TETANUS and VMMC with PrePex

RISK ANALYSIS: FINDINGS & RECOMMENDATIONS

For Expert Consultation with WHO

March 9th 2015
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EXECUTIVE SUMMARY

February 25, 2015

Recently, three cases of Tetanus occurring after PrePex Voluntary Medical Male Circumcision (VMMC) have been reported in two countries. Circ Medtech Ltd. (CMT) has conducted and completed a comprehensive risk analysis, performed by medical experts in the field of infectious diseases.

These medical experts have concluded that:

- Use of the PrePex device and method has a very low risk for the contraction of Tetanus and therefore no *Clostridium Tetani* vaccination is required prior to PrePex application.
- The proposed updates to CMT's PrePex Instructions for the User (IFU) are safe and effective and will further mitigate any potential risk of PrePex clients developing Tetanus.

Written opinions and recommendations have been provided by the following experts:

- Prof. Itzhak Brook M.D., M. Sc.  
  *Professor of Pediatrics and Medicine, Georgetown University, Washington DC, USA.*  
  World-renowned clinician, researcher and one of the leading authorities on anaerobic bacteria infections. ([Biography](#))

- Prof. Giampietro Schiavo, PhD FMedSci FSB  
  *Professor of Cellular Neurobiology, Sobell Department of Motor Neuroscience and Movement Disorders, UCL Institute of Neurology, University College, London, UK.*  
  Leading researcher of Tetanus toxin and the most prominent writer on the subject ([Biography](#))

- Dr. Parastu Meidany, MBCh, FCPath (Micro), MMED, DTM&H, Dip HIV  
  *Clinical Microbiology and Infectious Diseases Specialist, Johannesburg, South Africa.*  
  Clinician and researcher specializing in infectious diseases ([Biography](#))

This document contains 5 independent expert opinion letters:

1. **PrePex and Tetanus - Letter I - Professor Brook**  
   Date: 19 Jan, 2015  
   Subject: Evaluation of the risk of tetanus developing following utilization of PrePex for non-surgical circumcision.  
   Prof. Brook gives his opinion regarding the biological plausibility of Tetanus infection due to PrePex-induced necrotic foreskin.

2. **PrePex and Tetanus - Letter II - Professor Brook**  
   Date: 12 Feb, 2015  
   Subject: Further evaluation of the risk of tetanus developing following utilization of PrePex for non-surgical circumcision.  
   Prof. Brook gives his opinion regarding the biological plausibility of Tetanus infection due to anaerobic areas related to use of the PrePex device.  

/cont’d
EXECUTIVE SUMMARY cont’d

3. **PrePex and Tetanus - Letter III - Professor Brook**  
   Date: 21 Feb, 2015  
   Subject: Possible emergence of vegetative forms of *Clostridium tetani* in post-circumcision wounds: Comparison between post-surgical circumcision and post-PrePex wounds.  
   Prof. Brook gives his opinion regarding wound comparison and the biological plausibility of Tetanus infection due to anaerobic areas related to use of the PrePex device.

4. **Tetanus Following Use of PrePex - Professor Schiavo**  
   Date: 21 Feb, 2015  
   Subject: Evaluation of the risk of tetanus following the clinical use of PrePex for nonsurgical circumcision.  
   Prof. Schiavo gives his opinion regarding the risk of Tetanus following use of the PrePex device.

5. **Scientific Validation of Proposed PrePex IFU Updates – Doctor Meidany**  
   Date: 12 Feb, 2015  
   Subject: Scientific evidence of the safety and efficacy of the proposed updates to the PrePex IFU (Rev 15).  
   Dr. Meidany gives her opinion on the scientific background for the proposed updates to the PrePex IFU (Rev 15).

For any questions or further information, please contact:

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[www.prepex.com](http://www.prepex.com)
Re: Evaluation of the risk of tetanus developing following utilization of PrePex for non-surgical circumcision

Dear Mr. Kushnir,

I have been requested by you to evaluate the risk of tetanus developing following utilization of PrePex for non-surgical circumcision due to the foreskin tissue becoming devitalized and necrotic, and the creation of anaerobic conditions conducive to Clostridium tetani growth.

I have reviewed the following materials concerning the above matter.

1. WHO Safety notice (8th Dec 2014)
2. Circ MedTech Field Safety Notice (CMT_FSN_001_2014)
3. Uganda report of 2 cases of Tetanus post PrePex procedure
4. Rwanda report of 1 case of Tetanus post PrePex procedure
5. PrePex Information for Users rev 14
6. PrePex procedure videos – Placements and Removals
7. PrePex photos from day 0 to day 7
8. Photos of PrePex wound on day 7 – good wound and poor wounds
9. Photos of Adverse events including significant Edema following displacement
10. Reports from all PrePex studies
I am an infectious diseases physician with special expertise in anaerobic infections and special interest in clostridial infections. I am herewith attaching a copy of my C.V. After reviewing the above material I am enclosing my opinions regarding the possible risk of developing tetanus associated with performing non-surgical circumcision using PrePex.

**Background**

Placement of the PrePex band cuts off blood supply to the foreskin and venous and lymphatic drainage from the foreskin, thus inducing its complete atrophy, enabling its non-surgical removal within 7 days. Following the interruption of blood supply and drainage the foreskin develops necrosis that is expected to be associated with polymicrobial aerobic and anaerobic bacteria. Even though *Clostridium tetani* is infrequently isolated from necrotic infections in the perineal area (1), it is possible, that it may also be present in the polymicrobial infection within the foreskin and eventually release its exotoxin (tetanospasmin).

Tetanospasmin enters and travels through the peripheral nerves to the central nervous system, or is carried by lymphocytes. (2) The toxin selectively binds to surface membrane of nerve terminals, followed by uptake and subsequent retrograde axonal transport. (3) Following axonal transport, tetanospasmin eventually effects the peripheral and central nervous system.

**Risk of tetanus development after PrePex utilization**

Placement of PrePex band causes death of all human cells within the foreskin and the nervous system nerves cells and axons do not survive and function within hours of its application. Clinical studies demonstrated a significant reduction in pain sensation in the foreskin within 8 hours of Prepex placement and a complete skin anesthesia within 16 hours. (4) These sensory alterations are due to anoxic disruption of intracellular neural activity and eventual neural cell death. Active intracellular transportation of tetanoplasmin is not expected to occur in such settings. A complete death of neurons is known to occur within 48 hours of exposure to anoxia in an in-vitro model (5).
It is unreasonable to assume that *C. tetani* can enter to the foreskin immediately after PrePex application, as the foreskin's surface at that time is intact; providing a barrier to bacterial penetration. In the event *C. tetani* enters the foreskins within the first 48 hours anaerobic conditions necessary for its growth, vegetation and production of tetanospasmin may not exist.

Transportation of tetanospasmin would not be possible following the disruption of the foreskin's neural activity within 8-16 hours of PrePex and the subsequent neural cell and axons death.

The placement of the PrePex band also prevents the transportation of the toxin by lymphocytes or through tissue diffusion into the central nervous system.

**Risk of tetanus by the post PrePex removal wound**

Following removal of the Prepex band a superficial dry wound around the glans penis is exposed. The wound may become contaminated by environmental or human flora (i.e., skin, gastrointestinal). However, the wound's scar tissue (granulation) that has developed within the past 7 days provides protection from potential deep tissue invasion of potential pathogens including *C. tetani*. Such protection is not provided after surgical circumcision where the wound is deeper and has sutures. These sutures may actually serve as a nidus of infection for potential pathogens including *C. tetani*.

Appropriate wound care is expected to mitigate the potential of wound infection including *C. tetani*.

**Conclusions**

It is my opinion that the presence of necrotic foreskin during and after a Prepex procedure is not associated with the potential development of tetanus. This is because tetanospasmin cannot enter and/or travel through the devitalized nervous system within the foreskin. Furthermore, no transport of the toxin would be possible by lymphocytes through the PrePex band.
Sincerely,

Itzhak Brook M.D., M. Sc.

References:

February 11, 2015

Alon Kushnir

Circ MedTech

Re: Further evaluation of the risk of tetanus developing following utilization of PrePex for nonsurgical circumcision.

Dear Mr. Kushnir,

You have asked me to further evaluate the risk of developing tetanus during and after the PrePex procedure. Specifically, you have asked me to address the following issues:

1. The risk of contracting clinical tetanus due to the creation of three anaerobic spaces as part of the standard PrePex procedures. These spaces include (a) the space under the foreskin, (b) the space below the PrePex inner ring; and (c) the space between the foreskin and the PrePex inner ring (under the PrePex band)( see Figure).

2. The risk of contracting clinical tetanus due to the removal procedure of PrePex, i.e., the risk of introducing bacteria during the extraction of the Inner Ring or the cutting of the foreskin.
3. The reduction of the risk of contracting tetanus when employing proper wound care. This includes care by the provider immediately following removal of the PrePex (dressing, disinfection, etc.) and subsequent wound care by the patient (home care of wound, hygiene, use of non-medical substances, etc.), taking into consideration contact with the environment, both in cultural activities such as traditional dancing and work (making bricks, etc.)

4. Whether the proposed mitigations (as outlined in the PrePex Updates to Instructions for Use (IFU)) (item 11 below) are sufficient in reducing the risk of acquiring tetanus to an acceptable level that does not require mandatory complete vaccination for *Clostridium tetani* prior to PrePex placement.

I have reviewed the following materials concerning the above matter:

1. WHO Safety notice (8th Dec 2014)
2. Circ MedTech Field Safety Notice (CMT_FSN_001_2014)
3. Uganda report of 2 cases of Tetanus post PrePex procedure
4. Rwanda report of 1 case of Tetanus post PrePex procedure
5. PrePex Information for Users rev 14
6. PrePex procedure videos – Placements and Removals
7. PrePex photos from day 0 to day 7
8. Photos of PrePex wound on day 7 – good wound and poor wounds
9. Photos of Adverse events including significant Edema following displacement
10. Reports from published PrePex studies:

I am an infectious diseases physician with expertise in anaerobic infections and have a special interest in clostridial infections. I am herewith attaching a copy of my C.V. After reviewing the above material, I am enclosing my opinion regarding the 4 points for evaluation requested above.

1. **Background**

Placement of the PrePex band cuts off blood supply to the foreskin and venous and lymphatic drainage from the foreskin, thus inducing its complete atrophy, enabling its non-surgical removal within 7 days. Following the interruption of blood supply and drainage, the foreskin develops necrosis that is expected to be associated with polymicrobial aerobic and anaerobic bacteria. Even though *Clostridium tetani* is infrequently isolated from necrotic infections in the perineal area (1, 2) it is possible, on rare occasions, that it may also be present in the polymicrobial infection within the foreskin and eventually release its exotoxin (tetanospasmin).

2. **What is the risk of contracting clinical tetanus due to the three anaerobic spaces created as part of the standard PrePex procedures?**

The spaces under the foreskin (a in Figure); below the PrePex inner ring (b in Figure); and between the foreskin and the PrePex inner ring band (under the PrePex band) (see Figure); are interconnected and most likely harbor similar microorganisms. These include normal skin flora bacteria as well as some of the aerobic and anaerobic bacteria that are involved in the necrotic inflammation inside the foreskin. However these spaces are exposed to air at the tip of the
glans and are expected to have a lesser anaerobic environment than the necrotic foreskin tissue.

Considering the very rare events where *C. tetani* may be present under the foreskin, the current PrePex instructions to disinfect with chlorhexidine prior to device placement and the nature of the spaces, it is unlikely that *C. tetani* would vegetate or thrive in this environment. Furthermore, the proposed updates to the PrePex procedure which include initial scrubbing with povidone iodine and the proposed application of a broad spectrum antimicrobial cream prior to PrePex placement will eliminate most of the aerobic and anaerobic bacteria, including *C. tetani* (3,4), and will further reduce the anaerobic conditions in these spaces.

Placement of the PrePex band causes the death of all human cells within the foreskin. The nervous system nerve cells and axons do not survive and function within hours of its application. Even if in the very rare occasion that *C. tetani* could enter the spaces under the foreskin (a in Figure) and below the inner ring (b in Figure), conditions necessary for *C. tetani* growth, vegetation and production of tetanospasmin may not exist. Similarly, if preformed toxin could enter these spaces it could not be transported through the damaged nerves (see my opinion letter to you from Jan 17th).

The foreskin over the space between the foreskin and the PrePex ring (under the PrePex band) (c in Figure), where the live tissue and necrotic tissue are connected, undergoes scarring that is complete within 4 to 6 days, leading to detachment of the foreskin. This scarred area reduces the risk of any entry of potential pathogens through that site.

Even if in the very rare occasion that *C. tetani* or its toxin are present in the space between the foreskin and the PrePex ring (under the PrePex band) (c in Figure), they would not be able to cross the intact skin into the healthy, well-aerated tissues of the penis.

It is my opinion that the risk of contracting clinical tetanus via the spaces under the foreskin, below the PrePex inner ring; and between the foreskin and the PrePex inner ring band (under the PrePex band) is very low both during and after the PrePex procedure.

3. What is the risk of contracting clinical tetanus due to the removal procedure of PrePex?

With regards to the removal of the necrotic foreskin, since there is no breach of the skin at this procedure and since the removal of the foreskin is performed above the inner ring, I see no risk.
in it. In the updates for the PrePex procedure that you provided me, the extraction of the inner ring is done after thorough disinfection of the inner ring area with povidone iodine. This measure is expected to significantly reduce the risk of introducing *C. tetani* during the extraction of the inner ring.

4. What is the risk of contracting clinical tetanus when applying proper wound care?

Inappropriate wound care possess, in my opinion, the greatest risk of acquiring tetanus. Proper and improved wound care by the provider and by the patient is expected to reduce the risk of acquiring tetanus. The wound care by the provider immediately after removing the PrePex device, as presented in the proposed updated IFU, includes the use of dressing, disinfection with povidone iodine, and application of topical antibiotics under the dressing. Your selected antimicrobial agents provide broad spectrum coverage against aerobic and anaerobic bacteria, including *C. tetani* (by bacitracin). (5)

The care of the wound by the patient at home includes improved hygiene, eliminating the use of non-medical substances, and avoiding any exposure of the wound to the environment (by e.g., performing traditional dancing, working with soil, making bricks, etc.) by supplying men with replacement dressings and good counseling for wound care.

These measures are expected to significantly reduce the risk of introducing *C. tetani* into the wound following the removal of PrePex.

5. Are the proposed mitigations as outlined in the PrePex Updates to Instructions for Use (IFU) sufficient to reduce the above risks to an acceptable medical level that does not require mandatory complete vaccination for *C. tetani* prior to PrePex placement?

The proposed interventions outlined in PrePex Updates to Instructions for Use (IFU rev 15) are expected to further reduce the current low risk of tetanus. The disinfectants and antimicrobial agents to be utilized are very active and able to prevent local and systemic infections including tetanus:
a. Povidone iodine

Skin scrubbing and rinsing with 10 % povidone iodine which is sporicidal to *C. tetani*, (prior to application of PrePex) are expected to reduce aerobic and anaerobic bacterial presence under the foreskin and would also eliminate *C. tetani* spores. (6, 7)

Povidone iodine is a very effective antiseptic active against aerobic and anaerobic Gram-positive and Gram-negative organisms, fungi and protozoa, and, with increased exposure times as well as higher concentrations (e.g. 10%), also against Clostridium spores including *C. tetani* and various viruses.(6). It is often used for foreskin preparation in other circumcision methods. Iodine and its antibacterial properties have been used for the prevention or management of wound infections for decades.(7)

In the improved PrePex disinfection instructions, povidone iodine is expected to remain very effective, trapped under the foreskin and the device for 12 – 14 hours after its application without the potential of being wiped off.(8)

b. Topical antibiotics

Preventive application of topical antibiotics on the circumcision wound in newborns decreased the risk of neonatal tetanus to a similar level observed in babies who were not circumcised. (9)

Application of topical antibiotics (bacitracin, neomycin and polymyxin) is expected to reduce the bacterial load inside the foreskin and the space under it following PrePex placement and after removal of PrePex, thus reducing the risk of tetanus.

There is overwhelming clinical evidence that proper disinfection and wound care reduce the risk of local and systemic infection.(10)

The current risk for tetanus following the use of PrePex prior to any further mitigation is very low. The proposed mitigations of disinfection and wound care are expected to further reduce such a risk. The low risk for users to acquire tetanus, especially after the
implementation of the improved disinfection procedures, does not justify the mandatory requirement for vaccination prior to utilizing PrePex.

Conclusions

1. It is my opinion that the risk of contracting clinical tetanus via the spaces under the foreskin, below the PrePex inner ring, and between the foreskin and the PrePex inner ring (under the PrePex band) is very low during and after the Prepex procedure.

2. The mitigating measures to be used in the extraction of the inner ring, the cutting of the foreskin, and caring for the wound are expected to significantly reduce the risk of tetanus.

3. The low risk to users of acquiring tetanus, especially after implementation of the improved disinfection procedures, does not justify the requirement for vaccination prior to utilizing PrePex.

Sincerely,

Itzhak Brook M.D., M. Sc.
Figure: Spaces and areas under the foreskin in relation to the PrePex device

a. Space under the foreskin
b. Space below the inner ring
c. Space between the foreskin and the PrePex ring (under the PrePex band)
References:


February 22, 2015

Alon Kushnir  
Circ MedTech

Re: Possible emergence of vegetative forms of *Clostridium tetani* in post-circumcision wounds: Comparison between post-surgical circumcision and post-PrePex wounds.

Dear Mr. Kushnir,

You have asked me whether, upon analysis and comparison of post-surgical circumcision wounds to post-PrePex wounds, either is more prone to *Clostridium tetani* vegetation in case such bacteria is introduced into the wound. I have reviewed the following materials concerning the above matter as well as the listed references:

1. Photos of PrePex wounds – Good wounds and poor wounds
2. Photos of surgical wounds
3. Data of PrePex wound infections from published and non-published clinical studies
a) Clinical data from a randomized controlled study comparing PrePex to surgical circumcision from Zimbabwe

b) Clinical data from 2 implementation studies conducted by PSI in Zambia and South Africa

4. PrePex Information for Users rev 15

5. PrePex procedure videos – Placements and Removals


After reviewing the above material, I am enclosing my opinion comparing the post-surgical circumcision wound to the post-PrePex wound to determine whether each is prone to *Clostridium tetani* infection if this bacteria is introduced into the wound. I am also including recommendations regarding proper wound care to mitigate risk of tetanus:

In both procedures, a wound around the glans penis is created after removal of the foreskin. This wound can be exposed to environmental or endogenous flora (e.g., gastrointestinal, skin, etc.) microorganisms and also, rarely, to *C. tetani*. However, because the nature and pathology of each wound differ, the risk of acquiring tetanus is not the same for each wound, depending on the procedure used.

A post-surgical circumcision wound is a fresh wound created by a surgical incision that severs blood vessels and potentially exposes the skin, as well as deeper tissues of the shaft of the penis, to endogenous and exogenous bacterial contamination. (Fig 1, Table 1)

Infectious complications after surgical circumcision were found in 3% to 5% of circumcised males in Africa. (1, 2) These included local wound infection and abscess, bacteremia, and urinary tract infections. (3, 4) Multiple injections of a local anesthetic around the intended circumcision site also has the potential of introducing bacteria into the penile tissues. Furthermore, local swelling at the incision site, post-surgical bleeding and oozing, (5) and
placement of surgical sutures can promote the growth of potential bacterial pathogens. The growth of *Clostridium* species, including *C. tetani*, is enhanced by the presence of foreign bodies. (6-8) These sutures can serve as a nidus of infection and the production of a biofilm by potential pathogens, including *C. tetani*. (9)

Following removal of the PrePex band, a superficial dry granulated wound around the sulcus of the glans penis is exposed. The wound is superficial, and there is no active bleeding in >98% of cases that could potentially allow invasion of the vascular system leading to systemic bacterial infection. This wound may also become contaminated by environmental or human flora (e.g., skin, gastrointestinal, etc.). However, the scar (granulation) tissue that gradually forms during the previous seven days because of the pressure exerted by the PrePex band provides protection from deep tissue invasion by potential pathogens, including *C. tetani*. Such protection is not provided after surgical circumcision where the wound is deeper and has sutures (Figure 1).

The PrePex reported rate of wound infections in clinical studies is < 1%:

(a) In a randomized controlled study in Rwanda, no infections were found (5).

(b) In a randomized controlled study in Zimbabwe with 160 subjects, no infections were found (Not Published).

(c) In a cohort study in Rwanda with 518 subjects, no infections were found (10).

(d) In a pilot implementation study in Zambia (N=500) and South Africa (N=430), 4 (0.8%) and 5 (1.1%) infections were found respectively. (Not published)

(e) A 407 subjects study from Kenya showed no wound infections (11).

(f) A study from Uganda of 625 men had no wound infections (12).

Appropriate wound care both in surgical wounds and in PrePex wounds is expected to mitigate the potential of wound infection in both types of wounds, including clinical tetanus.
I would recommend to strengthen the wound care instructions for patients post-circumcision, regardless of technique, and to consider application of antibiotic cream over the wound at the time of dressing as implemented in Circ MedTech’s amended IFU (IFU Rev 15).

Providers of circumcision should improve and strengthen their counseling of patients on the risks of applying substances over the wound that potentially may introduce bacteria to the wound. Providers should also consider supplying patients with replacement dressings to ensure that the wound is protected from the environment for as long as possible.

Conclusions:

1. The wound post-PrePex removal is superficial, scarred, and dry, and is thus less likely to allow *C. tetani* infection compared to the fresh post-surgical circumcision wound which is deeper, oozes, and has sutures.

2. Appropriate wound care is expected to mitigate the potential of wound infection in both types of wounds, including any infection from *C. tetani*.

Sincerely,

Itzhak Brook M.D., M. Sc.
References


Table 1.

Comparison between post-surgical circumcision and post-PrePex wounds.

<table>
<thead>
<tr>
<th>Post-surgical circumcision wounds</th>
<th>Post-PrePex wounds</th>
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<tbody>
<tr>
<td>Deep</td>
<td>Superficial</td>
</tr>
<tr>
<td>Active bleeding</td>
<td>No bleeding</td>
</tr>
<tr>
<td>Sutures placed</td>
<td>No sutures</td>
</tr>
<tr>
<td>Swelling around the wound after circumcision</td>
<td>No swelling</td>
</tr>
<tr>
<td>An acute wound with no scar tissue</td>
<td>Scar tissue already formed</td>
</tr>
</tbody>
</table>
Figure 1. Comparison between post-surgical circumcision and post-PrePex wounds.
Pictures 1. Comparison between post-surgical circumcision and post-PrePex wounds.

<table>
<thead>
<tr>
<th>Post-Surgical Circumcision Wounds (day 1 after surgery)</th>
<th>Post-PrePex Wounds after removal of the device (day 1 after removal)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Post-Surgical Circumcision Wound" /></td>
<td><img src="image2" alt="Post-PrePex Wound after removal" /></td>
</tr>
<tr>
<td><img src="image3" alt="Post-Surgical Circumcision Wound" /></td>
<td><img src="image4" alt="Post-PrePex Wound after removal" /></td>
</tr>
<tr>
<td><img src="image5" alt="Post-Surgical Circumcision Wound" /></td>
<td><img src="image6" alt="Post-PrePex Wound after removal" /></td>
</tr>
</tbody>
</table>
Dear Mr. Kushnir,

You have asked me to evaluate the risk of contracting tetanus during and after the PrePex procedure. Specifically, I have been requested to address the following issues:

1. The risk of contracting clinical tetanus following implementation of the PrePex procedure for nonsurgical circumcision. This risk should be evaluated in light of the anaerobic conditions, which might develop upon positioning of the PrePex device.

2. The risk of contracting tetanus due to PrePex removal and in particular the possible contamination of the scar with bacteria and or spores during extraction of the PrePex inner ring and rubber band and removal of the devitalised foreskin.

3. The reduction of the risk of contracting tetanus when the proposed mitigations outlined in the PrePex Updates to Instructions for Use (IFU) (item 5), are implemented in the PrePex procedure for nonsurgical circumcision. In particular, are these mitigations sufficient in reducing the risk of contracting tetanus to levels similar or below the current risk for surgical circumcision and not requiring mandatory complete vaccination with tetanus toxoid prior to PrePex placement?

To address these questions, I have reviewed the following documents, scientific manuscripts and/or media concerning the above matter.

1. WHO Information Note on Tetanus and voluntary medical male circumcision (VMMC) with Annexes (08.12.2014).
4. Photos of PrePex devices at different times after installation (day 0 to 7) including examples of different types of healing patterns and examples of slough.
5. PrePex Updates to Instructions for Use (IFU) – IFU Rev 15
7. Randomized controlled studies comparing PrePex to surgical circumcision: Tshimanga M et al. (2015) A Phase II randomized control trial comparing the PrePex device to forceps...

8. Uganda report of 2 cases of tetanus post PrePex procedure.

9. MoH Draft report about 1 case of tetanus in Rwanda post PrePex procedure.

10. A drawing of the PrePex anaerobic spaces (as Figure 1 of Prof. I. Brook letter of 11th Feb 2015).

11. Dr. R. Gray summary concerning anaerobic growth on day 7 following PrePex application.

12. Information about wound infections associated with PrePex application:
   b) Cohort study in Rwanda with 518 subjects: no infections found. Mutabazi V et al. (2013) One-arm, open-label, prospective, cohort field study to assess the safety an efficacy of the PrePex device for scale-up of nonsurgical circumcision when performed by nurses in resource-limited settings for HIV prevention. J Acquir Immune Defic Syndr 63:315–22.
   f) Pilot implementation and active surveillance in Zambia (N=500) and South Africa (N=430): 4 (0.8%) and 5 (1.1%) infections found respectively.
   g) Scale-up in Rwanda with more than 28,000 subjects: 4 (0.01%) infections found.


15. Povidone-Iodine antimicrobial and sporicidal activity:

My expertise: I am a neurobiologist with a long lasting interest in tetanus and botulinum neurotoxins, and their biological and clinical effects. Tetanus neurotoxin is the sole cause of the clinical symptoms of tetanus, whilst botulinum neurotoxins cause botulism in humans and animals. I have an uninterrupted track record in tetanus neurotoxin research from 1985. I authored major breakthroughs in tetanus neurotoxin’s mechanism of action such as the discovery in 1992 of
tetanus neurotoxin’s activity on key molecules controlling synaptic function and neurotransmitter release, and in 2014, the identification of its neuronal receptor and of peptides antagonising the onset of tetanus in vitro and in vivo. I am a qualified European Pharmacist (University of Padua, Italy).

Based on the material listed above, I have formulated my opinion regarding the three issues stated at the beginning of this letter. These opinions have been formulated in my capacity as an expert of the tetanus field and are not linked to my function as an employee of University College London. As such, I am the only responsible of the statements below.

**Background.** Placement of the PrePex device cuts off blood supply to the foreskin and blocks venous and lymphatic drainage from the foreskin, thus inducing its complete atrophy. This allows the non-surgical removal of the foreskin within seven days.

The necrotic foreskin generated as a consequence of the application of the PrePex device may get contaminated by bacteria and spores present on the surrounding skin and from the environment, some of them potentially having microaerobic and anaerobic features. *C. tetani* spores are ubiquitous and may enter in contact with the foreskin or the glans surface. However only vegetative toxigenic forms of *C. tetani* are able to produce tetanus neurotoxin, which is the sole cause of the clinical symptoms of tetanus.

**Point 1. What is the risk of contracting clinical tetanus following implementation of the PrePex procedure for nonsurgical circumcision?**

Based on the material above and my knowledge of *C. tetani* biology, I believe that the risk of developing tetanus as a consequence of nonsurgical circumcision operated via the PrePex device is extremely low.

Indeed, the careful cleaning and disinfection of the foreskin and glans is likely to remove any significant contamination with *C. tetani* spores.

Even in the eventuality that some spores remain in situ, scrubbing of the area with povidone-iodine and a broad spectrum antimicrobial cream, which is implemented in the new updated PrePex IFU protocol, will inactivate residual *C. tetani* spores. Importantly, *C. tetani* spores do not represent a risk per se, since tetanus neurotoxin is produced only by the vegetative form of the bacterium and released in the surrounding environment (culture growth media or deep anaerobic wound) only if strict requirements of low oxygen tension, pH and nutrient availability are met (1). These are unlikely to occur in this area following application of povidone-iodine and antimicrobial cream prior to PrePex placement. This combined treatment will largely reduce aerobic and anaerobic bacterial growth and will further reduce the formation of anaerobic niches. The antibacterial washes with clorexidine solution during the week post PrePex application will further reduce this risk.

In the unlikely eventuality that tetanus neurotoxin is produced as a consequence of the germination of contaminating *C. tetani* spores between the glans and the inner PrePex ring and/or between the ring and the necrotic foreskin, two additional factors argue against an increased risk of contracting systemic tetanus.

- If the tissue remains intact and not blistered, the spores cannot enter areas suitable for germination, hence it is extremely unlikely, if not impossible, that *C. tetani* spore germination and vegetative growth could occur. Although the foreskin is necrotic and devitalised, the tissue would remain sterile if the skin is still intact.
- The strong compression operated by the PrePex band on the inner ring determines conditions similar to those experienced during nerve ligation (2). Under these conditions, axonal transport is compromised, hence tetanus neurotoxin eventually generated in the necrotic foreskin cannot be transported into the spinal cord and give rise to systemic tetanus. The delivery of tetanus neurotoxin to the central nervous system is totally dependent on axonal retrograde transport (3), as demonstrated by the strong inhibition of
tetanic symptoms found in vivo in chicks treated with axonal transport blockers such as organophosphorous compounds (4). Similar data have been shown in vitro in cultured mammalian neurons using tetanus neurotoxin derivatives (5,6).

- The distal part of neurons innervating the foreskin are likely to undergo degeneration starting from the day after the application of the PrePex device. This is eminently demonstrated by the lack of sensitivity shown in clients upon application of PrePex (item 3).

As such, even in the unlikely event that tetanus neurotoxin would be produced and would enter the tissue underneath the foreskin, it could not be transported to the central nervous system, an event that is essential for the onset and clinical symptoms of tetanus.

Therefore, the risk of contracting clinical tetanus is very low as a consequence of the PrePex procedure.

Point 2. What is the risk of contracting tetanus due to PrePex removal and in particular the possible contamination of the scar with bacteria and or spores during extraction of the PrePex inner ring and rubber band and removal of the devitalised foreskin?

On the basis of the documentation provided, the risk of contracting tetanus as a consequence to PrePex removal is extremely low.

Indeed, after one week after the application of the PrePex device, the foreskin is completely devitalised and can be easily removed without generating an open wound, if the PrePex IFU protocol is carefully implemented (cut of the devitalised foreskin must be performed above the inner ring).

It is highly recommended that the removal of the inner ring is performed after meticulous disinfection of area with povidone-iodine. This measure is expected to minimise the risk of contamination with C. tetani spores during the removal of the device.

Point 3. Are the mitigations introduced in the improved protocol sufficient in reducing the risk of contracting tetanus to levels similar or below the current risk for surgical circumcision and not requiring mandatory complete vaccination with tetanus toxoid prior to PrePex placement?

To minimise and further reduce the very low risk of tetanus associated with the use of the PrePex device, the following conditions aiming to an optimal wound care and prevention should be implemented in all clients subjected to the non surgical circumcision by PrePex:

a) Good genital hygiene
b) Pre-device application: washing and disinfection with povidone-iodine and broad spectrum antibiotic cream.
c) Pre-device removal: disinfection with povidone-iodine (after removal of necrotic foreskin or prior to in case of blistering/oozing).
d) Post-device removal disinfection with povidone-iodine and a broad spectrum antibiotic cream.
e) For seven weeks (or longer if healing is delayed), the client should observe careful hygiene and perform appropriate wound care.
f) During the same period, the client should refrain from traditional medical practice and sexual activity.
g) In case of infection or oozing, the client should apply povidone-iodine on the area. Povidone-iodine monodoses and replacement dressing should be provided to the client during the last schedule visit for Prepex removal.

These procedures, which are already largely in place in the updated PrePex IFU protocol, would further reduce inappropriate wound care, which represents, in my opinion, the greatest risk associated with PrePex-operated nonsurgical circumcision, including developing tetanus.

Povidone-iodine is very active against vegetative form of C. tetani and at high concentration (10%) and long exposure times (>17 h), it is sporicidal towards C. tetani spores (7,8). Furthermore, it is
very effective against aerobic and anaerobic Gram-positive and Gram-negative organisms, fungi, protozoa, viruses and spores, thus reducing the risk of infection and the creation of favourable conditions for *C. tetani* spore germination, especially in association with a broad-spectrum antibiotic cream.

Conclusions

- In my opinion, the risk of developing tetanus as a consequence of nonsurgical circumcision via the PrePex device is extremely low. Given that the surgical procedure generates an open and deep wound, the risk of infection and thus of contracting tetanus of this procedure is potentially higher than in the cases Prepex-operated circumcision.
- The risk of developing tetanus associated with Prepex-operated circumcision is further reduced by the updated PrePex IFU protocol and appropriate wound care, as suggested above.
- On the basis of the above considerations, the risk to developing tetanus as a result of PrePex-operated nonsurgical circumcision is very low and does not justify the requirement for preventive vaccination.

Your sincerely,

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References

Re: Scientific evidence of the safety and efficacy of the proposed updates to the
PrePex IFU (updates are in IFU Rev 15)

As a clinical microbiology and infectious diseases specialist, all the scientifically
proposed interventions proposed by Circ MedTech have been based on “evidence-
based clinical practice guidelines,” which means these interventions followed a
rigorous development process and are based on the highest quality scientific
evidence. They have been undertaken by Circ MedTech in consultation with
numerous experts (including myself) and they are expected to ensure aseptic
techniques and adequate skin preparation to prevent local and systemic infections.

Background

Following 3 reported cases of tetanus, occurring after PrePex Removal and the
issuance of the WHO Information Note dated 8 Dec 2014: "Considerations for
Tetanus Risk Mitigation in Voluntary Medical Male Circumcision for HIV Prevention
Programmes," which included recommendations to improve the hygienic care of
circumcision methods, Circ MedTech(CMT) updated the PrePex Instructions for Use
(IFU) to further mitigate any potential risk of bacterial infection to a low and
acceptable level.

The IFU updates include the following updates:

1. Use of 10% Povidone Iodine prior to PrePex Placement to reduce potential
   aerobic and anaerobic bacteria.
2. Application of antibacterial cream to the inner foreskin prior to placement to reduce potential aerobic and anaerobic bacteria.

3. An option for users that wish to reduce odor, to perform daily rinsing with 1% diluted chlorhexidine

4. Disinfecting the Inner Ring area before Inner Ring removal Povidone Iodine to reduce potential aerobic and anaerobic bacteria in the removal area

5. Application of antibacterial cream to the circumcision wound

6. Mandatory use of adequately sterilized removal tools

Safety and Efficacy

1. Povidone Iodine (PI) antiseptic use during skin preparation, prior to Inner ring removal and as wound cleansing agent

Clinically, PI has application not only in the management of wounds, but as a skin antiseptic prior to surgery. Its efficacy as a skin disinfectant is undisputed and there are numerous published articles regarding its efficacy and safety. Multiple publications describe the use of iodine in cleansing wounds, and as a topical agent to prevent or treat localized wound infections. The broad spectrum of antimicrobial activity as well as its residual anti-infective activity is well documented and its efficacy, particularly in relation to resistant micro-organisms, has been shown repeatedly.

PI has considerable activity against Gram-positive and Gram-negative organisms, fungi and protozoa, and, with increased exposure times as well as higher concentrations, also against spores and various viruses. Often, those increased exposure times are not attained so it may fail to eradicate spores and the concentration must be the 10% PI that has been studied in most cases (1).

In the PrePex procedure the Povidone Iodine will remain on the skin for the required increased exposure time, as it will be placed on the inner skin which is protected by the outer foreskin thus ensuring the agent will not be wiped.

With regards to safety of the use of PI:

Povidone iodine is only rarely associated with immediate allergic reactions, which are markedly more prevalent with chlorhexidine, which increase the safety of patients compared to the chlorhexidine currently used in the PrePex procedure (Thus explaining the suggested optional daily rinsing with chlorhexidine for anti-odor use). PI is commonly used in all surgical circumcision procedures.
2. **Application of antimicrobial cream during skin preparation and over the wound**

Bennett et al. demonstrated that circumcision could be a risk factor for neonatal tetanus in Pakistan (2). They also showed that the use of topical antibiotics on the circumcision wound decreased the risk of neonatal tetanus to a similar level observed in babies who were not circumcised. Based on these findings Bennett et al. suggest that topical antibiotics should be routinely applied to every circumcision wound.

In the assessment of the protective effect against neonatal sepsis of topical antibiotics used in the circumcision wound it is important to know whether topical antibiotics inactivate Clostridium tetani spores or, more likely, vegetative forms, or if there are alternative mechanisms that explain why the use of such ointments would prevent this disease.

Topical antimicrobial therapy, although not currently advisable for most clinically uninfected wounds, does have a role in specific circumstances. Evidence upholds its use for burn wounds in which blood vessels to the skin are often destroyed, both to prevent sepsis and help treat infection (3).

Antimicrobial creams that consist of 3 different antibiotics; Bacitracin, Neomycin and Polymyxin such as Neosporin (Bacitracin 400 units, Neomycin 3.5 mg and Polymyxin B 5,000 units) or other broad spectrum antimicrobial ointments containing a combination of bacitracin (250 I.U to 500 I.U per 1gr) plus neomycin (5mg per 1gr) and/or polymyxin (5,000 I.U to 10,000 I.U per 1gr) will reduce the bacterial load inside the foreskin and the space under it following PrePex placement and after removal of PrePex, thus reducing the risk of tetanus.

Bacitracin is active against clostridial sp., and has also been shown to enhance epidermal healing of wounds (4). This makes the observed protective effect of topical bacitracin on circumcision-associated sepsis effective.

Another potential application might be to help in the removal of biofilms, which have been implicated in persistent infections.

A study in total of 1053 patients with superficial burn injury, in which qualitative analysis showed Staphylococcus aureus and Pseudomonas spp. to be the most common infecting organisms. Quantitatively, fewer patients showed infection on the 7th and 18th day post-treatment in the povidone iodine plus neosporin group (PVP + N) than in silver sulphadiazine group (SSD). Similarly, healing times were also better with PVP + N, with a maximum number of patients having healed within 15 days (5).
With regards to the safety of the use of antibacterial creams such as Neosporin, the intended use and indication for use of this cream is for skin and wound care. The specific application of the cream during the PrePex procedure meets its intended indication for use. The cream contains a product insert that supplies safety data to users.

A potential risk of the use of the antibacterial cream was raised of potential growth of fungal infection. This risk is mitigated by application of Povidone iodine prior to the cream application and indication to users that the cream should be applied only on skin that was disinfected with Povidone iodine. Povidone iodine is a known effective agent against yeasts.

3. Optional method for patient selection for preventing unpleasant odor with 1% chlorhexidine daily rinsing

For patients that would like to implement an anti-odor procedure during the 1 week of wearing the device, rinsing the inner foreskin with chlorhexidine solution 2-3 times per day 30mL to 70mL bottle of 1% diluted chlorhexidine fluid has been incorporated in the IFU.

The safety and efficacy of the daily rinsing with 1% chlorhexidine was validated in a randomized controlled study that was performed in Rwanda (clinicaltrial.gov number NCT02153658; article under Review for publication), study main outcomes are presented below:

One hundred and one subjects were enrolled in the trial and randomly distributed between the 3 trial arms: 37 in control arm, and 32 in a daily wash with soap and chlorhexidine arms

Safety: There were no adverse events or complications during or after foreskin cleaning/rinsing procedure for all subjects; therefore, all methods were found to be safe. There were no adverse events in the trial.

Efficacy: Odor levels on day 7, measured by 3 blinded smellers, were significantly lower in the chlorhexidine daily rinsing arm compared to the other 2 arms (p=0.033), with the control arm showing the highest levels of odor.

4. Mandatory use of only adequately sterilized removal tools

This has been incorporated in the IFU. Using tools that have not been adequately sterilized may lead to infections, specifically during the extraction of the Inner ring when the spatula may come in contact with the patient's viable tissue.

Sterilization describes the use of a physical or chemical procedure to eliminate all microbial life, including highly resistant bacterial
spores.

Inadequate sterilization can lead to high probability for pathogen transmission (rarely documented due to the wide margin of safety associated with sterilization process).

Conclusion

“Evidence-based” implies that these interventions have been created using an unbiased and transparent process of systematically reviewing, appraising, and using the best available clinical research findings of the highest value to aid in the delivery of optimum clinical care to PrePex clients.

The scientific evidence presented above objectively evaluated the quality of clinical research (by critically assessing techniques reported by researchers in their publications) and a clinical study will only re-iterate existing data with regards to their efficacy. I do not believe a clinical trial involving these interventions and PrePex will add more information to these logical and already well established common clinical practices when there is a wealth of indirect evidence from randomized control trials per intervention.

After years of slow progress, the massive public health intervention of scaling-up of VMMC is finally accelerating as a critical component of combination HIV prevention. Overriding or ignoring clinical judgment through administrative mandates will only halt this process.

MBBCh, FCPath(Micro), MMED (Micro), DTM&H, Dip HIV.
References

Instructions for Use: for Authorized & Trained Users

Intended use:
PrePex is a single use, disposable, non-sterile device, indicated for circumcision of adult men, defined as circumferential excision of the foreskin or prepuce at or near the level of coronal sulcus, with minimal amount of preputial skin remaining.

Contraindications:
Dermatitis of the penis or foreskin; allergy to rubber or iodine; non-intact skin on the penis or foreskin; active genital infection; warts on the glans or the inner surface of the foreskin; anatomic abnormalities, including narrow prepuce, phimosis, paraphimosis, torn or tight frenulum, hypospadias, or epispadias; any active penile diseases; active infectious disease impairing health; history of bleeding disorders; and a narrow foreskin opening.

Disposal:
Follow local, state, and federal regulations with respect to environmental protection when disposing of general and infectious waste. In the absence of regulations, the infectious waste, including all device elements, tools, and materials that came in contact with the body or bodily fluids should be incinerated. Other general waste should be segregated and stored in bins marked "General." The waste should then be buried in a designated area.

Caution:
The device must not be used if the package has been compromised. Please verify that the package is intact prior to opening it. Visual inspection of the package edges can identify compromised package. Use by trained personnel only. All device components must not be reused due to risk of cross contamination. The device is intended for adults only and is not applicable for males under the age of 18. The device should be used only in settings in which suitable surgical facilities and skills are available within a short time frame (6-12 hours) in order to manage potentially serious complications resulting from device displacements.

Device displacement when wearing the device may lead to the risk of adverse events. Informing the patient of safe behavior when wearing the device is critical.

Clinical Experience:
Three clinical studies of PrePex were performed in Rwanda according to the WHO official Evaluation Framework of Adult Male Circumcision (MC) Devices.¹

1. A study that demonstrated the safety and efficacy of the PrePex device in 105 male subjects.² Results: All subjects achieved circumcision with 1 case of diffuse edema after device removal, which resolved with minimal intervention. Pain was minimal with brief discomfort during device removal. The entire procedure was bloodless, requiring no anesthesia, no suturing, and no sterile settings. Subjects had no sick/absent days associated with the procedure. Median time for complete healing was 21 days after device removal. There were no instances of erroneous placement and no mechanical problems with the device. Conclusion: The PrePex device was found to be safe and effective.

2. Randomized controlled study, comparing the safety and efficacy of the PrePex in 144 adult male subjects to a surgical circumcision method in 73 adult male subjects.³ Results: All subjects were circumcised in 10 working days. The nonsurgical MC mean procedure time of 3.1 minutes (skin to skin), was significantly shorter than the mean surgical procedure time (15.4 minutes skin to skin) (P=0.0001). There were no device-related adverse events. Healing
time of the PrePex arm was longer than the surgical arm. Conclusion: PrePex nonsurgical MC, takes significantly less time than surgical, is as safe, does not require injections or sterile settings, is bloodless, and seems to be suitable for application by nurses.

3. A cohort field study that demonstrated the safety and efficacy of the PrePex on 518 adult males when the procedure is performed by nurses. Results: All 518 subjects from the pilot and pivotal phases achieved complete circumcision. There were 5 AEs on 4 subjects (rate of 0.96%, 95% Confidence Interval: 0.31-2.24). AEs were moderate and were resolved with simple intervention. Conclusions: The study demonstrated that nurses can be easily trained to perform safe and effective circumcisions using the PrePex device.

Environmental Requirements and Storage Conditions:
Storage: -10ºC to 55ºC, away from direct sunlight, humidity up to 80%.

Shelf Life:
The PrePex expiration date is listed on the label following the manufacturing date.

Device Overview:
PrePex includes the following items:

1. Placement Ring
2. Elastic Ring
3. Inner Ring
4. Verification Thread

Accessories:
The PrePex Sizing Plate (PSP) is intended for single use for selecting an appropriate device size.

The use of PrePex requires additional tools and materials that are not supplied with the PrePex device. For placement: examination gloves, 10% povidone iodine solution, antimicrobial gel/cream containing a combination of bacitracin (250 I.U to 500 I.U per 1gr) plus neomycin (5mg per 1gr) and/or polymyxin (5,000 I.U to 10,000 I.U per 1gr), skin marker, gauze, 5% anesthetic cream and nurse utility scissors. For removal: 10% povidone iodine solution, antimicrobial gel/cream containing a combination of bacitracin (250 I.U to 500 I.U per 1gr) plus neomycin (5mg per 1gr) and/or polymyxin (5,000 I.U to 10,000 I.U per 1gr), examination gloves, sterile
Harvey wire scissors, sterile forceps, sterile spatula, sterile scalpel, 5 wound dressings and a 30mL to 70 mL bottle of 1% diluted chlorhexidine fluid.

**Patient Screening:**
Before performing the procedure, screen the patient for any contraindications and physically test if the opening of the foreskin is wide enough for the PrePex procedure. Perform the test with examination gloves. Stretch the foreskin as described in step 3 of the placement procedure below, and visually assess the flexibility of the foreskin and the opening. If there is narrow opening, phimosis, or tight frenulum (i.e., the opening is not wide enough for the Inner Ring insertion), the patient is contra-indicated for PrePex. It is important not to use excessive force when pushing the Inner Ring through the foreskin opening. Gently pull down the foreskin to expose the sulcus and examine whether the foreskin is tight in the area below the sulcus. If the foreskin is tight in the area below the sulcus, the patient is contra-indicated for PrePex.

**Patient & Procedure Preparation:**

During the PrePex MC procedure, providers should wear examination gloves after washing hands.

1) Use a new, single-use PSP. Select the appropriate size A, B, C, D, or E by sliding each opening of the PSP over the glans and placing it directly under the coronal sulcus. The appropriate size is the opening which fits best (Figure 3).

2) Choose PrePex based on the sizing outcome (A, B, C, D, or E).

<table>
<thead>
<tr>
<th>Type</th>
<th>Diameter</th>
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<tbody>
<tr>
<td>A</td>
<td>26mm</td>
</tr>
<tr>
<td>B</td>
<td>28mm</td>
</tr>
<tr>
<td>C</td>
<td>30mm</td>
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<tr>
<td>D</td>
<td>32mm</td>
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<tr>
<td>E</td>
<td>34mm</td>
</tr>
</tbody>
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Note – If the diameter under the coronal sulcus is too large and cannot fit in the E opening or if it is too small and cannot fit precisely to size A, do not perform the PrePex procedure and refer the patient for surgical circumcision.

3) Prepare the skin with Povidone Iodine (PI) antiseptic solution:

   (a) Soak one gauze in PI solution

   (b) Retract the foreskin and use one soaked gauze to clean the whole penis starting from the glans to the sulcus, the inner and outer foreskin and the penile shaft. Scrub well and remove all residual dirt using the PI solution, placing extra emphasis on scrubbing the inner foreskin and sulcus area (Figure 4).

   (c) Discard the used gauze while holding the penis with the free hand. (The penis should not come in contact with the body to avoid cross contamination).

   (d) Discard used gauze and let the clean penis lie on a clean gauze.

   (e) Dry the penis with a gauze.
4) After completing the scrub with the PI, pull the foreskin down toward the body and apply 1 g of antimicrobial gel/cream on the exposed shaft area up to the coronal sulcus (Figure 5). Assure that the cream is only applied to skin that has been scrubbed with PI. Verify the antimicrobial gel/cream is properly absorbed before continuing to the next step.

Warning: Prior to application of the cream read the cream labeling that may include warnings and contraindications.

5) Apply 1 g of 5% anesthetic cream on the exposed shaft area up to the coronal sulcus. Once the anesthetic cream has been applied, there is no need to wait for the anesthetic cream to take effect and the procedure can commence immediately.

Pull up the foreskin so the antimicrobial gel/cream and the 5% anesthetic cream are covered by the inner foreskin, and proceed to mark the circumcision line below the corona, per the WHO Manual for Male Circumcision Under Local Anesthesia:

1. Mark the outer circumcision line according to the WHO Manual for Male Circumcision Under Local Anesthesia (Chapter 5-15 and Fig 5.17; Chapter 5-27 and Figs 5.33/5.34) using a standard medical skin marker (Figure 6).
2. This step is common to all methods of circumcision. Stretch the foreskin past the glans and release. When the foreskin has returned to a natural “resting” position, indicate the intended line of the circumcision with a skin marker. The line should correspond with the corona, just under the head of the penis. Some uncircumcised men have a very lax foreskin, which is partially retracted in the resting position. In such cases it is better to apply a little tension to the foreskin before marking the circumcision line. However, it is important not to
pull the foreskin too hard before marking the line, as this will result in too much skin being removed.

3. Mark the intended circumcision line, as described above, with a V shape, pointed toward the frenulum, on the underside (ventral aspect) of the penis (**Figure 7**). The apex of the V should correspond with the midline raphe. Ensure the V shape is not too sharp. Ensure that the marked circumcision line will not be erased during the PrePex procedure. If the marking is not clearly visible, do not perform the procedure. Before continuing it is very important to mark the line again if necessary.

**Placement Procedure:**

1. Place the Elastic Ring on the Placement Ring (see **Figure 8**). Do not remove the Verification Thread; it is intended to correct Elastic Ring misplacement if needed.

2. Place the Placement Ring (with Elastic Ring in place) on the penis shaft with the Elastic Ring side facing away from the body (See **Figure 9**).

Steps 3 and 4 should be performed by 2 people.

3. The first person should stretch the foreskin up and to the sides for insertion of the Inner Ring, holding the foreskin dorsal and ventral sides. Use fingers only with a dry gauze for a good grip; never use a tool of any kind to stretch the foreskin (See **Figure 10**). Ensure that the foreskin is fully stretched by viewing the sulcus area, thus assuring there will be no doubly entrapped foreskin.

4. The second person should insert the Inner Ring with its flat parts toward the dorsal and ventral penis sides into the opening of the foreskin (**see Figure 11**), assuring that one of the flat sides is in the area of the frenulum and the other flat side is on the opposite side of the frenulum.

5. Warning: When introducing the Inner Ring through the foreskin opening, be very careful not to harm the foreskin. If it is hard to introduce the Inner Ring do not force it and do not perform the procedure.
6. Introduce the Inner Ring over the glans and place it just below the glans (on the sulcus).

7. Hold the foreskin closed at the tip of the penis to secure the Inner Ring in place (See Figure 12). Advance the Placement Ring and Elastic Ring toward the glans until the Elastic Ring can be visually seen circumferentially to be just over and inside the Inner Ring groove and that the Elastic Ring and Inner Ring are aligned.

8. Once the Elastic Ring and Inner Ring are aligned, support the Placement Ring with one hand, and with the other hand adjust the foreskin so the marked circumcision line is exactly underneath the Elastic Ring. Adjust the foreskin from beneath each of the 4 Legs by pulling the skin downwards (See Figure 13).

9. To place the Elastic Ring - Using 4 fingers of your dominant hand, hold the Elastic Ring and Inner Ring together in the space between each of the 4 Placement Ring Legs. Work with the thumb and finger of your non-dominant hand to release the Elastic Ring from the Placement Ring one leg at a time (Figure 14).

10. Make sure the Elastic Ring is mounted directly over the Inner Ring groove and above the marked circumcision line previously marked. If the Elastic Ring is not positioned as desired or if a doubly entrapped foreskin is observed, use the verification thread to pull it off the penis and start the procedure again.

11. Upon proper placement of the Elastic Ring, discard the Placement Ring, and cut the verification thread with the nurse utility scissors.

12. Supply the patient with 2 tablets of 400 mg Ibuprofen or other painkiller tablets, and post placement information.

13. Supply the patient with a bottle containing 30 mL to 70mL 1% diluted chlorhexidine solution

14. Optional - For patients that would like to implement an anti-odor procedure during week 1 of wearing the device, instruct and train the patient on how to rinse the inner foreskin with chlorhexidine solution 2-3 times per day using the following guidelines:
   i. On the first day when the foreskin is still flexible hold the foreskin tip with one hand and drip the chlorhexidine inside the sub-preputial space assuring it reaches the whole cavity under the foreskin.
   ii. When the foreskin becomes rigid, hold the penis below PrePex and pull it up so the foreskin separates from the glans, then place the bottle tip above or inside the foreskin and drip chlorhexidine inside the sub-preputial space assuring it reaches the whole cavity under the foreskin.
   iii. Wash with clear water – assure the inside is clean. Gently dry with paper or towel
   iv. Assure the patient understands the instructions by observing him perform one rinse.

Instruct the patient on the following before sending him home:
   a. Not to move the Device, even through clothes – emphasize that touching the device while urinating or bathing must not cause any movement of the device. Any movement of the device may lead to surgical MC.
   b. To return for device removal after 7 days. Early removal may result in surgical MC.
c. To return to the MC center if he wants to remove the device before the 7 day period is over.
d. Not to remove the device and not let anyone other than a designated PrePex provider remove the device.
e. To report any unexpected situation, such as uncontrollable pain or device displacement.
f. Not to pull on the foreskin in case of partial detachment.
g. To abstain from sexual intercourse and masturbation when the device is on the penis, to avoid displacement.
h. Not to place any non-medical substance on the penis or over the foreskin.
i. To wear well-fitted underwear to keep the penis in an upright position.

Inform the patient of the following when sending him home:

a. He may experience pain in the following days, and he should take the supplied painkiller tablets to control the pain.
b. The foreskin distal to the Elastic Ring will become darker and dry.
c. Unpleasant odor may occur while wearing the device.
d. Infection may occur while wearing the device.
e. There may be some partial skin detachments along the Elastic Ring.
f. He should bath normally and keep the inner foreskin clean.
g. For patients opting for odor reduction - patients should rinse the inner foreskin with the supplied chlorhexidine solution 2-3 times per day according to the instructions provided to him at the clinic.

Removal Procedure:

1. The device is removed 7 days after it has been placed.
2. It is mandatory to use only adequately sterilized removal tools. Using tools that have not been adequately sterilized, may lead to infection, particularly during the extraction of the Inner Ring when the spatula may come in contact with the patient’s viable tissue.
3. It is recommended to use Harvey wire cutting scissors (Figure 15), due to their blunt edges and serrated blades, specifically designed to cut tough tissue like dried necrotic foreskin.
4. During the PrePex MC procedure, providers should wear examination gloves.

**Foreskin Removal:**

5. Before removing the foreskin it is recommended to pull the penis and foreskin gently upwards to separate the foreskin from the glans. You may drip fluids (e.g. antiseptic solution) through the foreskin opening to enhance this separation.

6. If the opening of the foreskin is very narrow, it should be dilated gently with the forceps tip to allow insertion of one of the wire scissors blades. Use sterile forceps to hold the foreskin and to pull it away from the glans.

7. Warning: When cutting the foreskin using wire scissors, take care that the foreskin is held far enough away from the glans and the meatus in order to avoid injury.

8. The foreskin should first be cut vertically towards the Elastic Ring and then at an angle, spirally, to the line that the Inner Ring is visible ([Figure 16](#)).

9. Cut the foreskin as close to the Elastic Ring as possible, the tip of the Inner Ring should become visible.

**Elastic Ring Removal:**

1. Warning: The Elastic Ring should be removed only after the foreskin has been removed.

2. Use a sterile scalpel to cut the Elastic Ring placed over the flat part of the Inner Ring on the side that is opposite to the frenulum. Do not cut the Elastic Ring on the same side as the frenulum ([Figure 17](#)).

3. Take care not to harm the viable skin.


**Inner Ring Removal:**

1. The Inner Ring is removed after the Elastic Ring removal.

2. Before Inner Ring removal, thoroughly disinfect the area of the Inner Ring, the necrotic foreskin around it and the glans with PI and gauze, especially in the area where the spatula will be used.

3. Use a sterile spatula to separate the necrotic foreskin all around the Inner Ring, assure the spatula is properly sterilized.

4. Pull the Inner Ring out on a curved side using the spatula; take care to avoid the frenulum area ([Figure 18](#)).

5. Partial separation of the necrotic foreskin may occur; in such cases extra care should be taken when extracting the Inner Ring to minimize pain at the separation area.

6. Cut the Inner Ring with scissors before discarding it.
Post Removal Procedure:

1. Clean the circumcised penis with PI solution, put extra emphasis on disinfecting the post removal wound area.
2. Apply antimicrobial gel/cream (containing combination of bacitracin plus neomycin and/or polymyxin) over the wound site.
3. Dress the circumcised penis with a standard sterile non-adherent dressing.
4. Instruct the patient not to wet the dressing.
5. Supply the patient with 5 new sterile non-adherent dressings to take home. Instruct the patient that in case the dressing on the penis gets wet, he should remove it and replace it with a new, dry dressing.
6. Instruct the patient to remove the dressing every day, at which time he can wash the penis and the wound area normally and then dress it with a new dressing.
7. Instruct the patient to keep the wound dressed for at least 5 days, using the supplied dressings.
8. Instruct the patient to contact the MC clinic in case of pain, infection, swelling, or fever. Inform the patient that all of those risks may occur following device removal.
9. Instruct the patient to abstain from sexual intercourse for 6 weeks after device removal and to avoid masturbation as those actions may lead to disruption of the wound, which will result in delayed healing.
10. Educate the patient on the importance of using condoms, and that circumcision is not a completely protective solution for the prevention of HIV infection.
11. Explain to the patient the risks associated with inappropriate wound care and the risk of traditional practices.
12. Educate the patient on the great risks and potential damage to the wound and to his general health if patients use traditional or non-authorized substances over the wound of any type (e.g., animal feces, soaps; organic substances, such as butter, different powders, herbs, honey, etc).

Procedure and Device Associated Risks:

The following possible risks may occur while the patient is wearing the PrePex:
- Patient displacing the device from its original position may lead to pain and to diffused edema that will require surgical MC.

To mitigate such risks it is essential to explain to the patient that he should not move the device even if he has pain or discomfort, and he should not masturbate or have sex. In case of pain, the patient should take the supplied painkiller tablets. If the pain is uncontrollable, the patient should return to the MC center to be evaluated and clinically managed; early controlled removal of foreskin and device may be indicated. If there is displacement of the device with or without edema, the patient should return to the clinic as soon as possible where the provider may recommend surgical circumcision to avoid serious and possible life-threatening infection. Surgical circumcision should be performed within 6-12 hours after displacement.

The following possible risks may occur as a result of device misuse by the provider:
• If the Inner Ring is not pushed all the way down to the sulcus level, this may lead to disturbance of urine flow.
• If the Inner Ring is not pushed all the way down to the sulcus level this may lead to insufficient removal of foreskin.
• If the circumcision line is not marked according to recommendations presented in this document, this may lead to removal of too much foreskin and future problems with penile functioning, or to removal of insufficient skin.
• Penile injury during foreskin removal due to misuse of the wire scissors.

Other possible risks:
• Device displacement and edema requiring urgent surgical circumcision.
• Bleeding after device removal.
• Pain – mainly 2 days after placement procedure.
• Infection – such infections that are associated with anaerobic bacteria, such as *C. tetani* that may lead to tetanus.
• Delayed healing.
• Injury to the penis particularly during removal.
• Unpleasant odor while wearing the device.

It is important to report any complaint or incident occurring with the device to the manufacturer Circ MedTech, by email or phone as soon as possible.

**Training:**
To receive complete training materials, including presentations and videos, send an e-mail to info@prepex.com requesting the training material and a CD / flash drive will be sent as soon as possible.

**References:**
| Must Consult Instructions for use | Product meets the requirements of the applicable European Directive. | Do not reuse | MedNet GmbH * Borkstrasse 10 * 48163 Muenster * Germany Phone +49 251 32266-0 |

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