

MALE CIRCUMCISION FOR HIV PREVENTION

MEETING REPORT

WHO TECHNICAL ADVISORY GROUP ON INNOVATIONS IN MALE CIRCUMCISION

30 SEPTEMBER – 2 OCTOBER 2014
GENEVA, SWITZERLAND



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ACRONYMS AND ABBREVIATIONS

AE	adverse event
EMP	Essential Medicines and Health Products (WHO Department of)
FSCA	Field Safety Corrective Action
FSN	Field Safety Notice
GHTF	Global Harmonization Task Force
HLD	high-level disinfection
ISO	International Organization for Standardization
PEPFAR	The United States President's Emergency Plan for AIDS Relief
SAE	serious adverse event
SAL	sterility assurance level
STED	Summary Technical Documentation
TAG	Technical Advisory Group on Innovations in Male Circumcision
VMMC	voluntary medical male circumcision
UNAIDS	Joint United Nations Programme on HIV/AIDS
WHO	World Health Organization

EXECUTIVE SUMMARY

Introduction

The World Health Organization (WHO) Technical Advisory Group on Innovations in Male Circumcision (TAG) met in September 2014. This was the first meeting since the first male circumcision device, the PrePex™, was prequalified in 2013. The purpose of the meeting was to review new information on the safety of the PrePex™ device from pilot implementation studies and programme roll-out, the safety and suitability of the PrePex™ and the ShangRing™ devices for circumcision in adolescents, other new innovative methods for adult circumcision and the safety and clinical performance of infant circumcision devices used in African settings.

By the end of 2013 a cumulative total of 5.8 million circumcisions, out of a target of 20 million, had been performed. Of those, 2.7 million were performed during 2013. As of end 2014 a provisional estimate of an additional 2.2 million male circumcisions had been performed, with a cumulative total of 8 million. Most countries have focused on circumcising males 15–49 years old as part of the catch-up programme. Several countries, however, have considered how to move to sustaining a high prevalence of male circumcision by offering circumcision to annual cohorts of adolescents and infants. This transition has implications for the TAG's work, which in the future will turn towards the safety and acceptability of male circumcision innovations in adolescents.

Safety of conventional surgical circumcision

In reviewing the safety of conventional surgical male circumcision programmes, the TAG noted that it was difficult to collate information on safety in a standardized and consistent manner across programmes and implementing partners. However, some rare adverse events had been reported (Fournier's gangrene, glans injury and tetanus).

- The two cases of Fournier's gangrene reported from Uganda were successfully managed with intensive inpatient treatment. The TAG recommended that the prevention and management of Fournier's gangrene be included in revisions of the WHO *Manual for male circumcision under local anaesthesia*.
- A total of eight glans injuries were reported between 2010 and 2013. These were all among younger, prepubertal adolescents (ages 10–14 years) and using the forceps-guided method. The TAG reaffirmed the content of the WHO Information Note of July 2014, which gave a strong caution regarding the use of the forceps-guided method in younger adolescents and expressed a preference for other surgical circumcision methods that allow direct visualization of the glans. This caution is because it can be difficult to accurately distinguish the glans prior to placing the forceps in younger men who are not fully developed physically. Support should be given by implementing partners to programmes to move from the forceps-guided method to

safer methods in the younger age group. The TAG also noted that the safety of circumcision in adolescents needs increased attention; this age group may be a focus for voluntary medical male circumcision (VMMC) services as national programmes move from the catch-up phase to sustained circumcision programmes.

- VMMC programmes reported a total of five cases of tetanus by September 2014. These cases resulted in three deaths. They arose following conventional dorsal slit or forceps-guided surgical method or PrePex™ device circumcision. These cases highlight the limited coverage of tetanus vaccination in adolescent and adult men in some of the focus countries. The TAG:
 - established a working group to collect and review more data on tetanus cases and to coordinate with WHO and national vaccination programmes on strengthening national tetanus vaccination programmes, including coordination with the circumcision programmes;
 - recommended that wound care instructions be improved and substances, such as soil or dung, that may contain tetanus spores be avoided; and
 - stressed the importance of identifying cases and establishing more clearly the association between circumcision and tetanus, including whether there may be a differential risk according to circumcision method.

Following a general discussion regarding safety monitoring, the TAG noted the limited evidence available at the national and global levels. They recommended that countries establish formal Adverse Event Review Committees to which would be reported all serious adverse events (SAEs), including deaths, whether directly or indirectly related to the VMMC procedure or programme. The TAG proposed that countries report the following to the regional or global level:

- all deaths and hospital admissions to intensive care occurring within 30 days of circumcision,
- all cases of tetanus diagnosed within 30 days of circumcision, and
- all serious glans, penile or urethral injuries.

Given the wealth of experience that has accumulated since the development in 2009 of the *Manual for male circumcision under local anaesthesia*, the TAG proposed that WHO provide a clinical update, such as a revision to the manual.

Safety of the PrePex™ device among men age 18 years and over

At the January 2013 meeting the TAG reviewed the clinical experience with the PrePex™ device among men 18 years and older reported in a series of studies in Rwanda, Uganda and Zimbabwe. New information is now available from 14 pilot implementation studies in 10 countries, as well as data from bridging studies of safety and performance of the device in adolescents. National programmes and implementers have contributed information on almost 24 000 device placements. This included data from over 17 000 placements in Rwanda and 6887 placements in other countries. A TAG subgroup reviewed a total of 505 adverse events (AEs) among 492 patients to ensure uniform classification of events according to previously used AE definitions. The subgroup considered a total of 80 AEs to be serious and 133 to be moderate, with rates of 3.2 and 5.4 per 1000 placements, respectively. The overall rate of the SAEs due to displacement or self-removal was 4.8 per 1000 placements, very similar to the rate of 1 in 200 seen in the January 2013 data review.

The most common serious and moderate AEs were associated with bleeding requiring medical or surgical intervention such as cautery or sutures (44). Displacements (21), self-removals (14) and requests for early removal due to pain or discomfort (13) were the next most common types of reasons for serious and moderate AEs. Other AEs included 19 infections, 13 cases of oedema, five cases of invagination of the foreskin requiring surgical intervention, four difficult device removals, four serious wound disruptions, and two difficulties with urination. Pain was noted in a large number of cases: 58 were considered moderate and 243 mild. The two reports of tetanus with the PrePex™ device (see above) were not included in the 2014 compilation, as they occurred after the cut-off date.

In the safety information compiled by The United States President's Emergency Plan for AIDS Relief (PEPFAR), the majority of reported AEs were related to pain at the time of removal. In over 6000 placements there were 45 displacements and 13 requests for early removal. Key issues identified from regular discussions with investigators in sites implementing PrePex™ circumcision included the need for guidance on management of device displacements, safety and suitability of removing the device 1-2 days earlier than scheduled and management of odour while wearing the device.

Following the discussion, the TAG recommended that:

- The current prequalification of the PrePex™ device should be maintained, as the safety profile remained similar to that in 2013 except for the uncertainties related to acceptability and costs and the potential risk of tetanus.
- WHO should update guidance on clinical management of patients with device displacement.
- Procedures for improved penile hygiene and methods for preventing and mitigating unpleasant odour while wearing the device need to be studied.
- Transient pain (even if severe) at the time of removal should

no longer be considered an AE when monitoring the safety of the PrePex™ device in programme settings, but prolonged pain would be considered abnormal.

- Studies on pain relief at the time of removal should be encouraged.
- Active surveillance of men using the PrePex™ device should continue.
- Safety of the device should be reviewed at the next TAG meeting.

Following a review of arguments for and against high-level disinfection or sterilization of removal instruments, the TAG agreed it would be inappropriate to advise a change in the manufacturer's instructions for use of sterile removal instruments, at least until further information was available on the risk of tetanus.

Use of the PrePex™ device in adolescents under 18 years of age

TAG reviewed the data from a bridging study among adolescents in Zimbabwe (402 placements) and a small study in South Africa (89 placements). In Zimbabwe, special sizes 12 – 20 were produced for the study use, but were not yet part of the prequalified product (adult sizes A – E). Overall 28% of adolescents required one of the new sizes. The TAG noted the high proportion of adolescents on whom the device could not be placed due to adhesions and/or narrow foreskin. However, the clinical performance of the method in those on whom the device could be placed was similar to the performance in adults. The TAG recommended that:

- Providers must be trained to recognize when an adolescent is not eligible for the PrePex™ device due to inability to retract the foreskin or discomfort when attempting to do so. They must also be trained not to place the device when there are adhesions or phimosis.
- Use of the PrePex™ device could extend to adolescents ages 13–18 but only under active surveillance until at least 2000 placements have been completed in at least three countries.
- In view of the low proportion of younger adolescents eligible for PrePex™ circumcision, particularly those ages 13–14, logistics and acceptability need to be considered, together with appropriate provider training, revised pre-procedure counselling and consent information, and referral mechanisms for surgical circumcision or delay of circumcision with the PrePex™ device until an adolescent is eligible.

Use of the ShangRing™ device in adolescents under 18 years of age

The TAG reviewed the data from a bridging study among adolescents in Uganda (337 attempted placements) and summary information from a small study in Kenya (20 attempted placements). The TAG concluded that:

- The performance of the ShangRing™ device was similar in adolescents and adults.
- The main safety concern with the ShangRing™ device is whether service providers are competent and have supplies and equipment to deal with ring slippage at the time of placement or soon after.
- The ShangRing™ device was clinically efficacious and safe in adolescents ages 13–18 years, similar to its performance in men 18 years and older.
- The use of this method is advised but only under active surveillance for adverse events and complications.
- Active surveillance should continue until safety has been demonstrated in at least 2000 procedures in at least three countries in the age range 13–18 years.

Guidance on method use among adolescents

Adolescents represent a large proportion of the current male circumcision clientele and will continue to be an age group needing circumcision services in order for programmes to maintain high coverage. A literature review published in 2009 found very little information on the safety and acceptability of specific male circumcision methods among adolescents, particularly younger adolescents, ages 10–14 years. The TAG summarized the elements that need to be considered in developing programmatic guidance on methods and services for adolescents and listed their priority outcomes for evaluation:

- safety (compared with conventional surgery in adolescents and with device use in adults);
- eligibility: proportion eligible for a particular method by age group;
- acceptability (to client, disruption of activities of daily living, pain, odour, cosmetic result and ease of use for providers);
- efficacy;
- healing time.

Infant devices

The TAG reviewed results of three clinical studies of the AccuCirc™ early infant circumcision device, conducted in Botswana and Zimbabwe. Pending results of further studies and field studies conducted in Kenya, the TAG noted that:

- Circumcision had been successful in 99% (744 of 751) of infants.
- Four adverse events due to bleeding problems had occurred.
- Three cases of excessive skin removal had occurred, all of which were treated with hydrocortisone cream and appeared fully resolved by four months.

- It was not possible to give an upper age limit for safe device use in infants beyond 10 days, as data were limited.
- Care should be taken to verify and document that prophylactic vitamin K be given to all infants who undergo circumcision, particularly if the circumcision is performed within the first week.
- Careful screening for a family history of bleeding problems is essential to reduce the risk of bleeding complications associated with haemophilia, which is a contraindication to circumcision.
- Potential complications due to neonatal tetanus should be avoided. This can be done by verifying and documenting that the mother has received the recommended number of tetanus vaccinations to assure transplacental transfer to the fetus of antibodies that confer protection against tetanus.
- A systematic approach to classifying bleeding AEs should be adopted. The TAG suggested:
 - serious: bleeding resulting in blood transfusion, bleeding resulting in hospitalization and requiring sutures and/or other specialist intervention to control, bleeding requiring sutures or specialist intervention but not hospitalized
 - moderate: bleeding managed by special haemostatic dressing but sutures not required.
- The sequence, type and size of studies to evaluate circumcision devices defined in the WHO *Framework for clinical evaluation of devices for male circumcision* should also be applied to the assessment and progressive expansion of infant circumcision devices and procedures.
- The WHO prequalification programme has not prioritized infant male circumcision devices for review. Countries and programmes must recognize that the conclusions of the TAG refer only to the clinical performance of the devices and not to the quality of the manufacturing system. Purchasers would need to ensure through other means that devices used in early infant circumcision programmes are of adequate quality.

The TAG recommended that a full report on the assessment of the clinical performance of the AccuCirc™ device be prepared and submitted to UNICEF to inform policy and programme development. The TAG would be willing to continue to review the clinical performance and safety of early infant circumcision devices if requested.

Male circumcision device innovations

The TAG reviewed and discussed promising innovations in male circumcision devices. The group strongly encouraged further development and evaluation of the UniCirc™ and CircumQ™ surgical-assist device, in new settings in South Africa and other countries. The group gave low priority to the SurgiPex procedure, which involves a small dorsal slit in a tight or narrow foreskin to allow insertion of the PrePex™ device. They welcomed the development of the no-flip ShangRing™ approach as well as the potential for use of topical anaesthetic to replace injectable local anaesthetic with the ShangRing™. The TAG looked forward to reviewing and assessing further data on these innovations at its next meeting.

INTRODUCTION

In March 2007 WHO and the Joint United Nations Program on HIV/AIDS (UNAIDS) recommended that male circumcision be considered a part of a comprehensive HIV prevention package in countries with generalized epidemics following compelling evidence from three randomized controlled clinical trials confirming the results from ecological studies. Since then 14 countries in east and southern Africa have taken action to scale up voluntary medical male circumcision for HIV prevention.

Modelling studies indicate that in these priority countries VMMC will have the greatest public health impact, averting up to 3.4 million HIV infections through 2025 and will provide the largest cost-saving (USD 16.5 billion), if services are scaled up rapidly. Given that currently recommended surgical methods for male circumcision involve considerable time and skill, innovations in the surgical procedure, including male circumcision devices, have been under research and development over the past few years. Roll-out of these innovations has started in two countries.

In 2010 WHO established a Technical Advisory Group on Innovations in Male Circumcision with the purpose of reviewing and advising WHO on the safety, acceptability and public health need for male circumcision innovations. With the TAG's inputs, WHO developed a *Framework for the clinical evaluation of devices for male circumcision*, which describes the clinical evaluation pathways to provide sufficient evidence of safety and acceptability. WHO has also established a programme for the prequalification of male circumcision devices, which is led by the Department of Essential Medicines and Health Products (EMP). WHO prequalified the first device, the PrePex™, in 2013. The prequalification was based on the TAG's evaluation of the clinical efficacy and safety of the device and assessments by EMP that the device specifications, manufacturing and quality assurance systems were adequate. The TAG also evaluated the clinical efficacy and safety of a second device, the ShangRing™, which is in the prequalification process.

The TAG was convened in October 2014 to review new data on the use of the PrePex™ device from pilot implementation studies and programme roll-out on the safety and suitability of the PrePex™ and ShangRing™ devices for circumcision in adolescents. The group also reviewed and discussed current issues on device use, new innovative methods for adults and infants, considerations of clinical data requirements and priority needs in innovations.

Objectives of the TAG meeting

The objectives of the meeting were to:

- Update the TAG on the current WHO guidance on use of devices for adult MC, including:
 - the status of devices within the WHO Prequalification of Male Circumcision Devices Programme;
 - the current landscape of devices and male circumcision methods;

- adverse event rates in VMMC programmes using conventional surgical approaches by method and age groups.
- Review the safety of the PrePex™ device, including:
 - AEs from pilot implementation studies since January 2013 and surveillance of programme roll-out;
 - high-level disinfection versus sterilization of removal equipment.
- Conduct a detailed review of the clinical research findings on:
 - two male circumcision devices for adolescents, considering also the safety of conventional methods in this age group;
 - the PrePex™ device (studies from South Africa and Zimbabwe);
 - the ShangRing™ (studies from Kenya and Uganda);
 - the AccuCirc™ infant device: clinical evidence and quality assurance process.
- Advise WHO on innovations and research requirements, including:
 - the UniCirc™ surgical assist with glue and adherent dressing: clinical evaluation to date, further requirements, and considerations for the prequalification process;
 - use of topical anaesthesia (timing, use with different MC methods, use in cases of phimosis and during device removals);
 - a review of requirements for clinical evaluation (following the WHO clinical evaluation framework);
 - operational and programmatic considerations from above-mentioned reviews;
 - additional technical innovations that WHO should assess or encourage further development of to improve coverage, accelerate scale-up in priority countries;
 - priority research related to the innovations mentioned above.

Please see the detailed meeting agenda in Annex 1.

Participants

The participants included the TAG members, who have a wide range of clinical and programmatic expertise, and several are from the African region where VMMC interventions are being implemented. There were also observers from major organizations involved with male circumcision programmes for HIV prevention, including PEPFAR and the Bill and Melinda Gates Foundation. Consultants with expertise in evaluation of circumcision devices also participated. The WHO Secretariat included staff from the HIV Department, the Department of Essential Medicine and Health Products and the WHO Regional Office for Africa. Please see a detailed list of participants in Annex 2.

Meeting process and roles of participants

Rachel Baggaley welcomed the TAG members who serve in their personal capacity as clinical scientists, surgeons, urologists, public health policy leaders, biomedical engineers, statisticians, medical device regulators and programme managers in the field. Members of the TAG are experts appointed because of their expertise, and they are involved in the formulation of conclusions and recommendations for WHO. Observers from collaborating agencies and partner organizations working to expand male circumcision programmes for HIV prevention represent their institutions and contribute technical information and knowledge. Observers do not participate in the formulation of advice and recommendations. During the meeting final conclusions from the TAG were discussed with only members present. Given the confidential nature of some of the meeting documents under review, all TAG participants agreed to respect the confidentiality of the information and discussions and signed confidentiality agreements. An additional expert from the United States Centers for Disease Control and Prevention, Carlos Toledo, joined the meeting as an observer in order to provide information on pilot research and field issues. Additionally, Michael Maier joined the meeting in his capacity as a consultant representing the WHO Department of Essential Medicines and Health Products staff that were not available for all three days of the meeting. The group reviewed the objectives, key questions and agenda.

Declarations of interests

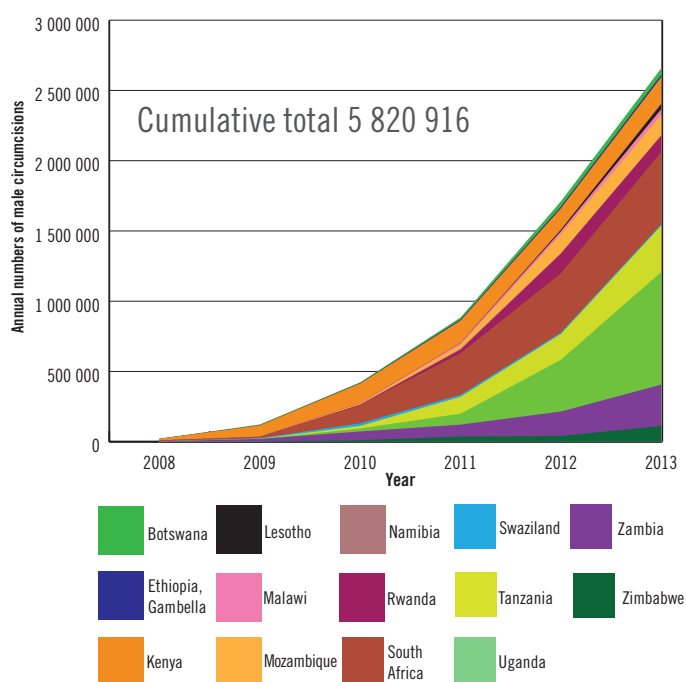
The WHO Secretariat explained the reasons for the written and verbal declarations of interests and summarized the pertinent interests that had been declared in writing prior to the meeting. Some participants had declared potential conflicts due to involvement on research teams that had studied, or were currently studying, one or more devices. Others had declared involvement in modelling studies. No participants declared commercial or financial interests with groups that might benefit from or be adversely affected by the topics of discussion or outcomes of the meeting. All participants were further invited to declare verbally to the group any other conflicts, or potential conflicts, of interests. No other members stated having any current or potential conflicts of interest that might affect their impartiality, judgment or advice. A review of the declarations by the WHO Secretariat and the TAG chairs identified no significant conflicts or potential conflicts of interest that would disqualify or restrict any participation in the meeting.

PROGRESS SINCE THE JANUARY 2013 TAG MEETING

Scale-up of VMMC programmes in priority countries

Buhle Ncube gave a summary of progress in scaling up VMMC programmes in the 14 priority countries in east and southern Africa. A total of 2.7 million male circumcisions were performed in 2013, with a cumulative total of 5.8 million at the end of the year (Fig. 1). This number represented 28% of the target of 20 million male circumcisions. There were very large increases in Lesotho, Mozambique, Uganda, Zambia and Zimbabwe, while much less progress was made in Malawi and Namibia. Most countries have focused on circumcising males 15–49 years old as part of the catch-up programme. Several countries, however, have begun to consider how to move to sustaining a high prevalence of circumcision by focusing on cohorts of adolescents and infants. This transition has implications for the TAG's work on the safety and acceptability of male circumcision innovations, which must increasingly turn toward adolescent and infant procedures.

Fig. 1. Annual number of medical male circumcisions performed in 14 priority countries in east and southern Africa, 2008–2013



Source: Global AIDS Response Reporting (WHO/UNAIDS/UNICEF).

Technical progress and publications

Julia Samuelson summarized the progress on technical issues and publications since the previous TAG meeting in early 2013. WHO finalized summary reports on the clinical performance and safety of the PrePex™ device and sent them to the WHO prequalification team. In October 2013 WHO first published the *Guideline on the use of devices for adult male circumcision for HIV prevention*, which recommended the use of prequalified devices among healthy men 18 years and older. The new technological innovations with the UniCirc™ and adhesive glue method have been investigated for potential. Also, there are now new safety data available for the TAG to review. This includes data from the implementation of surgical VMMC programmes, use of the PrePex™ and ShangRing™ devices in adolescents and use of the AccuCirc™ device in infants. It was noted that the January 2013 conclusions on the clinical performance of the ShangRing™ and PrePex™ devices were provisional and needed to be reassessed “as more experience and data accumulate with use of the device[s] in diverse programmatic settings outside the context of studies”.

WHO prequalification of male circumcision devices

Helena Ardura, WHO Department of Essential Medicines and Health Products, gave an update on the status of the male circumcision device prequalification process. The Department has defined six prioritization criteria for considering specific devices. These include the need for devices in adult males, the appropriateness of the product for use in resource-limited settings, requests from Member States for particular devices, the performance capabilities of particular devices, the availability of similar currently prequalified devices and the need for devices for adolescent male populations.

Currently, only the PrePex™ (elastic collar compression) device has been prequalified, and the ShangRing™ (collar clamp compression) device is in the prequalification process. The prequalification team has terminated applications from manufacturers of other clamp devices. For the Tara KLamp™, there were insufficient objective clinical performance data for review and the Alisklamp™ was withdrawn by the manufacturer pending generation of such data. The prequalification team received a pre-submission enquiry from the manufacturer of the RapideClamp™, another clamp device. The most up-to-date information is available on the WHO Prequalification of Male Circumcision Devices website.¹

On behalf of the WHO prequalification team, Michael Maier presented a proposed risk classification system that may be used for determining the prequalification pathway required for male circumcision devices. This system followed the Global Harmonization Task Force (GHTF) recommendations on

¹ Available at: http://www.who.int/diagnostics_laboratory/evaluations/140919_pqmc.pdf?ua=1.

conformity assessment. It included risk assessment principles of ISO-14971 and took into account the degree of invasiveness and time that the device remained in contact with the body. The assessment would consider the level of risk and define the level of scrutiny. The level of risk would be raised if the device had an innovative mode of action, if adverse event reports raised concerns, if the technology was new to the manufacturer or if the device user was a lay person instead of a trained health professional.

Anita Sands, a member of the WHO prequalification team from the Department of Essential Medicine and Health Products, summarized WHO's approach to post-market surveillance for prequalified male circumcision devices, which follows the principles established in ISO 9001:2000, ISO 13485:2003 and ISO 14971:2000. Post-market surveillance is a system that provides continuous feedback about a product once it is placed on the market. It helps to minimize exposure to risks arising from incidents or potential incidents, through effective warnings and field safety notices. A well-functioning system requires that key stakeholders report, assess and act on reports of incidents associated with the device. These stakeholders include the manufacturer as well as end users, national regulatory authorities (NRAs) for medical devices and the WHO Prequalification Team. WHO plays a role in post-market vigilance since oversight of medical devices by many NRAs is in the early stages of development or is non-existent.

In the case of male circumcision devices used in national VMMC programmes, there is an important role of the national programmes which may act through MC task forces. The responsible national body should establish a task force and appoint members. The task force could set up a MC adverse event review committee with support from WHO and partners. Responsibilities of the adverse event review committee could include reviewing the AE reports, reporting all AEs to the manufacturer and reporting to WHO any new AEs (all serious AEs and significant changes in trends of mild/moderate AEs), as well as keeping the national HIV programme informed. The manufacturer has a responsibility to receive complaints from users and the national AE review committee, investigate the problem and take appropriate action, including conducting root cause analysis and issuing Field Safety Corrective Actions (FSCAs) if required. As part of the post-market vigilance process, WHO will ensure that the manufacturer undertakes appropriate investigation, issues FSCAs and informs end users, programme managers, national regulatory authorities and WHO. The manufacturer or its representative issues a Field Safety Notice (FSN), communicating to users, the NRA and WHO about the FSCA. In addition, WHO may issue an Information Notice for Users in cases where the manufacturer has not undertaken an appropriate FSCA and/or has not issued a FSN in a timely manner. The WHO prequalification team will monitor the manufacturer's investigation, including the risk assessment related to the incident, and determine if WHO prequalification status is affected. WHO is developing more detailed guidance for post-marketing vigilance, including a flow chart for reporting complaints to WHO, rules for classification of AEs, standardized log books for recording AEs and guidance on the investigations to be undertaken by the manufacturer and how and when to issue FSCAs and FSNs.

Experience with male circumcision devices

Julia Samuelson summarized the evidence available for the evaluation of device efficacy and safety. At the January 2013 meeting, the TAG reviewed the clinical experience with the PrePex™ device among men ages 18 years or older. In Rwanda there was an initial safety study, a randomized comparison with conventional surgery and field studies with experienced and newly-trained nurses. In Zimbabwe there was a safety study, a randomized comparison and a field study. There was also additional information from two field studies in Uganda. Since the review in 2013, new information in adults has become available from 14 pilot implementation studies in 10 countries (Botswana, Kenya, Lesotho, Malawi, Mozambique, South Africa (3), Uganda (3), United Republic of Tanzania, Zambia, Zimbabwe), six active surveillance studies (Botswana, Rwanda, South Africa, Uganda (2), Zimbabwe), and passive surveillance in Rwanda and Zimbabwe. In addition, bridging studies involving adolescents ages 13 years and above were conducted in Zimbabwe with a small number of adolescents, and in a pilot study in South Africa. Appendix 4 presents a summary of these studies.

For the ShangRing™ device, the January 2013 review was based on safety studies in Kenya, randomized comparisons in Kenya and Zambia, field studies in Kenya and Zambia and an acceptability and safety study in Uganda. Since that 2013 review new data on safety and acceptability among adolescents were available from Kenya and Uganda.

In addition, the TAG reviewed clinical data on the performance of the AccuCirc™ early infant circumcision device in Botswana and Zimbabwe.

ADVERSE EVENTS IN VMMC PROGRAMMES

In preparation for the meeting, the WHO HIV Department Prevention team contacted all countries to request information on the number and type of moderate and serious adverse events that had been seen in the national programmes over the 5-year period 2009–2013. This request was motivated by the need to monitor the safety of surgical circumcision methods as the VMMC programmes expand and evolve. A limited number of men and boys under the age of 18 years participated in the three randomized controlled trials that demonstrated the efficacy of circumcision to reduce HIV risk (only Uganda enrolled participants ages 15–17 years) and only the forceps-guided and sleeve resection procedures had been studied. Among the nearly 6 million circumcisions performed by the end of 2013, about 15% were in adolescents under the age of 15 years.

WHO received responses from only three countries, with Kenya providing the most detailed information. The most common SAEs were bleeding, swelling/haematoma, infections and anaesthesia reactions. The overall SAE rate was 0.05%, but insufficient details were available to determine whether events had been classified in a standardized and comparable manner by type and severity. There was limited information on the age distribution of AEs and surgical procedures performed, and there was no standardization of age strata.

The majority of the eleven countries reported that they had no central repository or compilation of AEs, and the only way of retrieving this information was to contact individual implementing partners. It was noted that PEPFAR-supported programmes had a requirement to report deaths to the central level, but no other adverse events. PEPFAR introduced this requirement in mid-2014; no systematic compilation was available before that date. Several SAEs had come to the attention of TAG members and observers through informal channels, however. These included five tetanus cases since 2012, two cases of Fournier's gangrene, and eight glans injuries.

Fournier's gangrene

Moses Galukande described the two Fournier's gangrene cases that occurred in 2013; both cases were resolved successfully. Fournier's gangrene can be a rare complication of genital surgery, resulting from infection with multiple bacteria and causing progressive tissue necrosis. In this situation, the blood supply is cut off and the skin and underlying tissues become necrotic. After reviewing these case reports in detail, the TAG stressed the importance of early recognition of signs of advancing infection or gangrene and, upon suspicion, prompt transfer to a centre with the necessary clinical and surgical skills for management. TAG suggested that WHO review the *Manual for male circumcision under local anaesthesia* to determine the need for more detail related to this type of AE.

Glans injuries

Julia Samuelson provided information on the eight reported glans injuries during 2010–2013 that occurred among younger pre-pubertal adolescents (ages 10–14 years) with the use of the forceps-guided method. All cases had been closely followed and all cases resolved successfully. The TAG members and observers noted that additional cases had been anecdotally reported in countries. Comparative data on the safety of different male circumcision methods in adolescents were not available. Contributing factors cited by TAG members familiar with the cases included fatigue due to workload, no surgical assistant present and pressure to achieve scale-up targets leading to a decline in some quality standards (as noted in one of the SYMMACS studies²).

To clarify the role that age and physical development contribute to method safety, Tigistu Adamu shared findings from a 2009 study in the United Republic of Tanzania on biometric measurements undertaken to inform the development of different sizes of devices for efficient forecasting, manufacturing and procurement.³ Of the many measurements and correlations, the TAG was interested in the evidence on the correlation between age and physical development (Table 1) and physical maturity as defined by Tanner stages for three age groups, shown in Fig. 2. The TAG noted that the majority of the 10–13 year age group is not yet physically developed.

- 2 Jennings L, Bertrand J, Rech D, Harvey SA, Hatzold K, Samkange CA et al. Quality of voluntary medical male circumcision services during scale-up: a comparative process evaluation in Kenya, South Africa, Tanzania and Zimbabwe. *PLoS ONE*. 2014;9(5):e79524.
- 3 Chrouser K, Bazant E, Jin L, Kileo B, Plotkin M, Adamu T et al. Penile measurements in Tanzanian males: guiding circumcision device design and supply forecasting. *J Urol*. 2013;190:544-50.

Table 1: Penile and somatometric measurements, by age group

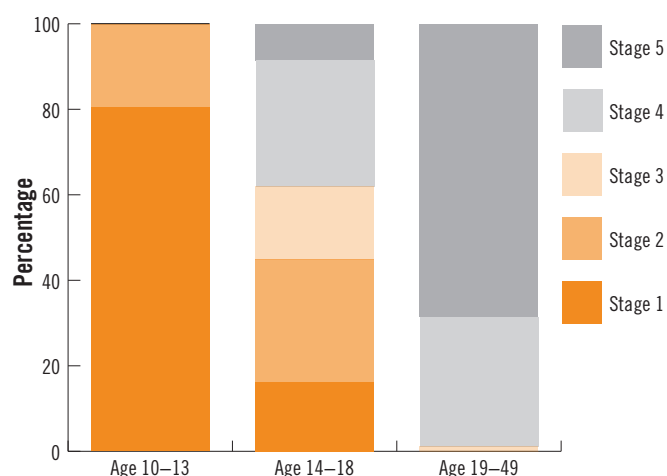
Measurement ^a	Ages 10–13	Ages 14–18	Ages 19–49
Penile			
Number of patients	52	107	93
L1—base-glans tip stretched penile length (cm)	7.4 ± 1.5 7.5 (6.4–8.3)	9.7 ± 2.0 10 (8.3–1.2)	11.5 ± 1.6 11.5 (10.7–12.3)
L2—coronal ridge-tip glans length (cm)	1.7 ± 0.4 1.8 (1.5–1.9)	2.4 ± 0.5 2.5 (2.1–2.8)	2.9 ± 0.4 2.9 (2.6–3.2)
C1—shaft proximal to corona girth/ circumference, foreskin retracted (cm)	5.6 ± 0.8 5.5 (5.0–6.0)	7.6 ± 1.3 7.9 (7.0–8.5)	8.7 ± 0.9 8.5 (8.1–9.0)
C2—coronal ridge/ margin girth/ circumference, foreskin retracted (cm)	5.5 ± 0.9 5.5 (5.0–5.8)	7.6 ± 1.4 7.9 (6.9–8.7)	8.8 ± 0.9 8.8 (8.2–9.4)
F2—most distal end foreskin stretched diameter (cm)	2.7 ± 0.6 2.6 (2.3–3.0)	3.9 ± 0.9 4.0 (3.3–4.5)	4.6 ± 0.7 4.6 (4.2–4.9)
F3—foreskin thickness under tension (mm)	1.2 ± 0.3 1.1 (1.0–1.2)	1.5 ± 0.5 1.3 (1.2–2.0)	1.5 ± 0.5 1.4 (1.2–1.8)
F5—coronal ridge-distal foreskin edge distance (cm)	2.5 ± 0.6 2.5 (2.0–2.8)	3.0 ± 0.6 3 (2.6–3.4)	3.3 ± 0.6 3.3 (3.0–3.6)
Somatometric			
Number of patients^b	47	90	61
Height (cm)	133.3 ± 0.9 135 (123.0–140.0)	151.5 ± 9.7 152.0 (146.0–158.0)	164.6 ± 7.6 165 (161.0–170.0)
Weight (kg)	29.5 ± 5.0 30.0 (26.0–32.0)	44.1 ± 8.4 44.0 (39.0–50.0)	57.7 ± 7.1 59 (51.0–61.0)
BMI (kg/m ²)	16.5 ± 1.8 16.5 (15.3–17.9)	19.1 ± 2.3 19.1 (17.3–20.4)	21.3 ± 2.7 20.8 (19.8–22.3)

^a Mean ± SD, median (interquartile range) unless otherwise stated.

^b Total of 198 since height and weight data were not available in all patients.

Source: Adapted from Chrouser et al.

Fig. 2. Tanner stage, indicating sexual maturity, by age



Source: Adapted from Chrouser et al.

The TAG discussed the WHO Information Note issued 1 July 2014 (Annex 3), and urged strong caution about use of the forceps-guided method in younger adolescents. The TAG noted that the risk of injury is likely greater in those adolescents who have not yet developed physically, as it is difficult to clearly distinguish the tip of glans when placing the forceps across the foreskin. They further noted that this injury is preventable.

- The TAG recommended that the WHO caution issued in July 2014 regarding the use of the forceps-guided method should remain for younger adolescents given their less mature physical development. The TAG noted that other circumcision methods that permit visualization of the glans are available. The forceps-guided method was used initially to help with circumcision of large numbers of adult men, and there is less urgency for MMC for HIV prevention among this younger age group, which is predominantly sexually abstinent. The TAG recognized the challenges that programmes face when changing methods, but stressed that safety is the priority.
- The TAG recommended that programmes be supported to move to other methods for younger adolescents and that they should stress that providers ensure that the glans is fully exposed and adhesions are released before surgical circumcision.
- The TAG recommended that, as each method has its unique risks, providers and programmes should strengthen their quality assurance frameworks to maintain quality standards. Further, they should train for competency in each method used and improve recording, reporting and synthesis of adverse events. In addition, countries should establish formal review committees and processes to discuss and respond to reported serious adverse events. This would provide an opportunity to identify risk mitigation strategies in a timely manner and prevent future serious adverse events. The safety of circumcision in adolescents could become increasingly important as programmes move from the catch-up phase to sustained circumcision programmes that will likely focus on adolescents.

Tetanus

Julia Samuelson described the information available on the five tetanus cases reported by VMMC programmes as of September 2014. These cases occurred between 2012 and 2014 in four countries, and they resulted in three deaths. Four cases were in adolescents (ages 12, 15 and 16 years and one age not specified). These cases occurred following conventional dorsal slit or forceps-guided surgical methods or the PrePex™ device. Initial symptoms of tetanus were reported to have occurred between days 8 and 13 following surgery or device placement. At the time of review, insufficient details were available to establish a causal link with the circumcision procedure, but TAG members recognized the potential risk associated with any wound. Given the limited information and small number of cases, interpreting differences in risk according to circumcision method was difficult.

Ahmadu Yakubu, WHO Department of Immunization, Vaccines and Biologicals, described the incidence and burden of tetanus in adults, which is not well known in the countries implementing VMMC programmes. Even neonatal tetanus cases are considered to be substantially underreported (as few as 10% of cases may be reported). The coverage of three tetanus doses within the infant vaccination programmes has increased over time, and most countries have reached 80% or higher coverage. However, protection from this initial series is not durable over time. It wanes after about five years and leaves the host without protective immunity unless there are booster doses of vaccine. Unlike other vaccine-preventable diseases, there is not person-to-person transmission of tetanus and herd immunity is not conferred by tetanus vaccination in the community. *C. tetani* spores are widely present in the environment, and only individual vaccination offers protection. As *C. tetani* spores are so ubiquitous, substances applied for traditional wound care practices to absorb liquid and odours may contain *C. tetani*.

The global elimination initiative on maternal and neonatal tetanus has resulted in a reduction of tetanus deaths among women and neonates. For protection against neonatal tetanus, the pregnant mother needs two vaccination doses at least four weeks apart with the second dose at least two weeks before delivery. The only reliable way to prevent tetanus related to circumcision is to ensure that clients are adequately vaccinated before the procedure. School-based tetanus vaccination booster programmes should include boys as well as girls. In the absence of a vaccine record, it is safest to assume the client is not protected. To confer tetanus immunity two doses are needed at a sufficient interval to raise antibodies to protective levels. Tetanus vaccine cost is very low, at 0.07 USD per dose and total of 0.25 USD including syringe and needle. It is important that VMMC programmes coordinate with vaccine programmes. Logistics may be the greatest challenge. The availability of appropriate medicines for management is important, including tetanus immunoglobulin which is often not readily available.

The TAG discussions covered the potential association between circumcision and tetanus given the limited information available, wound hygiene, other surgery-related tetanus cases and standards of care in surgery. They also discussed the potential for increased tetanus risk with secondary intention healing, ischemic tissue, necrotic tissue, and the anaerobic environments necessary for tetanus growth. A TAG member commented that in Rakai, most adolescents and adult men likely have not been vaccinated, and wound education has been stressed. Changing hygiene and wound care behaviours takes time, but it may have improved within the Rakai Health Sciences catchment area. The TAG stressed prevention and noted that the 2007 recommendations on MC for HIV prevention included a call to strengthen health programmes as VMMC interventions were rolled out.

Given that tetanus has not been addressed previously in the context of VMMC for HIV prevention, the TAG recommended that a small working group be established to review the issues in more detail, to collect more information on cases and risks, to begin collaboration with vaccination programmes, to consider the implications of tetanus vaccination for future programming, to clarify the efficacy of tetanus immune globulin and the value of a centralized source, and to draft an information note on key issues to be considered by Ministries of Health in countries implementing VMMC programmes, including education of providers and men regarding response and monitoring. The following volunteered for the small group: Tigistu Adamu, Afua Hesse, Pius Musau, Christopher Samkange and 1–2 PEPFAR staff, along with the WHO staff.

The TAG recommended that wound hygiene instructions should be improved, with a strong emphasis on use of clean water and soap and avoidance of substances such as soil or dung that may contain *C. tetani* spores. Service provider in-service training should be updated to include emphasis on counselling on the risk of tetanus and its prevention. Service providers currently providing VMMC services should be retrained to improve counselling on wound care including tetanus prevention. It may be useful also to work with traditional providers to ensure that safe wound hygiene practices are encouraged.

The TAG recommended that VMMC programmes coordinate with national immunization programmes to review the historical coverage of neonatal tetanus vaccination programmes and consider how to provide vaccination in, or parallel with, the VMMC programme.

The TAG stressed the importance of early recognition of and response to tetanus infection, with prompt intervention and referral to a specialist facility that could manage tetanus including to make tetanus immunoglobulin available.

In view of the seriousness of and high mortality from tetanus, the TAG stressed the importance to VMMC programmes of understanding more clearly the link between circumcision and tetanus and whether there may be a differential risk according to circumcision method.

Improving reporting and monitoring of VMMC safety

Following a general discussion regarding safety monitoring, the TAG noted the limited evidence available at the national and global levels, and recommended that countries establish formal adverse event review committees to which all serious adverse events would be reported, whether directly or indirectly related to the VMMC procedure or programme. The purpose of the review of serious adverse events is for countries to focus positively on quality improvement and maintain a reputation of safe services that keep risks as low as reasonably possible by identifying and responding to serious adverse events. The TAG proposed that an eastern, central and southern African adverse events group be established with the WHO inter-country support team and headquarters engaged to support. The group could be composed of the MC adverse event focal point from each priority country. The TAG emphasized that all implementing partners should report serious adverse events to national programmes and to WHO, as well as follow PEPFAR reporting instructions.

The TAG proposed reporting to the global level:

- all deaths and hospital admissions to intensive care occurring within 30 days of a circumcision procedure,
- all cases of tetanus within 30 days of circumcision, and
- all serious glans, penile or urethral injuries.

Given the wealth of experience that has accumulated since the development of the *Manual for male circumcision under local anaesthesia*, the TAG proposed that WHO, in collaboration with other partners, update the manual.

SAFETY OF THE PREPEX™ DEVICE AMONG MEN AGE 18 YEARS AND OVER

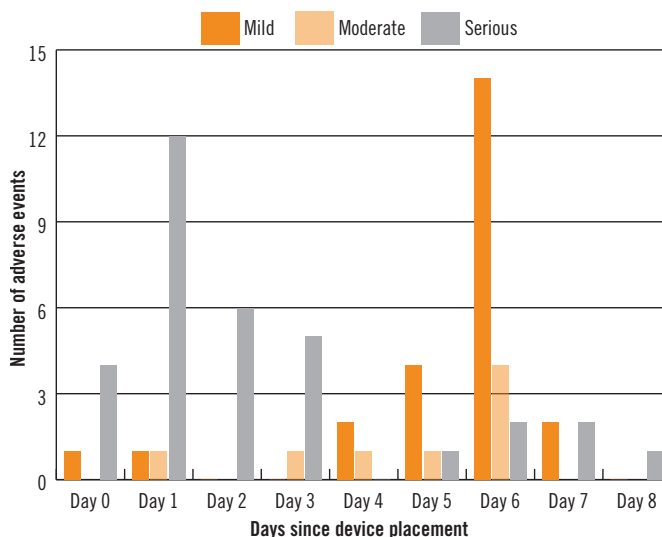
The PrePex™ device was prequalified by WHO in early 2013. The TAG, in its conclusions on the device's clinical safety, noted that the safety evaluation should be considered and reviewed periodically as use expands. Additionally, once a device is prequalified by WHO, post-market safety vigilance is required. In preparation for this 2014 TAG meeting, WHO contacted all national programmes and implementing agencies that had been using the PrePex™ device to provide information on the number of placements and moderate and serious adverse events between 1 January 2013 and 30 June 2014.

Tim Farley provided details on the data collected. Over 24 000 devices were placed since the previous TAG review. Of these, 17 000 placements were in Rwanda in the context of a passive surveillance programme. The other 6887 placements were made in the context of pilot studies or active surveillance. Site investigators or managers reported a total of 505 AEs among 492 patients. A subgroup of the TAG reviewed summary clinical details (including photographs where available) to ensure uniform classification of events in line with AE definitions used at the January 2013 TAG meeting. The reviewers considered a total of 80 of the AEs to be serious and 133 moderate, with rates of 3.2 and 5.4 per 1000 placements, respectively. The overall rate of the SAEs due to displacement or self-removal was 4.8 per 1000 placements, very similar to the rate of 1 per 200 seen in the January 2013 data review. There were no reported cases of penile injury or permanent damage. The rate of serious and moderate events was reportedly higher from pilot implementation sites than the two countries implementing active or passive surveillance. This may be due to improved skills with experience as well as limited follow-up and reporting of AEs.

The most common serious and moderate AEs were associated with bleeding that required medical or surgical intervention, such as cautery or sutures (44). Five SAEs occurred immediately after removal; the remaining occurred most frequently on the same day or the day after removal. These were managed with cautery or one or more sutures, sometimes under local anaesthesia. In discussion with one national programme manager, where sites reported a number of bleeding events, the impression was that most events could have been managed with pressure dressing alone and that bleeding events had decreased with more experience by the providers and better education to men.

Displacements (21), self-removals (14) and requests for early removal due to pain or discomfort (13) were the next most common types of reasons for serious and moderate AEs. Of the 31 removals on Days 0–3, 87% required prompt and specialized surgical intervention (serious), compared with 18% of the 34 removals on Days 4–8 (Fig. 3).

Fig. 3. PrePex™ device displacements, self-removals and early removals by day and severity



Pain was noted in a large number of cases: 58 cases were considered moderate and 243 mild. The majority of pain was reported at the time of removal of the device with Visual Analog Scale (VAS) scores in the range 6–10.

Other adverse events included:

- Nineteen infections were reported, with 17 classified as moderate and two as serious; information was too limited to make further interpretations but most were reportedly treated with antibiotics.
- Thirteen cases of oedema were reported: four moderate and one mild while wearing the device, two moderate and three mild at the time of removal and one moderate and two mild after removal. The cases were treated with anti-inflammatories and analgesics, and thus were considered moderate in most cases. Swelling at the time of removal was severe in two cases.
- Five cases of invagination of the foreskin requiring at least minor surgical intervention.
- Four cases of problems with device removal in which the foreskin had everted over the outer ring; three of the four cases required surgical intervention.
- Four cases of wound disruption considered serious.
- Two cases of difficulty urinating.

A new type of AE, premature sloughing of the foreskin, which was not reported in the data available in January 2013, was reported to WHO during 2014. WHO issued an information note to programmes and partners in February 2014 (Annex 5). There were five cases of this type of AE, two of which were considered serious. Other new types of AEs included difficult urination and invagination. The two reports of tetanus following PrePex™ use (see above) were not included in the 2014 compilation as they were reported after the WHO requested cut-off date.

Jason Reed presented data received by PEPFAR as of 1 July 2014 on 22 types of adverse events, disaggregated by timing and severity, but without further specific details. The report included 6055 individual placements with 391 individuals experiencing one or more AEs and a total of 491 AEs. The overall adverse event rate was 6.5%. Most of the AEs were reported to be moderate (377) and were related to pain at the time of removal (76%). Forty-five displacements and 13 requests for early removal were reported. Surgical correction was required for 73% of the displacements.

Carlos Toledo summarized feedback received from site investigators during routine monthly calls. This qualitative input provides insight into issues related to implementing the PrePex™ method. Key issues raised included appropriate management of device displacements (particularly those occurring soon after placement); safety and suitability of device removals on Day 5 or 6 instead of Day 7 as planned; recording and reporting of pain while wearing the device and during removal; protocols for pain management or mitigation; and the importance and management of odour while the device is worn. Odour is reported in most settings, but is not considered an issue in all settings. There were requests from site investigators for advice from the TAG on these issues (addressed under different agenda items). It will be important to continue regular exchanges with site teams in order to understand how recommendations are interpreted and implemented by teams performing the circumcisions.

TAG recommendations

After discussing the data and clinical details available, the TAG advised that:

- The current prequalification of the PrePex™ device should be maintained since the safety profile remains similar to the 2013 profile, except for the uncertainty related to potential risk of tetanus. The number of PrePex™ procedures performed was still limited, and there were new uncertainties regarding the difference in the risk of tetanus compared with other methods, as well as uncertainties related to acceptability and costs since the device has not been extensively rolled out. The TAG should review this recommendation once more information becomes available, including more information on safe use in younger men and tetanus risks.
- Displacements have remained a relatively rare event. A displacement may include both rings or the O-ring may displace in relation to the inner ring. With information from additional cases since 2013, the TAG advised that the clinical management of patients with device displacement be changed slightly to recommend the following (see Table 2):
 - Even if there was no interference with the device by the user, surgical removal of the foreskin is advised if the device was displaced. (This change was due to the observation that men with thicker foreskins may be at higher risk of displacement even without interference, and the foreskin was usually oedematous after displacement.)
 - Patients with displacement should be seen and assessed by an experienced clinician within 6–12 hours of displacement.
- Use of the forceps-guided method following displacement was not recommended due to reduced ability to palpate the glans secondary to oedema and the need for good visualization of the glans.
- If ulcerations are present, oral antibiotics should be considered to prevent infection.
- Although invaginations were rare AEs, they were considered to be a potential reason for displacement. Training on awareness of this type of event and good placement was noted to reduce the occurrence.
- It is important to develop better procedures for penile hygiene and the prevention of unpleasant odour while the device is worn.
- Transient pain (even if severe) at the time of removal should no longer be considered an AE when monitoring the safety of the PrePex™ device in programme settings. It was considered an AE earlier, as the method had initially been promoted as pain free. Prolonged pain would be considered abnormal and should be monitored. It is important to improve the education, counselling and expectations of men related to pain, especially at the time of device removal.
- Small studies on pain relief at the time of removal were encouraged; findings should be shared across countries as pain may affect acceptability.
- Methods for preventing and mitigating unpleasant odour while wearing the device need to be studied, and the TAG looks forward to the forthcoming results of a randomized comparison in Rwanda.
- Active surveillance of men using the PrePex™ device should continue, and safety will be reviewed by the TAG at its next meeting, with interim coordination between PEPFAR and WHO.

Table 2: Clinical management of PrePex™ device displacements

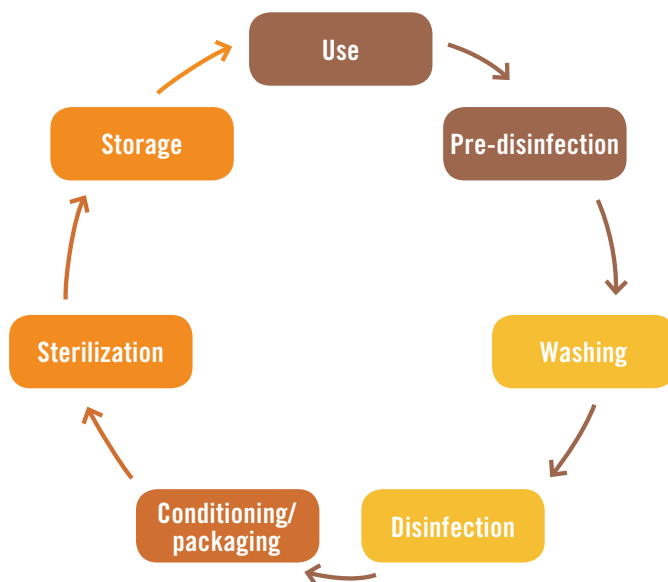
Scenario	
I: PrePex™ displacement with no adverse clinical signs	
	This clinical picture usually occurs within 4–6 hours of device placement. Any swelling is minimal and distal to the line of placement, and the circumcision marking line is usually still visible. Regardless of the cause of device displacement, it is not advised to replace it but instead to proceed to surgical MC by an appropriately trained competent provider. Surgical MC by the dorsal slit or sleeve method (described in the WHO/UNAIDS/Jhpiego <i>Manual for male circumcision under local anaesthesia</i>) is preferred to the forceps-guided method, as it may be difficult to palpate the glans due to even slight oedema.
II: PrePex™ displacement with oedema	
	This clinical picture is usually seen after 4–6 hours of placement and before 3–4 days. Oedema may be very pronounced and may be proximal to line of placement. There may also be blistering, ulceration, loss of skin or necrosis. The marking line is usually visible and distinct, but may be distorted. When present, the marking line easily defines the plane of surgical resection. The man should be seen within 6–12 hours in a facility with surgical back up and skills to manage surgical circumcision in the context of distorted anatomy. Management comprises surgical MC by the dorsal slit or sleeve method, performed by a trained competent provider who has the skill to deal with distorted anatomy. Local anaesthesia may not be needed. The forceps-guided method is contraindicated. Clinical judgement must prevail regarding management, including referral to a more qualified or experienced provider.
III: Late displacement with advanced or complete foreskin necrosis	
	This clinical picture is usually seen 4–5 days after placement. The foreskin is partially or fully necrotic. Management involves excising the necrotic foreskin and removing the device rings according to normal 7-day device removal practice. The wound is likely to be wider than normal (i.e. at 7-day removal), and there may be a delay in healing. Slight bleeding may require one or two sutures. Clinical judgement must prevail regarding management including prescription of antibiotics and referral to a more experienced provider.

HIGH-LEVEL DISINFECTION OF PREPEX™ REMOVAL INSTRUMENTS

Several programme managers and partners have requested that WHO relax the requirement for sterilization of the removal instruments of the PrePex™ device, arguing that high-level disinfection (HLD) is sufficient and aligns with the Spaulding criteria for semi-critical conditions. This has in part been motivated by the observation that clean, rather than sterile, gloves are used by providers during the removal process and the instruments become contaminated immediately on contact with the necrotic foreskin. Additionally, sterilization of instruments requires access to more resources such as a functioning autoclave and suitable packaging and storage.

Michael Maier described the cleaning and disinfection or sterilization cycle (Fig. 4). He noted that HLD requires moderate technical and logistics requirements to achieve a sterility assurance level (SAL) of 10⁻³ to 10⁻⁵, while sterilization requires higher technical logistic requirements to achieve an SAL of 10⁻⁶. He emphasized that all instruments require appropriate cleaning after use and before processing, whether by HLD or sterilization, or the sterilization process will not be effective. Other challenges with HLD are that the chemicals involved require special handling and dilution, and they have a short shelf life, which may result in ineffective disinfection.

Fig. 4. Use cycle for reprocessing of instruments



The TAG stressed that whatever method was adopted for preparing reusable instruments, it was essential that the basic infection prevention and control methods be followed carefully and correctly, particularly the cleaning step. Given the concerns and uncertainties about tetanus with circumcision, particularly with regard to the PrePex™ device, it would be inappropriate to advise a change in the manufacturer's instructions for use of sterile removal instruments, at least until further information is available on tetanus and male circumcision.

USE OF THE PREPEX™ DEVICE IN ADOLESCENTS UNDER AGE 18 YEARS

Tim Farley presented new data on the safety and acceptability of the PrePex™ device in men under age 18 years that were available from a bridging study involving successful placements in 402 adolescents ages 13–17 years in Zimbabwe. The most important findings were:

- Five additional smaller sizes of devices (12, 14, 16, 18, 20) than the currently prequalified sizes (labelled A–E) were produced and provided specially for this study. Overall 28% of adolescents required one of the new sizes (65%, 30%, 17%, 6% and 3% of clients age 13, 14, 15, 16, and 17 years, respectively).
- The proportion of clients not eligible for the PrePex™ procedure due to adhesions or narrow foreskin was considerably higher than in men age 18 years and over. Fifty-three per cent of the 13 year olds, 40% of the 14 year olds, 29% of the 15 year olds and 11% of the 16–17 year olds were not eligible. This compares with about 5–7% in adults.
- Among those on whom the device was placed, circumcision was successful for 99.8% (in one case insufficient skin was removed).
- The rate of adverse events (2 SAEs in 402 placements) was low and similar to that seen in adults, but no displacements or early self-removals were reported. One SAE was difficulty with urination.
- Pain scores appeared somewhat lower than in adults, but it was not clear whether this was because device removal was easier and less painful or because expectations about pain improved as providers gained more experience with counselling. Nearly all (94%) experienced some pain with removal (the highest VAS score was 4, on a scale of 0–10).
- Healing times were on average 2 days less in the 13 year olds compared with the 17 year olds (30.4 compared with 32.4 days), although it was not clear whether this was of clinical importance or would affect acceptability.

A second study conducted in South Africa included 89 adolescents, mostly 16–17 years of age, in a series involving a total of 393 successful placements. The proportion excluded due to adhesions or phimosis was not reported. Although numbers were small, the AE rates appeared similar in adolescents and older men, but healing time was significantly shorter in the adolescents. Further details and a full report from the study are awaited.

TAG recommendations

The TAG recommended that:

- Providers must be trained to recognize when an adolescent is not eligible for the PrePex™ device due to inability to retract the foreskin or discomfort while attempting to do so, or when there are adhesions or phimosis. Failure to recognize non-eligibility is likely to lead to adverse events such as failure of skin preparation prior to device placement leading to increased infection risk or failure to apply the device in the correct anatomical position resulting in incomplete skin removal.
- Use of the PrePex™ could extend to eligible adolescents 13–18 years of age, but only under active surveillance since the numbers assessed were small but within the range noted in the WHO clinical evaluation framework for a bridging study and given the potential risk of tetanus as noted above. The TAG advised that active surveillance be undertaken until at least 2000 placements have been completed in at least 3 countries.
- In view of the low proportion of younger adolescents eligible for circumcision by this method, particularly in the 13–14 year age group because of physical ineligibility and also the large proportion requiring use of device sizes that are not yet prequalified, the logistics and acceptability of offering PrePex™ circumcision will need to be considered in each context, together with:
 - Training considerations for providers to understand adolescent development, precautions for the PrePex™ and eligibility assessment.
 - Revised pre-procedure counselling and consent information that is relevant to younger adolescents.
 - For those who are not eligible for PrePex™, programmatic considerations need to be addressed, i.e. referral mechanisms for surgical circumcision or delay of circumcision with the PrePex™ device until the adolescent is eligible.

USE OF THE SHANGRING™ DEVICE IN ADOLESCENTS UNDER AGE 18 YEARS

Tim Farley presented new data on use of the ShangRing™ in adolescents under age 18, which was available from two studies conducted in Africa (Rakai, Uganda⁴ and Homa Bay, Kenya⁵) and one study in Chongqing, China.⁶

In the Rakai study, eligible adolescents were given a choice between dorsal slit surgery and the ShangRing™. Among 787 adolescents 13–17 years of age who were screened, 80 chose to be circumcised by the conventional dorsal slit surgical method and 384 selected the ShangRing™ device. For 47 of the adolescents, the correct size of ShangRing™ was not available, and they were offered conventional surgery. There were a total of three placement failures where the ring slipped off after the foreskin had been cut away. The circumcision procedures were completed by securing haemostasis and closing the skin with sutures, and they were otherwise uneventful. The failures all occurred with the same surgeon early in the study and were considered to be due to provider inexperience. The remaining placements were straightforward with a mean placement time of 5.2 (SD 1.8) minutes compared with 12.3 (SD 3.5) minutes for the dorsal slit method. The mean device removal time was 3.4 (SD 1.1) minutes. There were no adverse events with the dorsal slit method. With the ShangRing™, there were five moderate AEs (3 insufficient skin removed, 1 wound dehiscence, 1 self-removal) and 7 mild AEs. The proportion that was considered healed 28 days after placement or surgery was moderately lower for those circumcised with the ShangRing™ than with the dorsal slit method (92% and 99% respectively, $P = 0.002$). There was a high level of satisfaction with both methods. When interviewed after the study, almost 100% in both groups reported being satisfied or very satisfied with the procedure and the appearance of the result.

At the time of the review summary, information on the study in Homa Bay, Kenya was available from a conference poster and summary tables. The study involved 80 boys and adolescents under 18 years with body weight >2.5 kg and penile shaft >1 cm in length. The youngest participant was age 3 months, and only 20 were in the 13–17 year age range. The number of adolescents not eligible was not reported, nor the number of attempted placements. All 20 completed circumcisions resulted in successful outcomes, with three mild adverse events (one wound disruption and mild infection, one mild infection and not healed by Day 42, and one not healed by Day 42). The mean placement and removal times were 7.0 (SD 4.1) and 4.9 (SD 2.3) minutes, respectively. Overall, 80% were healed by 35 days. Information on pain and acceptability were not available for review.

The study in China was a retrospective review of 702 successful adult and 216 successful child (ages 7–17 years) circumcisions during the period 2010–2012. The procedure differed somewhat from the standardized method evaluated in Kenya and Zambia on adults and adolescents, in particular routine use of antibiotics, planned removals at 12–16 days after placement and use of oral diethylstilbestrol for 7 days to prevent erection.

TAG recommendations

After reviewing the available information, the TAG concluded that:

- More weight should be given to the results of the studies in Kenya and Uganda, as they were directly relevant to the scale-up of VMMC programmes for HIV prevention in Africa.
- Although numbers were limited, the Uganda study included 337 placements in adolescents ages 13–17 years, which exceeded the minimum size of bridging study defined in the WHO clinical evaluation framework.
- Available data suggested that the performance of the ShangRing™ device was similar in adolescents and in adults.
- The main safety concern with the ShangRing™ device was the need for competent providers and equipment and supplies to deal with ring slippage at the time of, or soon after, placement.
- The ShangRing™ device is clinically efficacious and safe in adolescents ages 13–18 years, and its performance is similar to that in men 18 years and older. The TAG advised that use of this method be subject to active surveillance for adverse events and complications in any programmes implementing the method. Active surveillance should continue until safety has been demonstrated in at least 2000 procedures in the age range 13–18 years in at least three countries. The TAG advised a phased approach to implementation, similar to that undertaken with the PrePex™ method, should apply also to ShangRing™ use among adolescents, including the programmatic considerations noted above for PrePex™.

4 Kigozi G. The acceptability and safety of the Shang Ring for adolescent male circumcision in Rakai, Uganda (Draft 2). Rakai, Uganda: Rakai Health Sciences Program; 2014 January 12.

5 Poster A. et al. Use of the Shang Ring for male circumcision in boys in Kenya: results from a pilot study. Presented at the International AIDS Conference, Melbourne, July 2014. Summary tables dated 28 August 2014.

6 Wu X, Wang Y, Zheng J, Shen W, Yan J-a, Ji H, et al. A report of 918 cases of circumcision with the Shang Ring: comparison between children and adults. *Urol.* 2013;81(5):1058–63.

GUIDANCE ON METHOD USE AMONG ADOLESCENTS

Adolescents represent a large proportion of the current male circumcision clientele, and they will continue to be an age group needing MMC services in the long term in order for programmes to maintain high coverage. Alice Armstrong described the findings from a literature review that was undertaken on the safety of male circumcision methods among adolescents 10–19 years of age. The review looked at articles published since a previous review in 2009.⁷ Out of 187 abstracts on conventional surgical methods, only four included evidence on safety with use of devices among adolescents. Two articles focused on the sleeve resection method, one on the forceps-guided method and one on the dorsal slit method. Data, however, was presented in wide age bands so that interpretation within narrower adolescent age groups, such as 10–14 years, was not possible. Among the 132 articles identified on male circumcision devices, three were relevant: two focused on the ShangRing™ in China and one on the PrePex™. These studies, supplemented with evidence from unpublished reports, had been presented and discussed earlier in the meeting. In summary, the data available from the literature review on the clinical safety and acceptability of specific circumcision methods among adolescents, particularly younger adolescents 10–14 years of age, was very limited. Safety data from the monitoring of adverse events has also been limited. The TAG encouraged improved reporting of adverse events with age disaggregation that will better inform the safety of all methods.

Alice Armstrong and Nuhu Yaqub listed key points raised during the meeting relevant to development of programmatic guidance on methods and services for adolescent. These included:

- balance of benefits and harms for different circumcision methods;
- quality of training for providing services to adolescents;
- training curriculum to include principles of adolescent-friendly services, adolescent development, counselling relevant for adolescents, assessing eligibility for specific methods, reporting and monitoring of adverse events, referrals for complications;
- quality assurance and improvement to ensure services and procedures meet defined standards;
- service delivery models:
 - minimum service package, including considerations about tetanus vaccination;
 - age- and development-appropriate adolescent-friendly services, history taking, HIV testing, counselling and disclosure guidance;
 - linkages with other services and programmes as necessary;
- training needs and logistics for including new circumcision methods in the services;

- appropriate age disaggregation to provide the most useful information for monitoring.

The TAG discussed information requirements in order to revise or develop guidance on methods, including device use for adolescents, as a complement to the guidance for adults issued in early 2013. It was agreed that guidance is needed to inform programme decisions, and that it must go beyond the clinical performance and safety of devices and conventional surgical methods. This is particularly important as countries move from the catch-up phase focusing on adults to sustained circumcision programmes for adolescents.

After discussing which outcomes to evaluate for new guidance, each TAG meeting participant listed five outcomes of greatest importance. Among the twelve responses, the priority outcomes were:

- safety (device use compared with conventional surgery in adolescents and with device use in adults);
- eligibility (proportion eligible for a particular method by age group);
- acceptability (to client, including disruption of activities of daily living, pain, odour, cosmetic result and provider ease of use);
- efficacy;
- healing time.

Other important outcomes listed, though given lower priority overall, included:

- procedure time (deemed less important for sustainable services than in the catch-up programmes for adults);
- feasibility (ease of training, logistics);
- inclusion of a range of circumcision methods that would expand eligibility, acceptability and uptake of circumcision services;
- perspectives of parents and caregivers;
- costs;
- maximizing advantages and optimizing the contact of the adolescent with the health system when they present for VMMC services;
- the potential to integrate circumcision and other services for adolescents.

The TAG recommended that WHO, together with key partners, map the data needed to inform evidence-based guidance and develop the guidance with strong inputs from policy-makers, programme managers and clients in countries implementing adolescent circumcision programmes.

⁷ UNAIDS/WHO. Neonatal and child male circumcision: a global review. Geneva: UNAIDS; 2010. Report No.: UNAIDS/10.07E (http://www.who.int/entity/hiv/pub/malecircumcision/neonatal_child_MC_UNAIDS.pdf).

INFANT DEVICES

The TAG reviewed results of three clinical studies of the AccuCirc™ early infant circumcision device conducted in Botswana and Zimbabwe. They concluded that the studies provided valuable information on the safety, efficacy and acceptability of the device in resource-limited settings. The WHO *Framework for clinical evaluation of devices for male circumcision* requires at least two comparative studies against an established standard method, each involving at least 100 uses of the new device, and two field studies, each including at least 500 procedures with the new device. While the TAG noted that the WHO framework had been developed for evaluation of adult male circumcision devices, the minimum requirements to demonstrate safety and efficacy of devices were also applicable to assessment of new infant devices. While results from two comparative studies were available, only one field study has been conducted to date.

AccuCirc™ device and procedure

The AccuCirc™ device consists of a flexible foreskin probe and shielding ring with a single-action clamp that contains a circular blade. The device is available in two sizes corresponding to penile diameters 1.1 and 1.3 cm. It is presented in a sterile pack with a surgical marker pen, surgical drape, two haemostats, three betadine swabs, Xeroform™ petrolatum wound dressing, gauze and cleansing wipes (all items disposable).

Before the procedure, 1 g EMLA™ topical anaesthetic cream is applied to the external skin of the penis, covered with an occlusive dressing and allowed to realize its anaesthetic effect before being wiped off at the start of the procedure. The infant's genital area, lower abdomen, and upper legs are cleaned and disinfected with betadine. A surgical pen mark is made on the foreskin at the level of the corona, and the normal adhesions between the foreskin and glans are removed using the flexible foreskin probe. Using haemostats, the shielding ring is inserted into the preputial space between the foreskin and glans. The adjustable foreskin holder is deployed and the tissue is aligned according to the pen mark, within the inner and outer foreskin holder rings using haemostats. The AccuCirc™ clamp is then applied and activated to deliver a circumferential, haemostatic crush while simultaneously incising the foreskin. After 5 minutes of haemostatic pressure, the clamp is released and the wound dressed.

The TAG made the following conclusions on the AccuCirc™ device, pending results of further studies and field experience:

- 1) The device has been evaluated in 751 healthy term infants with normal birth weight and no genital abnormalities. In 744 infants (99.1%) the circumcision was successful. The unsuccessful circumcisions were due to an incomplete cut of the foreskin (4 cases, completed with surgical scissors) and insufficient skin removal (3 cases, one of which was corrected surgically).
- 2) There were four adverse events due to bleeding problems (0.5%). The most serious occurred in a boy with an unreported and undetected family history of haemophilia who was hospitalized and required a 200 ml blood transfusion. A case of prolonged bleeding (for 90 minutes) occurred in an infant to whom prophylactic vitamin K had not been given at birth because of administrative oversight. The bleeding resolved within 30 minutes after administration of a vitamin K injection. A third case of bleeding that started at home after discharge required three sutures and the fourth case required clamping the bleeding vessel with a forceps and application of a haemostatic dressing.
- 3) There were three cases of excess skin removal that were treated with hydrocortisone cream and appeared fully resolved by four months.
- 4) The AccuCirc™ device has been approved by the United States Food and Drug Administration for circumcision of newborns in the USA up to age 10 days. In the three studies, two in Botswana and one in Zimbabwe, the median ages at circumcision were 2, 8 and 22 days, with the oldest infant age 56 days. It is not possible to give an upper limit for safe and efficacious use of the device based on currently available data, although it was used safely in a limited number of boys older than 10 days.
- 5) WHO recommends that to prevent vitamin K deficiency bleeding, all newborns should be given 1 mg vitamin K intramuscularly 1 hour after birth (after the first hour during which the infant should be in skin-to-skin contact with the mother and breastfeeding should be initiated). This particularly applies to neonates undergoing a surgical procedure in the first week of life.⁸ Even in settings where prophylactic vitamin K is standard, lapses in administration can occur, and providers should verify vitamin K administration before performing circumcisions in the first week of life.
- 6) Careful screening for a family history of bleeding problems is essential to reduce the risk of bleeding complications associated with haemophilia, which is a contraindication to circumcision.
- 7) Potential complications due to neonatal tetanus should be avoided by verifying that the mother has received the recommended number of tetanus vaccinations to assure transplacental transfer to the fetus of antibodies that confer protection against tetanus. Where vaccination status is not documented, providers should consider delaying neonatal circumcision until the infant is adequately protected.

⁸ Guidelines on maternal, newborn, child and adolescent health approved by the WHO Guidelines Review Committee: recommendations on newborn health. Geneva: World Health Organization; 2013 (http://www.who.int/maternal_child_adolescent/documents/guidelines-recommendations-newborn-health.pdf).

- 8) For classifying bleeding adverse events in future early infant circumcision studies, the TAG recommended a systematic approach as follows:
- Serious AE: bleeding resulting in blood transfusion, bleeding resulting in hospitalization and requiring sutures and/or other specialist intervention to control, bleeding requiring sutures or specialist intervention but not hospitalization.
 - Moderate AE: bleeding managed by special haemostatic dressing but sutures not required.
- 9) The three research studies showed a very low acceptance of early infant circumcision. This may have been partly due to the research context and may not reflect the eventual acceptability and uptake of the procedure once a programme and services have been implemented and promoted.
- 10) Further information on the safety and performance of the AccuCirc™ device will become available from two field studies to be undertaken in Kenya in 2015.
- 11) The TAG noted that the WHO clinical evaluation framework on phased implementation developed for adult male circumcision programmes is also relevant for early infant circumcision programmes. Once field studies involving at least 500 cases in each of two independent sites have been completed, the next steps are pilot implementation studies and careful monitoring for adverse events with progressive expansion using active surveillance followed by passive surveillance studies.

The TAG noted that the WHO prequalification programme has not prioritized infant male circumcision devices for review. Countries and programmes must recognize that the conclusions of the TAG only refer to the clinical performance of the devices and not the quality of the manufacturing system. Purchasers would need to use other mechanisms to ensure that devices used in early infant circumcision programmes are of adequate quality.

The TAG recommended that a full report on the assessment of the clinical performance of the AccuCirc™ device be prepared, reviewed electronically after the meeting and submitted to UNICEF (the lead agency on early infant MC within the UN family) to inform policy and programme development. The TAG would be willing to continue to review the clinical performance and safety of early infant circumcision devices if requested.

MALE CIRCUMCISION DEVICE INNOVATIONS

UniCirc™ device and procedure

Kasonde Bowa described the sterile single-use UniCirc™ circumcision device and method and the site visit by a subgroup of the TAG to Simunye Primary Health Care Centre in Mitchells Plain, Cape Town in March 2014. Published reports of the development and clinical performance of the UniCirc™ procedure were also presented. The development of this method involved several innovations, including the use of topical EMLA™ instead of injectable anaesthesia for a clamp compression device and the use of medical grade tissue adhesive and Hypafix™ surgical tape to sustain wound closure. The method is very innovative and promising for male circumcision programmes for adults and adolescents, particularly as it avoids the use of injectable anaesthesia and suturing, the foreskin is removed at the time of the procedure and the result is a neat wound. The device and method have not yet been standardized; some breaches in infection prevention protocols were noted and reporting was weak. The advice of the subgroup to the UniCirc™ team was to improve the consistency in definitions and recording.

The TAG concluded that:

- The technical and manufacturing problems with the devices seen in the development and early clinical studies of the method need to be resolved before using the device in other studies.
- Although the device is a surgical-assist method, the TAG recommended that it undergo a thorough evaluation by the WHO prequalification team since the method is new and several manufacturing problems have been noted in the early clinical studies and during the site visit. While the device and method have only been assessed in adults, it is likely to be safe and acceptable in adolescents requesting circumcision. In addition, given the current and future needs of adolescents for MC, the TAG recommended that clients presenting for circumcision, including adolescents, could be invited to volunteer for the research on the device, subject to the necessary institutional approvals and individual age-appropriate informed consent and assent.
- The TAG encouraged the developer to make the product available for evaluation by other research and implementation teams to generate clinical data on safety, efficacy and acceptability in a wider range of providers and programme settings, as per the WHO clinical evaluation framework. A comparative study would be the most appropriate design to evaluate outcomes, particularly systematic assessment of bleeding and infection and healing times. Evaluation of cost and human resource considerations were also encouraged.

SurgiPex procedure

Julia Samuelson shared and the TAG reviewed a report from Rwanda on an efficacy and safety study using a revised PrePex™ method called the SurgiPex procedure. This study was conducted among 36 men with phimosis or narrow foreskin openings. The method involved a small dorsal slit in the foreskin to allow

placement of a sterile PrePex™. This required the injection of a local anaesthetic directly into the foreskin and preparation of a sterile field. After placement of the PrePex™ device, the standard procedure was followed with removal of the necrotic foreskin and the device scheduled at 7 days.

The TAG members were concerned about the safety of the procedure, particularly as the open wound in the foreskin may be prone to infection, even though it was distal to the elastic compression ring. Members were also concerned that there is a high risk of invagination or other incorrect placement of the device in cases of adhesions, phimosis and/or narrow foreskin. Although the investigators were attempting to address the ineligibility problem, the method did not appear to offer many advantages over conventional surgery in cases where the PrePex™ device could not be placed according to the current procedure. The TAG noted that this approach is a low priority for further evaluation.

No-flip ShangRing™ approach

Renee Ridzon presented and the TAG reviewed preliminary reports of the no-flip approach to ShangRing™ circumcision. This method was pioneered in children, in whom the conventional procedure for placement of the ShangRing™ device is difficult and risks tearing the delicate foreskin tissue. The no-flip approach involves placing the inner ring under the foreskin and clamping the outer ring outside before cutting off the residual skin. A preliminary study with 200 procedures in Homa Bay, Kenya is underway, and the TAG looks forward to reviewing a full report in due course including all classifications of wound infections.

Use of topical instead of injectable local anaesthesia

In light of the experience in South Africa with topical anaesthesia with the UniCirc™ procedure, use of topical instead of injectable local anaesthesia is being assessed for use with the ShangRing™ device. The TAG noted that given the limited evidence, data on use of topical anaesthesia would be needed for each class of method, since they have different mechanisms of action and effects on the nerves. The TAG looks forward to receiving reports from such studies, as this approach offers several advantages including increased acceptability to clients and lower risk of anaesthesia-induced adverse events. The TAG suggested that the primary outcome of pain should be assessed at several time points, including immediately before and during the procedure, and two to three hours and two to three days after the procedure.

The TAG noted that modifications to the method without device design changes would not necessarily require bridging studies. The TAG will review evidence on the safety, effectiveness and acceptability of method modifications as it becomes available and advise whether further assessment is required for making recommendations.

ANNEX 1. MEETING AGENDA

Day 1: Tuesday, 30 September 2014		
Time	Topic	Presenter/Facilitator
8:00–8:30	Registration – Welcome coffee	
8:30–9:00	Opening <ul style="list-style-type: none"> Welcome and introductions Objectives and expected outcomes, review of agenda Roles of members and observers, declarations of interests 	R. Baggaley J. Samuelson
9:00–10:00	Session I: Updates <ul style="list-style-type: none"> WHO update: Guidance on use of devices for male circumcision and current landscape of devices and methods WHO prequalification: status of devices and post market vigilance Inventory of research and surveillance on MC devices (adults, adolescents and infants) Discussion	Co-chair: S. Watya J. Samuelson B. Ncube H. Ardura/A. Sands T. Farley
10:00–10:30	Coffee break	
10:30–12:30	Session II: All methods: adverse events update <ul style="list-style-type: none"> Adverse events in VMMC programmes and select SAE case reports (including tetanus, Fournier’s gangrene, glans injuries) Discussion	Co-chair: T. Hargreave T. Farley/J. Samuelson A. Yakubu M. Galukande
12:30–13:30	Lunch break	
13:30–15:30	Session III: PrePex™: safety among men age 18 years and older <ul style="list-style-type: none"> Detailed review of safety data: January 2013–July 2014 DIOR data Key technical questions and issues: <ul style="list-style-type: none"> » Displacements and self-removal: review of 3 scenarios of clinical management » Side-effect management: odour and pain at device removal » High-level disinfection vs sterilization of removal equipment – review of technical statement Discussion Recommendations (TAG members only)	Co-chair: T. Hargreave T. Farley J. Reed T. Hargreave C. Toledo J. Samuelson or B. Allegranzi
15:30–16:00	Coffee break	
16:00–17:00	Session IV: Adolescent studies: PrePex™ <ul style="list-style-type: none"> Measures of physical development in boys PrePex™ device bridging studies (Zimbabwe, South Africa) Discussion Recommendations (TAG Members only)	Co-chair: S. Watya T. Adamu Ashengo T. Farley

Day 2: Wednesday, 1 October 2014

Time	Topic	Presenter/Facilitator
8:00–9:00	Welcome coffee	
9:00–10:30	Session IV: Adolescent studies: ShangRing™ <ul style="list-style-type: none"> ShangRing™ bridging studies (Kenya, Uganda) Discussion	Co-chair: T. Hargreave T. Farley
10:30–11:00	Coffee break	
11:00–12:00	Session IV: Adolescent methods guidance <ul style="list-style-type: none"> Acceptability Safety of methods for adolescents and programme perspectives Discussion Recommendations (TAG members only)	Co-chair: T. Hargreave A. Armstrong J. Samuelson
12:30–13:30	Lunch break	
13:30–15:30	Session V: Infant devices <ul style="list-style-type: none"> AccuCirc™ infant device: clinical evidence Discussion	Co-chair: S. Watya T. Farley
15:30–16:00	Coffee break	
16:00–17:00	Session V: Infant studies (cont.) <ul style="list-style-type: none"> AccuCirc™ infant device: clinical evidence Discussion Recommendations (TAG Members only)	Co-chair: S. Watya T. Farley

Day 3: Thursday, 2 October 2014

Time	Topic	Presenter/Facilitator
8:00–9:00	Welcome coffee	
9:00–10:30	Session VI: Advice on innovations and research requirements <ul style="list-style-type: none"> Surgical assist methods: UniCirc™, glue and adherent dressing. Clinical evaluation, further evidence requirements. <ul style="list-style-type: none"> » Updates needed in the <i>Framework for clinical evaluation</i> » Prequalification decision pathway Method variations: SurgiPex, ShangRing™ no-flip Use of topical anaesthesia with different MC methods and in cases of phimosis Discussion	Co-chair: T. Hargreave K. Bowa T. Farley M. Maier J. Samuelson R. Ridzon
10:30–11:00	Coffee break	
11:00–13:00	Session VI: Advice on innovations and research requirements (cont.) <ul style="list-style-type: none"> Priority research needs 	Co-chair: S. Watya R. Baggaley
13:00–14:00	Lunch break	
14:00–15:30	Session VII: Operational and programmatic implications for WHO guidance <ul style="list-style-type: none"> Highlights of Day 1 & 2 to address in guidance on use of devices and programme considerations Discussion	Co-chair: T. Hargreave S. Dalal/A. Armstrong
15:30–16:00	Coffee break	
16:00–17:00	Next steps and Closing	J. Samuelson, R. Baggaley

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ANNEX 3. WHO INFORMATION NOTE ON FORCEPS-GUIDED METHOD

1 July 2014

WHO Information Note:

Voluntary medical male circumcision (VMMC) for HIV prevention – caution on use of forceps-guided method for young adolescents

This information note provides a strong caution about the use of the forceps-guided method for younger adolescents in the context of HIV prevention and a call for improved safety reporting among this age group.

A small proportion of clients circumcised in the HIV prevention programmes have been in the early adolescent⁹ age group (10–13 years).¹⁰ Adolescent males 10–14 years are being considered for strategic inclusion in the catch-up phase of VMMC programmes, as well as being one of the main age groups to receive VMMC in the sustainable services phase. It is essential that the appropriateness and safety of MC methods are respected for this age group given the less mature physical development of many boys in this age range compared with older adolescents. Safety monitoring and reporting by the MMC programmes must be improved, in particular among adolescents in the younger age range.

Three widely used conventional surgical methods of circumcision (sleeve resection, dorsal slit and forceps-guided methods) that produce a good long-term result are described in the WHO/Jhpiego Manual for male circumcision under local anaesthesia. These methods were selected on the basis of extensive experience worldwide, as well as use in the three randomized controlled trials of male circumcision and HIV prevention in Kenya, South Africa (18 years and older, forceps guided) and Uganda (15 years and older, sleeve resection). To improve quality and safety of MMC, many country programmes train providers on a single method, and the majority of countries have selected the forceps-guided method. This method has the advantage that it is a simple technique to learn and suitable for use in a clinic setting. A disadvantage is that the glans cannot be visualized during the cutting of the foreskin. When performed by well-trained providers the complication rates are low.¹¹

In most younger adolescents the penis and glans are small, as enlargement has not yet occurred.¹² In such cases, it may be difficult to clearly identify the tip of the glans by palpation (even for experienced providers) prior to placing the forceps across the foreskin, resulting in an increased risk of glans or urethral injury. Because of this risk, the forceps-guided method is not the preferred surgical method for younger adolescents; IF it is used, great care must be taken and training on this risk is essential.

For all methods, the male circumcision clinical team needs to ensure that clients are well informed and suitable for circumcision under local anaesthesia in their clinic. The circumcision team should take a focused medical history and perform a clinical examination of the penis including fully retracting the foreskin and inspecting the glans. If there is any doubt as to a younger client's suitability with the forceps-guided method, he should be referred to a site or provider competent in more appropriate surgical methods (e.g., dorsal slit or sleeve); or an alternative for younger adolescents is to wait until the age and physical condition suitable for circumcision with the forceps-guided method have been reached.

9 There is slight difference in ages included in terms relating to young adolescents. Early adolescence is generally referred to people age 10–13 years. However, data on adolescents are generally disaggregated into five year intervals, such as 10–14 years.

10 Although age-disaggregated data and safety monitoring remain limited from the fourteen priority countries, data from six countries for calendar year 2012 were applied to all 14 countries / regions and suggested that 36% of males circumcised were between 15–19 years and 15% between 10–14 years (Source: unpublished WHO estimates, GARPR MOH data 2012). Since 2009, in two regions of Tanzania, 82% of clients were aged 10–19 years, and in Zimbabwe 48% were aged 10–19 years and 22% were 10–14 years old (further age disaggregation not available) (Source: Ashengo TA, Hatzold K, Mahler H, Rock A, Kanagat N, Magalona S, et al. Voluntary medical male circumcision (VMMC) in Tanzania and Zimbabwe: service delivery intensity and modality and their influence on the age of clients. *PLoS ONE*. 2014; 9(5): e83642)

11 Auvert et al *PLoS Med* 2005, Bailey et al *Lancet* 2007; Krieger JN et al. *BJU Int*. 2005.

12 According to the Tanner stages for boys, which recognizes normal age variation at each stage, the length of the penis starts to increase, generally about age 13 years as part of Stage 3. During Stage 4 – usually around age 14–15 years – the breadth of the penis increases and the glans becomes more developed.

All MMC methods carry some risks, many of which can be mitigated and it is essential that countries have the capacity to detect, investigate and respond to safety concerns. National programmes are now reporting annually on the numbers of VMMCs performed. However, safety monitoring is quite limited and noted to be a weakness in recent assessments.¹³

In the WHO *Guide to Indicators for Male Circumcision Programmes in the Formal Health Care System* an indicator focusing on MMC service safety is recommended, with adverse events related to conventional surgical methods specifically mentioned. As new male circumcision methods using prequalified devices are introduced and post-market surveillance established, there is an opportunity to strengthen safety monitoring, reporting, serious adverse event reviews and response systems, for all male circumcision methods, including conventional surgical methods.

As progress is made on the catch-up phase, which is primarily focused on males 15 years and older, MMC services must be offered to each cohort of males who reach an appropriate age during adolescence and/or infants (0–60 days) to maintain a high prevalence of circumcision and preserve the HIV prevention benefit at the community level. As countries transition to sustainable circumcision services, service delivery approaches will need to be re-considered. The age at which services are provided for new cohorts of uncircumcised adolescents will be determined according to local context, service delivery options and must take into account evidence on safety. Although VMMC for young adolescents is currently not a priority, it is important that a safe method is available if circumcision is offered to this age group. In order to determine the relative risks and benefits of different circumcision methods among younger adolescents (10–14 years) and inform recommendations, WHO requests that method- and age-disaggregated information on safety is systematically collected and reported to WHO. A separate communication requesting such information will be provided soon.

13 Jennings L et al, Quality of VMMC Services during Scale-up: A comparative Process Evaluation in Kenya, South Africa, Tanzania, and Zimbabwe. PLoS One, May 2014; Rech et al. Implications of the Fast-evolving Scale-up of adult voluntary medical male circumcision for quality of services in South Africa. PLoS One, May 2014, Vol 9 (5), e80577).

ANNEX 4: MALE CIRCUMCISION DEVICES RESEARCH INVENTORY

PrePex™ device

Studies completed by January 2013

Study (type)	Location	Clients	Type of providers
Safety study	Rwanda	50 healthy HIV-negative men	Physicians and nurses
Randomized comparison with surgery	Rwanda	144 PrePex, 73 surgery	Physicians and nurses
Pilot study	Rwanda	49 healthy HIV-negative men ages 21–54 years	Nurses
Field study	Rwanda	666 generally healthy men (5 HIV-positive)	Lower cadre nurses
Safety study	Zimbabwe	53 HIV-negative men	Physicians and nurse assistants
Randomized comparison with surgery	Zimbabwe	240 HIV-negative men	Physicians and nurse assistants
Field study	Zimbabwe	641 HIV-negative men	Nurses with physician back-up support
Field study	Uganda (IHK)	634 healthy men	Surgeons, medical officers, clinical officers and nurses
Field study	Uganda (Rakai)	187 HIV-negative men	Not stated

New studies since January 2013

Study (type)	Location	Notes
Pilot implementation	Botswana, Kenya, Lesotho, Malawi, Mozambique, South Africa (3), Uganda (3), United Republic of Tanzania, Zambia, Zimbabwe	Typical size 300–800 placements
Active surveillance	Botswana, Rwanda, South Africa, Uganda (2), Zimbabwe	1000 placements (ongoing)
Passive surveillance	Rwanda (>17 000), Zimbabwe (~1400)	
Adolescent bridging studies	South Africa (50 adolescents, 13–18 years of age), Zimbabwe (262 adolescents, 13–17 years of age)	
HIV+ men bridging studies	Kenya, Zimbabwe	Not yet started

ShangRing™ device

Studies completed by January 2013

Study (type)	Location	Clients	Type of providers
Safety study	Kenya	40 healthy HIV-negative men	Physicians and nurses experienced in conventional surgical circumcision
Spontaneous detachment study	Kenya	50 healthy HIV-negative men	Physicians and nurses experienced in conventional surgical circumcision
Randomized comparison with surgery	Kenya, Zambia	200 ShangRing™, 200 surgery, healthy HIV-negative men	Physicians and non-physicians, all with extensive experience with surgical male circumcision
Field study	Kenya, Zambia	1256 healthy HIV-negative men	Physicians and non-physicians, all with extensive experience with surgical male circumcision
Acceptability and safety study	Rakai, Uganda	621 healthy HIV-negative men, 508 of whom chose ShangRing™	Clinical officers in sterile conditions in outpatient operating rooms

New studies since January 2013

Study (type)	Location	Notes
Randomized comparison with surgery	Mbarara, Uganda	Compared with forceps-guided
Adolescent bridging study	Rakai, Uganda	384 adolescents ages 13–17 years choosing ShangRing™, 80 choosing dorsal slit
Adolescent bridging study	Homa Bay, Kenya	80 boys and adolescents under age 18 years (only 20 ages 13–17 years)

AccuCirc™ Device

Study (type)	Location	Notes
Randomized comparison of Plastibell vs Mogen clamp	Botswana	147 Plastibell, 153 Mogen clamp
Cohort study AccuCirc™ device	Botswana	151 AccuCirc™
Randomized comparison AccuCirc™ vs Mogen clamp	Zimbabwe	100 AccuCirc™, 50 Mogen clamp
AccuCirc™ introductory field study	Zimbabwe	500 healthy term infants up to age 30 days

ANNEX 5. WHO INFORMATION NOTE ON PREMATURE DIFFERENTIAL SLOUGHING OF FORESKIN

18 February 2014

Brief Update from WHO Technical Advisory Group on Innovations in Male Circumcision (TAG) Co-chairs and Secretariat: New type of adverse event with use of PrePex device

Adverse event:	Premature differential sloughing of foreskin layers distal to PrePex device
Description of adverse event and potential aetiology:	<p>There was premature sloughing of different layers of the foreskin distal to the PrePex device involving:</p> <ul style="list-style-type: none"> • the epidermis, • epidermis and subcutaneous tissue, or • the inner mucosa of the foreskin with out-pouching from the epidermal meatus. <p>In the three reported cases, the early sloughing occurred on Days 2, 4 and 5 after placement, prior to the scheduled Day 7 removal visit.</p> <p>Aetiology unknown.</p> <p>Note: this 'premature sloughing' is not the same as the normal 'sloughing' of the residual band of necrotic tissue after device removal on Day 7.</p>
Clinical commentary:	<p>Common clinical observations among the three cases were:</p> <ul style="list-style-type: none"> • All had 'long foreskins' (subjective assessment) with associated trapping of urine under and ballooning of the foreskin • The unpleasant appearance of out-pouching of the inner mucosal layer was distressing to clients <p>Case 1. Day 2: Epidermis and subcutaneous foreskin sloughed off exposing shiny mucosal layer (appearing like a condom)</p> <p>Case 2. Day 4: Protrusion of inner mucosal layer with external foreskin intact</p> <p>Case 3. Day 5: Peeling of epidermis of foreskin exposing underlying subcutaneous layer</p> <p>No information available on use of products such as antiseptics for hygiene purposes, sexual activities or related trauma.</p> <p>In all three cases the foreskin distal to the PrePex device was excised surgically. In two cases the PrePex device was removed at the same time, while in the third case the PrePex was left in place for removal as scheduled on Day 7.</p> <p>In all three cases the final outcome was a successful fully healed circumcision</p>
Risks	Potential for infection; potential for bleeding with early device removal
Management advised (based on 3 cases; to be modified when further information available)	<p>Excision of foreskin distal to device and device removal. As needed, control bleeding by applying pressure; clinical judgment to determine need for sutures and/or debridement; refer as needed dependent on skill level.</p> <ul style="list-style-type: none"> • Timing: within 6–12 hours; this is not assessed to be an emergency. • Clinical judgment of an experienced circumcision surgeon needed primarily to better characterize event and to inform clinical intervention.
Events	3 events reported, Kenya, 2013

Actions to be taken by national programmes and partners implementing research and services with PrePex device:

- 1) Train providers regarding this type of (rare) event and the clinical management of such events.
Educate clients about the potential for this type of event (albeit uncommon to date) and the need to return to the clinic. In particular men with 'longer foreskins' should receive this advice as they may be more likely to experience this undesirable event.
- 2) Reinforce the importance of the need for surgical backup when such events are identified and that performance of surgery with this adverse event may require additional skills and expertise.
- 3) Monitor and report on such events. Obtain and document in as much detail as possible:
 - a) appearance (documented with photographs if possible)
 - b) course of events including
 - type of anaesthetic cream used
 - any intervention/use of products for hygiene or otherwise that were used by the client
 - surgical approach required and medications administered, especially antibiotics
 - healing time
 - other adverse events
 - c) other illness or health conditions, including HIV status
 - d) device: size, batch/lot number, expiry date

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E Oduyo-June, medical researcher Nyanza Reproductive Health Society; T Hargreave and S Watya, TAG Co-Chairs; J Samuelson WHO Secretariat, T Farley, device consultant Sigma3 Services

APPENDIX. SUMMARY OF EARLY PREPEX™ REMOVALS ON ACCOUNT OF EARLY SLOUGHING: KENYA

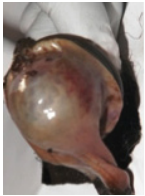
Credit: Images courtesy of a Bill & Melinda Gates Foundation grant to FHI 360 in partnership with UIC and NRHS

Case 1. Removal on Day 2

Day 0 just after device placement



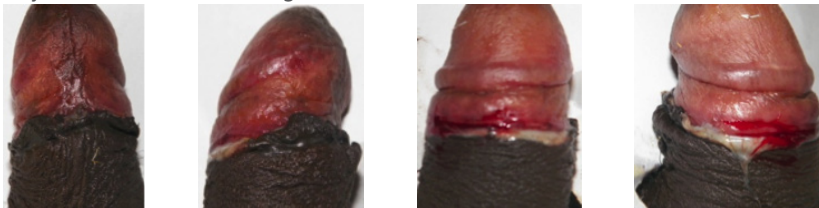
Day 2 before device and foreskin removal



Day 2 after foreskin removal



Day 2 after foreskin and ring removal



Day 42 after placement



Client had long foreskin and experienced premature sloughing on Day 2. Complete removal done on Day 2.

Case 2. Removal on Day 4

Day 0 just after placement



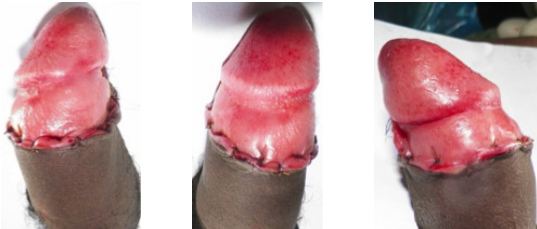
Day 4 before device and foreskin removal



Day 4 after foreskin removal



Day 4 after ring and foreskin removal



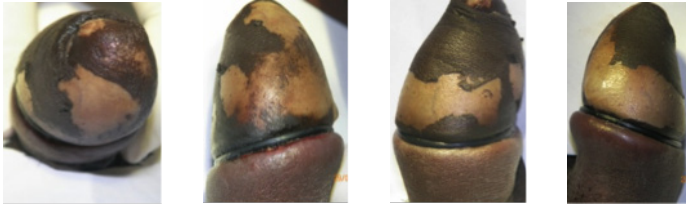
Client had long foreskin with separation of mucosa from partially necrotic foreskin. Clinician assumed that this was a case of allergy to local anaesthetic cream. Client did not return for Day 42 visit and declined photography at subsequent visit on Day 61 when there was complete healing.

Case 3. Foreskin excised on Day 5 and rings removed on Day 5

Day 0 photos showing long foreskin



Day 5 (before excision of foreskin)



Day 5 (after excision of foreskin)



Client had long foreskin. Foreskin sloughed off early exposing tissue with retained urine causing bad smell. Foreskin was excised on Day 5 but both outer and inner ring were left in situ to reduce risk of bleeding. Retrospectively clinicians believed this was not necessary and both rings could have been removed at the time of presentation on Day 5.

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