 boys ages 2 – 4 years in Utrecht, NL using surgical dissection
  - 93% of Turkish or Moroccan origin
  - Median operating time 7 minutes compared with 15 minutes for surgery
  - 2 cases started with TK, but reverted to surgery (device slipped when cutting foreskin, device opened during procedure)
  - Complications: bleeding (2), infection (3)
  - Comparable to complication rates seen with surgery

Randomized Controlled Trial in Orange Farm

- **Men from control group in Orange Farm male circumcision trial for HIV prevention invited to participate in randomised assessment of Tara KLamp device**
- **166 men invited, 97 declined to participate, 69 randomised**
- **Tara KLamp**
  - 35 men randomised
  - 7 did not return, 4 switched to surgery
  - 12 adverse events (sepsis, bleeding, erythema, cellulitis, tube adhering to tissue, …)
- **Forceps-guided surgery**
  - 34 men randomised
  - 6 did not return
  - 0 adverse events
- **Retraining by manufacturer's agent did not result in improved outcomes**

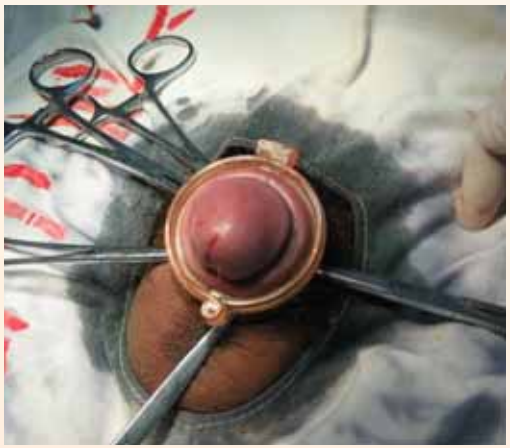
Lagarde et al (2009) *South African Medical Journal*; 99:163

Tara KLamp Circumcisions in KwaZulu Natal

- **Circumcision programme launched in 2009 by King Goodwill Zwelithini based on traditional approach**
  - Preparation and sensitization in community, including HIV test
  - Circumcision camps over 2-3 days
    - Civic education, sexual and reproductive health counselling, circumcision procedure
  - Approximately 35,000 circumcisions performed in the camps
  - Chose to use Tara KLamp device as one circumcision method
    - Used in about 25% of cases
    - Remainder circumcised using forceps guided method
    - VERY controversial choice and extensive public campaign led by Treatment Action Campaign against this decision
  - Few data have emerged from KZN circumcision camps on number of circumcisions performed and complication rates
  - Apparently higher acceptability and lower complication rates than seen in Orange Farm
- **No further clinical studies of Tara KLamp planned**

Shang Ring Device

- Developed in Wuhu, China and quite extensive successful clinical use
- Particular feature of everting foreskin over inner ring, placing outer ring then cutting off residual foreskin
- Leaves glans exposed during healing
- Device removed after 7 days



Wuhu Snnda Medical Treatment Appliance Technology Co. Ltd.

http://www.snnda.com

Shang Ring Clinical Data

- **Low complication rates in China**
- **0.58% bleeding, 0.67% local infection, 2.42% wound dehiscence**
  - Peng et al (*Asian J Androl*. 2008;10: 447–454)
- **0.6% bleeding, 0.6% wound infections, 0.6% wound dehiscence, 4.5% wound oedema**
  - Cheng et al (*Zhonghua Nan Ke Xue*. 2009; 5:584–592)
- **Pilot introductory study, Homa Bay, Kenya**
  - 40 HIV negative men
  - Device placement 4.8 (sd 2.0) minutes
  - Device removal 3.9 (sd 2.6) minutes
  - 6 mild adverse events (3 skin injury, 2 oedema, 1 mild infection)
  - 3 partial ring detachments
  - Device safe for further study in Africa
  - Barone et al, *JAIDS* 2011; 57: e7

Shang Ring Research

- **Acceptability, safety and provider attitudes**
  - Self-selection to device or surgery (dorsal slit)
  - 250-400 devices, 1000 dorsal slit
  - Uniform recording of healing times
  - Rakai, Uganda, currently underway
- **Healing times and spontaneous detachment**
  - Assess effects on healing time & determine whether the device will spontaneously detach if removal is delayed
  - Acceptability of the Shang Ring and surgical result
  - 50 men, Homa Bay, Kenya
  - Poster TUPE385, IAS 2011 Rome

Shang Ring Research

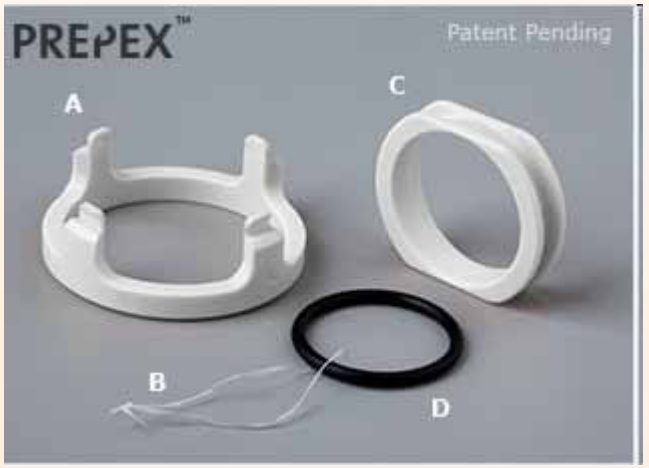
- **Comparison of the Shang Ring with Conventional Surgical Methods: A Randomized Controlled Trial**
  - Device(s): Shang ring vs forceps guided (Kenya) or dorsal slit (Zambia)
  - Objectives/endpoints:
    - Compare the pain and acceptability of the Shang Ring procedure with surgical approach; compare the safety and course of wound healing, including time to complete healing; compare the ease of methods
    - Compare the cost of the Shang Ring procedure to the cost of the surgical techniques; assess adherence to post-surgical instructions for wound care & sexual abstinence
  - Design: Randomized trial 400 men total
  - Location: Homa Bay, Kenya; Lusaka, Zambia
  - Status: Enrolment complete, follow-up to be complete by end August 2011

Shang Ring Research

- **A Prospective Observational Study of Male Circumcision Using the Shang Ring in Routine Clinical Settings in Kenya & Zambia**
  - To estimate rates of adverse events during routine service delivery, especially those that are rare or unexpected
    - Evaluate the acceptability of the Shang Ring procedure; Explore understanding of post-VMMC abstinence period and related issues; Document training methods and the cost of training; Record HIV status to evaluate whether HIV positive men are at higher risk for complications or delayed healing following Shang Ring circumcision
  - Location: Homa Bay, Kenya; Lusaka, Zambia
  - Numbers: 1000 men total
  - Status: Planned

PrePex Device

- Developed in Tel Aviv, Israel with initial clinical work conducted in Rwanda
- Inner ring (C) placed between glans and foreskin
- Outer O-ring (D) applied externally to foreskin using the applicator (A) and pinches foreskin in groove in inner ring
- O-ring causes ischaemia
- Necrotic foreskin removed, together with device, after 7 days
- No anaesthesia required



- Circ MedTech, Tel Aviv, Israel
- http://www.prepex.com/

PrePex Research

- **Clinical development in Rwanda**
  - Initial studies, fine tuning development and characteristics of device
- **Formal clinical study**
  - 40 men, Kanombe Hospital, Kigali, Rwanda
  - No adverse events at placement, 1 AE (mild diffuse oedema) after removal
  - Healing time ("complete epithelialization and no drainage") 16.9 (sd 4) days post removal
  - Minimal pain
  - Presented at CROI, Boston, 2011 (Bitega et al, paper # 1007, http://retroconference.org/2011/Abstracts/40740.htm)

PrePex Studies

- **A Prospective, Randomized, Open Label, Trial Comparing the PrePex™ System to Surgical Circumcision**
  - Device(s): PrePex vs dorsal slit
  - Objectives/endpoints:
    - Operating time
    - AEs, pain, patient satisfaction, time to complete healing, difficulties and complications
  - Design: Randomised controlled trial, Kigali, Rwanda
  - Numbers: 144 randomised to PrePex, 73 to surgery
  - Status: Completed, results being prepared for publication

PrePex Studies

- **Open label prospective study to assess the safety and efficacy of different management methods of the PrePex circumcision device**
  - Device(s): PrePex
  - Objectives/endpoints:
    - Safety when procedure performed by nurses
    - Discomfort during daily activities
  - Design: Field study
  - Location: Kanombe Military Hospital, Kigali Rwanda
  - Numbers: 49
  - Status: Completed, results being prepared for publication

PrePex Studies

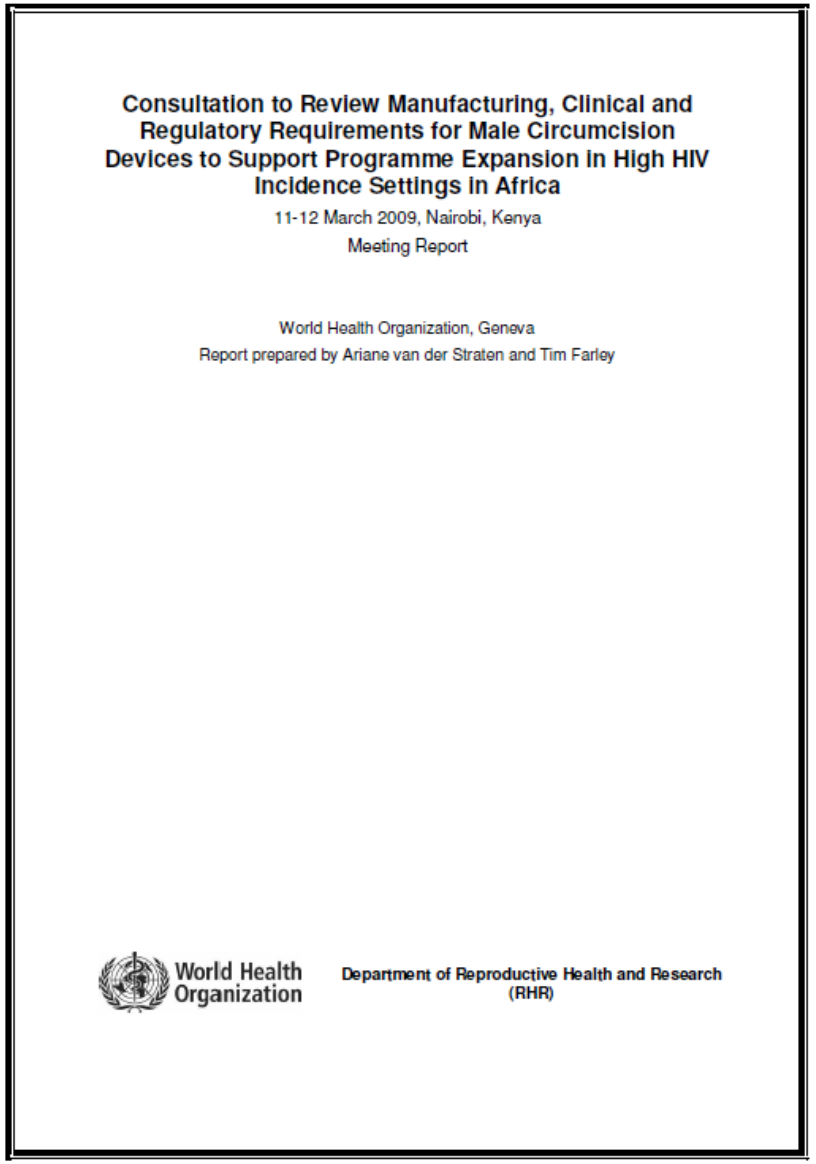
- **Open Label Field Study to Assess the Safety of PrePex Circumcision Device when Performed by Non-Physicians**
  - Device(s): PrePex
  - Objectives/endpoints:
    - Safety when procedure performed by nurses;
    - Cost-effectiveness
    - Training needs, acceptability (men, partners, providers)
  - Design: Field study
  - Location: Kanombe Military Hospital, Kigali Rwanda
  - Numbers: Training phase – 75; Pilot phase – 100; Pivotal phase – 403
  - Status: Planned

PrePex Studies

- Randomized comparison of PrePex and surgery in Zimbabwe
  - Device(s): PrePex vs. forceps guided
  - Objectives/endpoints:
    - Safety (Adverse events)
    - Procedure times (placement, removal)
    - Resource needs
    - Healing times (photographs)
    - Pain over first 16h following placement and during removal
  - Design: Randomised trial
  - Location: Zimbabwe
  - Numbers: 120 + 60 men
  - Status: Planned, under review
- Proposed to expand research to larger number of men and mid-level providers if/when product shown safe and acceptable

Male Circumcision Devices Consultation

Nairobi, March 2009



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

11-12 March 2009, Nairobi, Kenya

Meeting Report

World Health Organization, Geneva

Report prepared by Ariane van der Straten and Tim Farley

World Health Organization

Department of Reproductive Health and Research (RHR)

Framework for Clinical Evaluation of Adult Male Circumcision Devices

- Male circumcision devices have potential to accelerate programme scale up and expansion to areas not well served by existing surgical services.
- Have the potential to be used by mid-level providers
- Transferring clinical experience to new populations and/or providers needs to be done cautiously and progressively, ensuring that the safety, effectiveness and acceptability of the devices in populations with good access to care are established before proceeding to more widespread implementation.

Regulatory Requirements for Male Circumcision Devices

- Medical device regulations do not necessarily require any clinical data before obtaining US FDA approval, or approval to market in the European Union (CE Mark)
- Device regulations in resource-constrained countries are less well developed and enforced or enforceable
- Since male circumcision programmes being implemented as a public health intervention for HIV prevention among healthy men, important to proceed cautiously and avoid any major complications or adverse events
- Public acceptance of circumcision devices and confidence in the male circumcision programmes could easily be undermined if adverse events occur

Conclusions and Recommendations

- Requirements outlined for evaluation of male circumcision devices are more stringent than requirements for registration of medical devices that present minimal risks to the provider or patient.
- Desired end result is to ensure that safe, effective and acceptable devices can be introduced rapidly into national programmes
- Requires more extensive data on clinical experience and acceptability than required for a device to be authorized for distribution in the country.

Framework Defines Progression of Clinical Studies

- Clinical studies by skilled surgeons in the country of origin or manufacture
- Clinical studies by skilled surgeons in the country of intended use,
- Comparative clinical study by skilled surgeons in a low resource setting
- Field studies by trained clinical personnel in a low resource setting, reflecting anticipated conditions of intended use

Framework for Evaluation of Devices

- **Compilation of manufacturing, performance and clinical experience in country of origin**
  - Case-series plus comparative study
  - Safety, effectiveness, document potential advantages, generate data independent of developer or manufacturer
- **Studies in country of intended final use**
  - Case series, comparative study, acceptability, field study, post-marketing surveillance

Clinical Studies in Country of Origin

- **Case series (non-comparative study)**
  - Target numbers: 50 (range 25-100)
  - Endpoints
    - Adverse events, device-related incidents
    - Technical difficulties, pain, healing process
- **Comparative study**
  - Target numbers: 100 (50-300) with device
  - Endpoints
    - Operative and removal times
    - Adverse events, device-related incidents
    - Technical difficulties, pain, healing process
  - Provided by trained physicians, compared with an established circumcision method
  - Consider 2:1 randomisation

Clinical Studies in Country(ies) of Intended Final Use

- **Case series (non-comparative study)**
  - Target numbers: 50 (range 25-100)
  - Endpoints
    - Adverse events, device-related incidents
    - Technical difficulties, pain, healing process
  - Intensive follow-up to complete wound healing
- **Comparative study**
  - Target numbers: 100 (50-300) with device
  - Endpoints
    - Operative and removal times
    - Adverse events, device-related incidents
    - Technical difficulties, pain, healing process
  - Provided by trained physicians, compared with an established circumcision method
  - Consider 2:1 randomisation

Field Studies in Settings of Intended Final Use

- **Pilot field studies**
  - Target numbers: 100 (range 50-200)
  - Endpoints
    - Adverse events, device-related incidents
    - Provider training needs
  - Careful follow-up to document AEs and wound healing
- **Cohort studies**
  - Target numbers: 500 (300-800)
  - Endpoints
    - Adverse events, device-related incidents
    - Provider training needs
    - Careful follow-up to document AEs and wound healing
  - Collect data to inform cost effectiveness and acceptability

Requirements for WHO to Recommend a Device for Use in Male Circumcision Programmes

- **WHO Technical Advisory Group on Technical Innovations in Male Circumcision**
  - First face-to-face meeting in Lausanne, Switzerland, 12-13 July, 2011
  - Reviewed clinical framework and made operational definitions of requirements for clinical data
  - Defined requirements for documentation about the device and manufacturing process
  - Extended clinical framework to consider new devices for infant circumcision or expansion of existing devices to new population or user groups
- **Procedures informed by processes leading to recommendations for condoms, intrauterine devices, HIV diagnostics and other innovative technologies**
- **Procedures and principles are applicable to assessing other innovations in male circumcision**
  - Haemostatic gauze, super-glue, anaesthesia, analgesia, …

Requirements for WHO to Recommend a Device for Use in Male Circumcision Programmes (ct'd)

- **Underlying principles**
  - Male circumcision devices have potential to reduce procedure time and/or facilitate service delivery by mid-level providers
  - Strike a balance between encouraging innovation, avoiding unnecessary barriers to entry and recommending unsafe devices for use in programmes, or devices used in unsafe ways
- **Clinical data in country(ies) and settings of intended final use**
  - Defined minimum number of studies and minimum number of patients from different populations to demonstrate safety of device
  - Defined minimum requirements for bridging studies to new types of provider or settings
- **Surveillance requirements**
  - Mechanism to compile, analyse, interpret and act on adverse event reports
  - Careful surveillance of initial introduction
  - Can be relaxed to less intensive surveillance if safety data are reassuring

Requirements for WHO to Recommend a Device for Use in Male Circumcision Programmes (ct'd)

- **Device specifications and manufacturing requirements**
  - Clear description of device and design specifications
  - Clear risk analysis and description of mitigation measures, including potential environmental impact
  - Specification of relevant ISO standards that apply to materials and packaging
  - Clear description of manufacturing processes, including quality assurance procedures (ISO-13485 certification) and capacity to manufacture or scale up manufacturing to meet potential demand
  - Registration in either USA or EU
- **Product pricing**
  - Cost per device needs to be considered in the context of the cost of the whole circumcision procedure, including preparation and disposing of instruments and environmental impact.
  - Cost per device needs to be reasonable in relation to manufacturing and distribution costs, considering the public health goals of circumcision programmes and responsible use of public funds that are supporting such programmes.