World Health Organization

WHO technical guidance and specifications of medical devices for screening and treatment of precancerous lesions in the prevention of cervical cancer

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ISBN 978-92-4-000263-0 (electronic version)
ISBN 978-92-4-000264-7 (print version)

Suggested citation. WHO technical guidance and specifications of medical devices for screening and treatment of precancerous lesions in the prevention of cervical cancer. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

Printed in Switzerland.

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Acknowledgements

The WHO technical guidance and specifications of medical devices for screening and treatment of precancerous lesions in the prevention of cervical cancer was developed under the WHO-led Secretariat to accelerate plans for the elimination of cervical cancer, under the coordination of Adriana Velazquez, lead of Medical Devices and in Vitro Diagnostics team of the Health Products Policy and Standards, of the Access to Medicines and Health Products Division in WHO.

These specifications are the result of a collaboration of experts from different backgrounds and organizations, including WHO, UNFPA, CHAI, and PATH, with funding support from The German Federal Ministry of Health (Bundesministerium für Gesundheit, BMG).

Catherine Behrens, Cai Long and Ying Ling Lin (WHO consultants), along with Marjorie Murray (PATH) for thermal ablation and Minna Soikkeli (UNFPA), for vaginal specula, drafted sections of this document. The general writing, integration and overall document compilation was notably achieved by Martha Gartley and Melissa Leavitt (CHAI).

WHO addresses its sincere gratitude to the following people for their knowledgeable contribution during the development of these technical specifications and for their review of this document:

Mohammed Ameel (NHRSC India), Partha Basu (IARC), Paul Blumenthal (Stanford University and Populations Services International), Miriam Cremer (Cleveland Clinic and Basic Health International), Eunice Lourenco (WHO consultant), Noni Gachuhi (Intellectual Ventures), Babacar Gueye (MOH & SW, Senegal), Karen Hariharan (CHAI), Jose Jeronimo (Peruvian League Against Cancer/ Liga contra el Cancer, Peru), Paolo Lago (Fondazione IRCCS Policlinico San Matteo – WHO Collaborating Centre), Ricky Lu (JHPIEGO), Mauricio Mazo (Basic Health International), Mona Mazgani (Cancer Clinic, BC, Canada), Miriam Mikhail (Rad-Aid International), Seloi Mogatle (UNFPA), Raul Murillo (Centro Javeriano de Oncología – Hospital Universitario San Ignacio), Nicolas Pallikarakis (INBIT Greece), Groesbeck Parham (University of North Carolina, Chapel Hill), Mercedes Perez Gonzalez (WHO), Colin Pfaff (Baylor College of Medicine, Malawi), Walter Prendiville (IARC), Anita Sands (WHO), Silvia de Sanjose (PATH), Linda Serwaa (UNFPA), Dario Trapani (WHO Consultant), Vivien Tsu (University of Washington), Dinsie Williams (WHO consultant), Safina Yuma (MOH, CD, G, E & C Tanzania), and Laura Alejandra Velez Ruiz Gaitan (WHO Consultant).

Technical editor: Anthony C. Price, Polyglotte Sàrl.

Illustrations and document layout: Studio FFFOG.

Abbreviations

3D	Three-dimensional or stereoscopic
AA	Acetic acid
AC	Alternating current
AI	Artificial intelligence
AGC	Atypical glandular cells
CADTH	Canadian Agency for Drugs and Technologies in Health
CE	Conformité Européenne, whereby a CE marking is evidence of conformity to applicable European Directives
CHAI	Clinton Health Access Initiative
CIN(2)	Cervical intraepithelial neoplasia (grade 2)
CME	Continuing medical education
CO_2	Carbon dioxide
CQM	Contact quality monitor

DNA	Deoxyribonucleic acid
E*	Early gene, as in E6
EMC	Electromagnetic compatibility
ENT	Ear, nose, throat
ESU	Electrosurgical unit
FDA	Food and Drug Administration (USA)
HAI	Healthcare associated infections
HLD	High level disinfectant
HPV	Human papillomavirus
HSIL	High-grade squamous intraepithelial lesion
IARC	International Agency for Research on Cancer
ICC	International Chamber of Commerce
IED	Implanted electronic device
INBIT	Institute of Biomedical Technology (Greece)
ISO	International Standards Organization
IVD	In vitro diagnostic
Jhpiego	John Hopkins programme for international education in Gynaecology and Obstetrics
kPa	Kilopascal
L*	Late gene, as in L1
LBC	Liquid-based cytology
LEEP	Loop Electrosurgical Excision Procedure (also called LLETZ)
LIS	Laboratory information systems
LLETZ	Large loop excision of the transformation zone (also called LEEP)
LoD	Limit of detection
LRS	Low resource settings
MDR	Medical Device Regulation (EU No. 2017/745 replacing Medical Device Directive 93/42/EEC)
MoH	Ministry of Health
N_2O	Nitrous oxide
NAT	Nucleic acid test
NHSRC	National Health Systems Resource Center, Government of India
NRA	National Regulatory Authority / Agency
OEM	Original equipment manufacturer
PAHO	Pan American Health Organization
PCR	Polymerase chain reaction
PICO	Population, intervention, comparison, outcome
POCT	Point of care test
PPM	Planned preventative maintenance
psi	Pounds per square inch
QALY	Quality adjusted life year
RF	Radiofrequency
RNA	Ribonucleic acid
SaMD	Software as a medical device
SCJ	Squamocolumnar junction
SW	Social Welfare
TMA	Transcription-Mediated Amplification
TZ	Transformation zone
UNFPA	United Nations Population Fund
UPS	Uninterruptible power supply
VIA	Visual inspection with acetic acid
WHO	World Health Organization

Executive Summary

Globally, 311,000 women die of cervical cancer every year, 85 percent of them in resource limited regions of the world.[1] To address this grave threat to women, the WHO made a call to action in 2018, resulting in accelerated plans to improve cervical cancer control under the elimination threshold with respect to cervical cancer incidence.

Early screening of women at risk for cervical cancer gives clinicians an opportunity to treat precancerous lesions when they are found. The major cause of precancerous lesions is high-risk HPV genotypes, and persistent high-risk HPV infections pose as a significant risk factor in progression to cervical cancer. HPV is currently the most common sexually transmitted infection[2] and it is estimated that 80% of women will be infected with HPV at some point in their lifetime.[3]

As part of WHO's approach to cervical cancer control, availability of high quality, affordable medical devices for HPV screening, and treatment of precancerous lesions in low resource settings is indispensable. In previous WHO guidance books of Priority medical devices for cancer[4] and Guidelines for screening and treatment of precancerous lesions of cervical cancer,[5] these medical technologies were listed. In order to increase access to these devices, WHO is presenting here the technical specifications and associated guidance to facilitate the procurement, and therefore availability of high quality medical devices for screening, diagnosis and treatment for precancerous lesions. This document is to serve as a guide for the selection and procurement of the aforementioned product groups, describing the technical specifications as well as providing associated technical guidance required for proper use.

Early screening of women at high risk for cervical cancer gives clinicians an opportunity to treat precancerous lesions when they are found.

The WHO's team of medical devices of the Health Product Policy and Standards department of the Access to Medicines and Health Products Division, worked in collaboration with medical device and cervical cancer experts from CHAI, PATH, and UNFPA to develop technical specifications for the screening and treatment of precancerous lesions, which are described in each of the following sections and chapters:

The end goal is to save women's lives worldwide through the elimination of cervical cancer.

Section 1 Screening and diagnostic devices

- Chapter 1: Technical guidance and specifications for vaginal specula
- Chapter 2: Technical guidance and specifications for HPV NAT IVDs
- Chapter 3: Technical guidance and specifications for acetic acid for VIA
- Chapter 4: Technical guidance and specifications for colposcopes

Section 2. Treatment devices

- Chapter 5: Technical guidance and specifications for thermal ablation units
- Chapter 6: Technical guidance and specifications for cryotherapy units
- Chapter 7: Technical guidance and specifications for ESUs for LLETZ (or LEEP)

The purpose of the WHO technical specifications for the screening and treatment of precancerous lesions is to provide the requirements to meet the increasing demand to procure high quality and appropriate screening and treatment products. The specifications are intended to support policy-makers, managers, procurement officers, manufacturers, regulators and nongovernmental agencies, especially in low- and middle-income countries to select, procure, use, reprocess and decommission appropriate products and equipment. The end goal is to save women's lives worldwide through the elimination of cervical cancer.

This document has been developed according to existing international standards, published WHO clinical and technical guidance, and evidence-based publications from other reputable sources, corroborated by field expert experience. All content developers and expert reviewers of this document have declared their interests. It is foreseen that this document will be updated every 5 years due to the development of new technologies.

References for executive summary

[1] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F (2015). Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J. Cancer, 136(5), E359–386. doi:10.1002/ijc.29210.

[2] World Health Organization. (2019). Fact sheet: Human papillomavirus (HPV) and cervical cancer. https://www.who.int/news-room/fact-sheets/detail/human-papillomavirus-(hpv)-and-cervical-cancer

[3] American Sexual Health Association, 2019. HPV fast facts. http://www.ashasexualhealth.org/stdsstis/hpv/fast-facts

[4] https://www.who.int/medical_devices/publications/priority_med_dev_cancer_management/en

[5] https://www.who.int/reproductivehealth/publications/cancers/screening_and_treatment_of_precancerous_lesions/en

Introduction

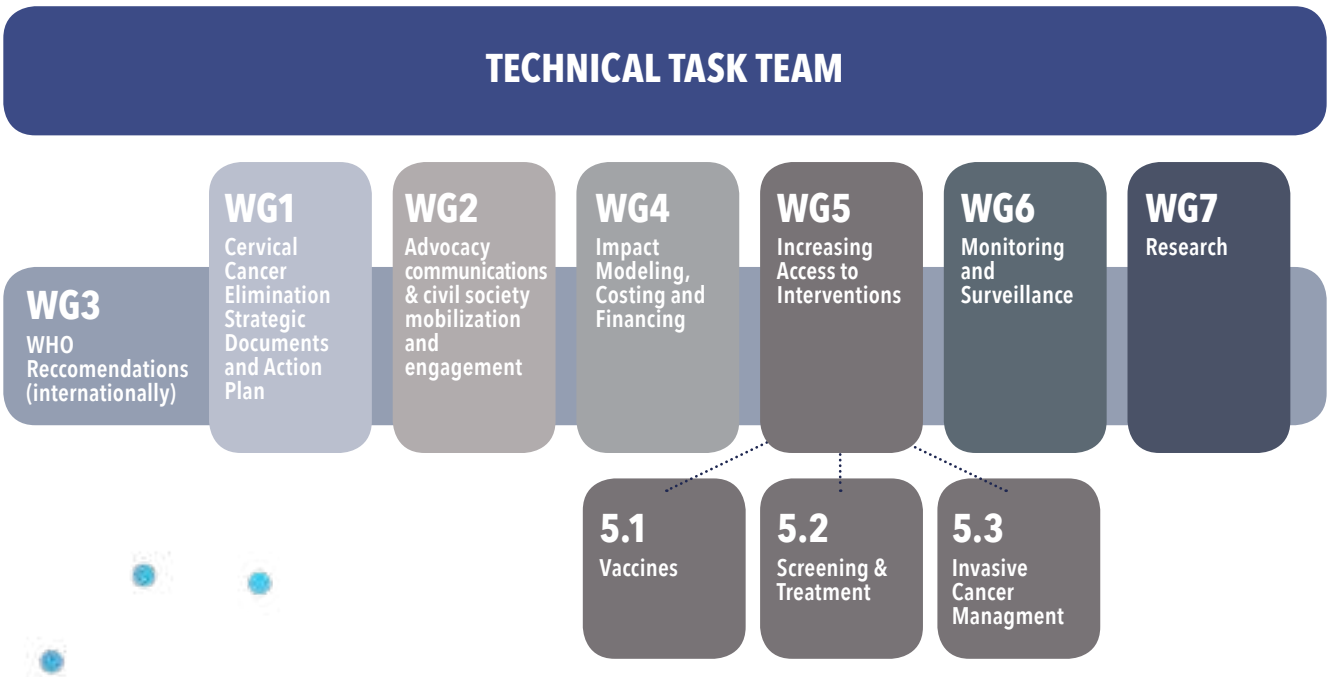
The call to action made by Dr Tedros Adhanom Ghebreyesus, Director General WHO, in May 2018 has resulted in accelerating plans to meet the challenge of improving cancer control under the elimination threshold in terms of cervical cancer incidence. Achieving elimination of cervical cancer requires collective effort of countries and partner organizations to ensure that effective interventions reach all girls and women. For this elimination initiative to be effective, it must be conducted in a manner in which all core challenges are specifically and comprehensively approached.

Cervical cancer remains one of the gravest threats to women's lives worldwide; globally, one woman dies of cervical cancer every two minutes

WHO's comprehensive approach to cervical cancer control includes HPV vaccination, screening and treatment, and cancer management. In response to this major public health concern, several Working Groups have been formed under the WHO-led Secretariat in 2018 to accelerate work on the various elements of this initiative.

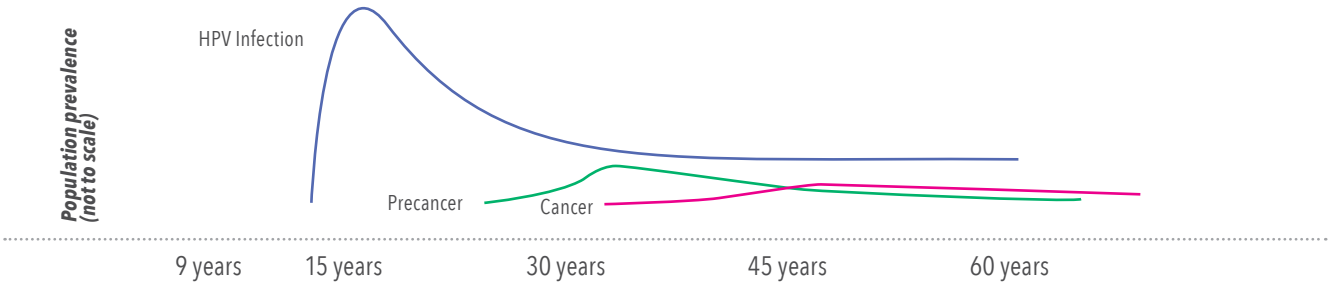
Working group 5.2 refers to all processes related to Screen and Treatment, and it is under this iniciative that this publication is developed, to ensure technologies are available to screen and treat patients that have pre-cancerous lesions, as can be seen in figure 1.

Figure 1: Working groups in WHO towards cervical Cancer elimination.



Cervical cancer remains one of the gravest threats to women's lives worldwide; globally, one woman dies of cervical cancer every two minutes[1]. However, it can be one of the most preventable and treatable forms of cancer: prevention by HPV vaccination, along with broad practice of screening and subsequent treatment of cervical precancer lesions, and if necessary, timely and effective management of invasive cervical cancer as can be seen in the figure 2 on life course approach to Cervical Cancer.

Figure 2: Life course approach to Cervical Cancer to Cervical Cancer Prevention and Control.



Primary Prevention

Girls 9-14 years

- HPV vaccination

Girls and boys, as appropriate

- Health information and warning about tobacco use
- Sexuality education tailored to age & culture
- Condom promotion/provision for those engaged in sexual activity
- Male circumcision

Secondary Prevention

Women > 30 years of age

Screen and treat - single visit approach

- Point-of-care rapid HPV testing for high risk HPV types
- Followed by immediate treatment
- Onsite treatment

Tertiary Prevention

All women as needed

Treatment of invasive cancer at any age and palliative care:

- Ablative surgery
- Radiotheraphy
- Chemotherapy
- Palliative Care

One of the key activities required is the development of technical specifications to facilitate the procurement and availability of HPV tests as well as other technologies for screening and treatment of precancerous lesions, as well as technologies and medicines to diagnose and manage invasive cervical cancer. Development of this content has been identified as necessary for subsequent stakeholder efforts to increase access to these technologies, which are necessary elements of the overall acceleration plan to eliminate cervical cancer as a public health problem.

Background on cervical cancer and treatment of precancerous lesions

Persistent infection of the cervix with "high risk" genotypes of human papillomavirus (HPV) is the major cause of precancerous lesions, which can lead to invasive cervical cancer if they are not treated. According to GLOBOCAN 2018, 311,000 women die of cervical cancer annually, 85 percent of them in low and middle income regions of the world.[2] Progression to cancer usually takes many years, which gives clinicians an opportunity for early detection and time to treat lesions when they are found during screening. Incidence of cervical cancer can be seen in figure 3, developed by IARC.

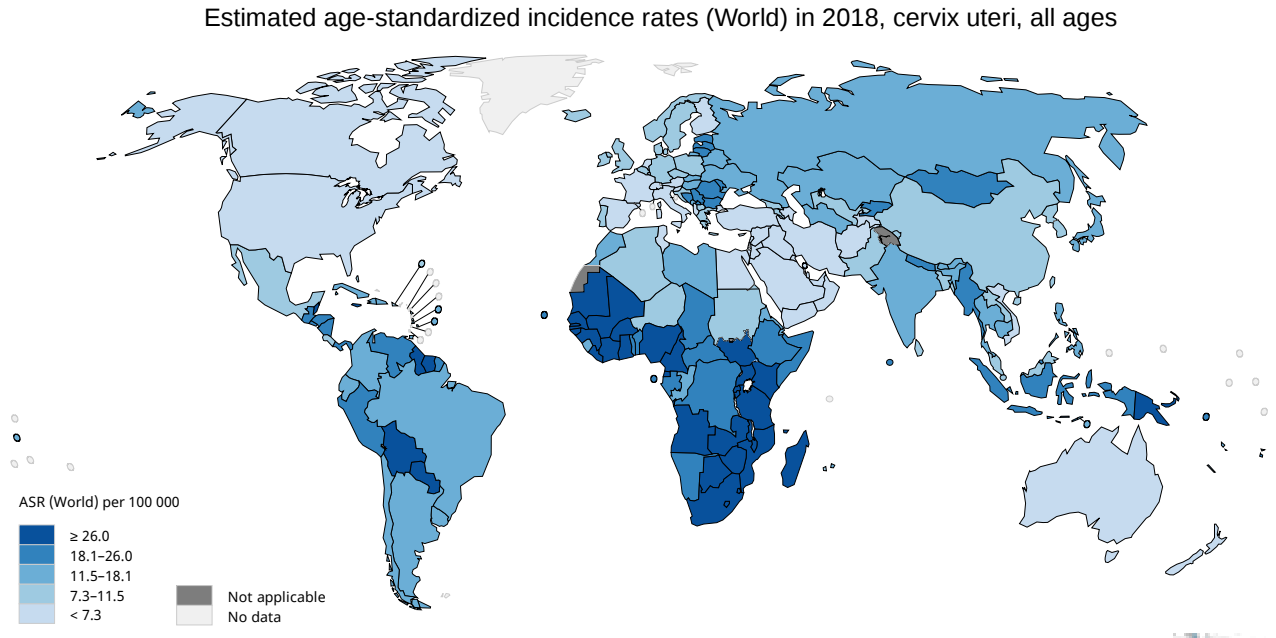
The goal of cervical cancer screening is to accurately detect high-grade precursor lesions of the cervix to allow timely treatment of cervical intraepithelial neoplasia (CIN)

HPV as the causative agent of cervical cancer

HPV is currently the most common sexually transmitted infection[3] and it is estimated that 80% of women will be infected with HPV at some point in their lifetime.[4] Most HPV infections are transient and will clear spontaneously without any long-term consequences. However, the persistence of high-risk HPV infection is a significant risk factor in progression to cervical cancer.

HPV is a double-stranded DNA virus with over 100 documented genotypes, approximately 40 of which are known to infect the oropharyngeal and anogenital tract. The genotypes are further classified as "low risk" for those that do not cause

Figure 3: Incidence of cervical cancer in 2018.



Data source: GLOBOCAN 2018
Graph production: IARC (http://gco.iarc.fr/today)
World Health Organization

cervical cancer and "high risk" for those that can cause progression to cancer. There are at least 12 high risk or oncogenic types: HPV 16, 18, 31, 35, 39, 45, 51, 52, 54, 56, 58, 59, and limited evidence for HPV 66 and 68 to cause cancer.[5]

HPV contains eight genes within the double-stranded DNA that are characterized as either early (E) or late (L) genes. Early genes are produced early in the virus life cycle and are associated with DNA replication, regulatory functions and activation of the host cell cycle; late genes are involved with the production of viral capsid parts. Particular attention has focused on the so-called E6 and E7 genes since their expression is thought to be a signal of dysplastic cell transformation;[6] the L1 region of the HPV gene is also of interest because it tends to exhibit the most variability from genotype to genotype.[7]

The goal of cervical cancer screening is to accurately detect high-grade precursor lesions of the cervix to allow timely treatment of cervical intraepithelial neoplasia (CIN). Persistent high-risk HPV infection is the causative agent of virtually all cervical cancers and its precursors,[8] in vitro diagnostics (IVD) that can accurately detect high-risk HPV can be used both to identify women with existing precursor lesions and also to predict those who may be at risk for developing cervical precancer at a later date. IVDs that can detect HPV will therefore play an important role in cervical cancer prevention programmes.

Access to screening and treatment of precancerous cervical lesions and management of cervical cancer remains a challenge for many women in low and middle-income countries, further highlighting inequities in women's healthcare.

Purpose of the document

This document provides an overview of seven product categories classified as recommended for the screening, diagnosis, and treatment of precancerous lesions, and their technical specifications to aid in the selection, procurement, and quality assurance of these products for the prevention of invasive cervical cancer. These product categories were selected as the primary products to facilitate the screen-and-treat paradigm, and that are suitable for the use scenarios and climates in low resource settings (LRS). Recognizing the need to increase the quality, accessibility and availability of "screen and treat" commodities and devices in LRS, this document highlights the minimum performance, operational, and quality requirements for: HPV NAT IVDs; acetic acid for VIA; colposcopes; thermal ablation; cryotherapy ESUs for LLETZ, as well as vaginal specula.

Scope of the document

This document provides technical guidance based on available evidence and advice for procurement officers, managers and biomedical engineers, to help them make evidence-informed decisions when choosing products that meet performance and design standards. The specifications herein are a reference only for products available in the market, and do not preclude appropriate upcoming

"Screen-and-treat" Approaches

A 'screen-and-treat' approach has been recommended for non-invasive cervical cancer prevention in LRS. In this approach, treatment is provided after a positive screening test.[12] A "single visit approach" is a screen and treatment approach when treatment is provided on the same visit.

To ensure safety and efficacy, the assessment of eligibility for immediate treatment with cryotherapy, thermal ablation, or LLETZ after a positive screening test is crucial. Many factors need to be considered such as: grade and size of lesion, pregnancy, concurrent infection, and recurrent lesions;[13] referrals are made as needed to ensure appropriate management of women who are not eligible for immediate treatment with cryotherapy, thermal ablation, or LLETZ. For more information, please see *Guidelines for screening and treatment of precancerous lesions for cervical cancer prevention*, which can be found at:

https://www.who.int/reproductivehealth/publications/cancers/screening_and_treatment_of_precancerous_lesions/en

products and/or technologies, which will be analysed in future revisions of this publication.

This document also includes guidance for manufacturers so that they may better understand the needs in LRS and may be beneficial for local manufacturers to make local supply products.

Whom this document is intended for

This document is intended primarily for policy-makers, managers, procurement officers, or professional health workers who have responsibility for procuring, supplying, or using devices for screening and treating cervical precancer, particularly in LRS. Manufacturers can benefit from the specifications in this document to produce quality products. Nongovernmental agencies will find useful information to support the access to quality products that comply with the present specifications, whether by in-kind donation or procurement.

How to read this document

This document is divided into three main sections: screening and diagnostic devices, treatment technologies, and procurement guidance and further research, followed by the annexes.

Chapters within sections 1 and 2 each contain comprehensive, need-to-know information on an aspect of cervical cancer screening and diagnostic tools and treatment technology respectively, preceded by a summary of specifications. WHO-standard template technical specifications tables are presented in the annexes. Detailed clarifications are provided for certain technical characteristics when needed. The technical guidance and specification chapters are as follows:

Section 1 – Screening and diagnostic devices

- Chapter 1: Technical guidance and specifications for vaginal specula
- Chapter 2: Technical guidance and specifications for HPV NAT IVDs
- Chapter 3: Technical guidance and specifications for acetic acid for VIA
- Chapter 4: Technical guidance and specifications for colposcopes.

Section 2 – Treatment technologies

- Chapter 5: Technical guidance and specifications for thermal ablation units
- Chapter 6: Technical guidance and specifications for cryotherapy units
- Chapter 7: Technical guidance and specifications for ESUs for LLETZ (or LEEP).

Section 3 – Procurement guidance and further research

- Chapter 8: Procurement guidance for medical devices
- Chapter 9: For further research.

Section 4. Annexes technical specifications

Where possible, existing relevant WHO publications have been referenced to avoid duplication of content and materials and to aid in version control.

How this document was developed

Content was generated by a team of authors selected for expertise in their respective field. Where applicable, content was pulled from internationally recognized standards or sources of guidance published by WHO and/or other groups or individuals who have given non-conflicting declarations of interest and thus deemed non-biased groups. For content not covered by aforementioned sources, recommendations herein are based on evidence-based peer reviewed publications, a series of meetings (see Annexes 8 and 9), and reviews with experts and several non-governmental organizations and scientific institutions.

The following WHO publications are complementary to the main body of this technical guidance and specification document:

World Health Organization (2013). WHO guidelines: Guidelines for screening and treatment of precancerous lesions for cervical cancer prevention.[10] https://www.who.int/reproductivehealth/publications/cancers/screening_and_treatment_of_precancerous_lesions/en/

World Health Organization (2014). Comprehensive Cervical Cancer Control.[11] https://www.who.int/reproductivehealth/publications/cancers/cervical-cancer-guide/en/

World Health Organization (2017). WHO list of priority medical devices for cancer management.[12] https://www.who.int/medical_devices/publications/priority_med_dev_cancer_management/en/

World Health Organization (2015). Interagency List of Medical Devices for Essential Interventions for Reproductive, Maternal, Newborn and Child Health.[13] https://www.who.int/medical_devices/publications/interagency_med_dev_list/en/

This document is divided into four main sections: screening and diagnostic tools, treatment technologies, and procurement guidance and further research, followed by the annexes.

Figure 4: WHO publications complementary to this document

World Health Organization (2017). Guidance for procurement of in vitro diagnostics and related laboratory items and equipment.[14] https://www.who.int/reproductivehealth/publications/cancers/cervical-cancer-guide/en/.

These complementary publications are presented in figure 4.

The present book replaces the WHO technical specifications for Cryosurgical equipment for the treatment of precancerous cervical lesions and prevention of cervical cancer.[15]

References from Introduction

[1] Based on 311,365 deaths globally from cervical cancer in 2018, according to GLOBOCAN: http://gco.iarc.fr/today/online-analysis-table?v=2018&mode=cancer&mode_population=continents&population=900&populations=900&key=asr&sex=0&cancer=39&type=1&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=5&group_cancer=1&include_nmsc=1&include_nmsc_other=1.

[2] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F (2015). Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J. Cancer, 136(5), E359–386. doi:10.1002/ijc.29210.

[3] World Health Organization. (2019). Fact sheet: Human papillomavirus (HPV) and cervical cancer. https://www.who.int/news-room/fact-sheets/detail/human-papillomavirus-(hpv)-and-cervical-cancer.

[4] American Sexual Health Association, 2019. HPV fast facts. http://www.ashasexualhealth.org/stdsstis/hpv/fast-facts/.

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[9] World Health Organization (2013). WHO guidelines: Guidelines for screening and treatment of precancerous lesions for cervical cancer prevention. https://www.who.int/reproductivehealth/publications/cancers/screening_and_treatment_of_precancerous_lesions/en/.

[10] Gaffikin, Lynne, et al. "Safety, acceptability, and feasibility of a single-visit approach to cervical-cancer prevention in rural Thailand: a demonstration project." Lancet (London, England) 361.9360 (2003): 814-820.

[11] World Health Organization (2014). Comprehensive Cervical Cancer Control. https://www.who.int/reproductivehealth/publications/cancers/cervical-cancer-guide/en/.

[12] World Health Organization (2017). WHO list of priority medical devices for cancer management. https://www.who.int/medical_devices/publications/priority_med_dev_cancer_management/en/.

[13] World Health Organization (2015). Interagency List of Medical Devices for Essential Interventions for Reproductive, Maternal, Newborn and Child Health https://www.who.int/medical_devices/publications/interagency_med_dev_list/en/.

[14] World Health Organization (2017). Guidance for procurement of in vitro diagnostics and related laboratory items and equipment. https://www.who.int/reproductivehealth/publications/cancers/cervical-cancer-guide/en/.

[15] World Health Organization (2012) WHO technical specifications: cryosurgical equipment for the treatment of precancerous cervical lesions and prevention of cervical cancer. https://apps.who.int/iris/bitstream/handle/10665/75853/9789241504560_eng.pdf?sequence=1.

Section 1 – Screening and Diagnostic Tools

Chapter 1: Technical guidance and specifications for vaginal specula

1.1. Background on the speculum

A vaginal speculum, or simply 'speculum' is a medical device used to open the vaginal canal, enabling a healthcare provider to visually inspect and collect samples from the vagina and cervix, or to perform gynaecological or surgical procedures in a woman's lower genital tract. There are different types of specula in the following categories: cylindrical, single-blade (retractors), two blades (bivalve), three blades, and four blades. This document will only cover self-retaining bivalve specula.

Bivalve specula are available in a variety of sizes and forms in order to be more accommodating to different anatomies of women. Depending on type, specula may be reusable or single-use. Reusable specula are made from metal alloys (typically non-quenched, non-magnetic, austenitic stainless steel) and shall be autoclavable. Single-use specula are made of high-strength plastic (for example acrylics) and are supplied as sterile. They sometimes have an integrated light source. Specula intended specifically for cauterization procedures may have a non-conductive medical grade polymer coating and an integrated smoke tube; however, this does not preclude the use of another type, if it can serve the intended purpose.

Brief description

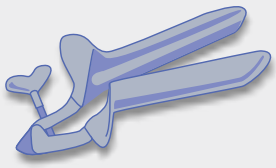
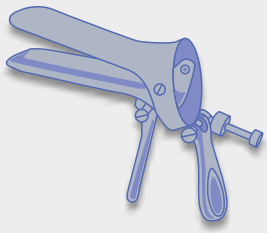
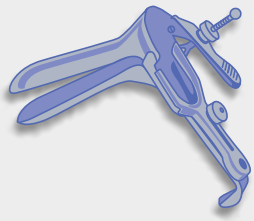
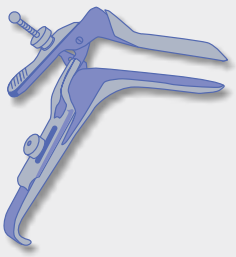
A vaginal speculum is a device intended to hold open the vaginal canal to enable a healthcare provider to visually inspect the cervix and collect vaginal or cervical specimens and/or perform surgical operations in a woman's lower genital tract. They are available in a variety of sizes and models to accommodate all patients, and a variety of materials to allow for single-use, reuse or specific use such as electrosurgery.

1.2. Scope of chapter

This chapter defines technical specifications for self-retaining vaginal specula used in the screening and/or treatment of precancerous cervical lesions in line with WHO's Comprehensive Cervical Cancer Control: a guide to essential practice.[2]

Content herein focuses on present state of practice using up-to-date available technologies; however, authors are aware that innovations in manufacturing, healthcare facilities and practice will advance the field of cervical cancer screening, diagnostics and treatment. The specifications herein do not preclude appropriate upcoming products and/or technologies, which will be analysed in future revisions of this publication.

Table 1: Examples of bivalve, self-retaining vaginal specula

Collins	Cusco	Graves	Pederson
			
• Commonly used for inspection, smear sampling and colposcopy. • Can be used for minor gynaecological procedures	• Commonly used for inspection, smear sampling and colposcopy. • Can be used for minor gynaecological procedures	• Used for pelvic and cervix examination, smear sampling and gynaecological procedures. • Available in normal or wide-mouthed formats.	• Used for pelvic and cervix examination, smear sampling and gynaecological procedures for narrow vaginas and/or adolescents
Advantages			
• Available as reusable or single-use • Available in different sizes • Protects vaginal walls during procedures	• Available as normal or wide-mouthed • Provides greater aperture at the introitus than Cusco and Collins	• Can provide greater aperture than the Cusco and Collins • Most narrow blades compared to Cusco, Graves and Collins	
Limitations			
• Blades of bivalved specula may hide some of the vaginal wall findings			
• Takes significant amount of space in vagina and thus it is not suitable for all types of procedures.	• Large blades may cause discomfort for women with narrow vaginas, and for adolescents and young women.		

1.3. Types of specula for "screen and treat"

1.3.1. Collins

Collins specula are bivalve and self-retaining.

Collins specula are bivalve and self-retaining. It retracts the vaginal walls laterally, or horizontally. Similar to the Graves, both blades are used to retract the vaginal walls and are used to examine the vagina and cervix.

The blades of a Collins speculum are kept in place by screws; thus, an assistant is not required and the healthcare provider can work hands-free. The blades also serve to protect the vaginal walls while performing any procedure; however, it has a limitation in that it restricts space in the vaginal cavity, and blades might mask lesions on the vaginal walls.

Collins speculum minimum technical requirements:

- Lateral edges must be blunt;
- Material: must be biocompatible following ISO 10993-1, -5 and 10. If stainless steel, it must also follow ISO 7153-1; typical materials include austenitic stainless steel (non-quenched, non-magnetic steel), or biocompatible medical grade plastic (e.g. acrylic, non-PVC, non-latex).
- Single use specula are supplied as sterile;
- Recommended sizes (all should be available):
  - » **Large** – blade length: 110mm (+/- 5%), blade width: 40mm (+/- 5%)
  - » **Medium** – blade length: 100mm (+/- 5%), blade width: 35mm (+/- 5%)
  - » **Small** – blade length: 85mm (+/- 5%), blade width: 30mm (+/- 5%).

1.3.2. Cusco

Cusco specula are bivalve, self-retaining vaginal specula.

Cusco specula are bivalve, self-retaining vaginal specula. They are used for examining the vagina and cervix, and are generally used for colposcopy and other minor procedures.

The upper blade retracts with screws that also allow for the blades to be kept in place; thus, an assistant is not required and the healthcare provider can work hands-free. The blades also serve to protect the vaginal walls while performing any procedure; however, it has a limitation in that it restricts space in the vaginal cavity, and blades might mask lesions on the vaginal walls.

Cusco speculum minimum technical requirements:

- Lateral edges must be blunt;
- Material: must be biocompatible following ISO 10993-1, -5 and 10. If stainless steel, it must also follow ISO 7153-1; typical materials include austenitic stainless steel (non-quenched, non-magnetic steel), or biocompatible medical grade plastic (e.g. acrylic, non-PVC, non-latex).
- Single use specula are supplied as sterile;
- Recommended sizes (all should be available):
  - **Large** – blade length: 11.5cm (+/- 5%), blade width: 3.5cm (+/- 5%)
  - **Medium** – blade length: 9.5cm (+/- 5%), blade width: 3.5cm (+/- 5%)
  - **Small** – blade length: 7.5cm (+/- 5%), blade width: 2cm (+/- 5%).

1.3.3. Graves

Graves specula are bivalve and self-retaining, they are also known as the "duckbill speculum". By retracting both the anterior and posterior vaginal walls, they are used to examine the vagina and cervix.

Graves specula are bivalve and self-retaining, also known as the "duckbill speculum".

Because of the upper blade, no anterior vaginal wall retractor is needed, and screws keep the blades in place; thus, an assistant is not required and the healthcare provider can work hands-free. The blades also serve to protect the vaginal walls while performing any procedure; however, it has a limitation in that it restricts space in the vaginal cavity, and blades might mask lesions on the vaginal walls.

The Graves speculum has the widest blades of any speculum and can accommodate women with especially long vaginas. The blades can also come angled.

Graves speculum minimum technical requirements:

- Lateral edges must be blunt;
- Material: must be biocompatible following ISO 10993-1, -5 and 10. If stainless steel, it must also follow ISO 7153-1; typical materials include austenitic stainless steel (non-quenched, non-magnetic steel), or biocompatible medical grade plastic (e.g. acrylic, non-PVC, non-latex).
- Single use specula are supplied as sterile;

- Recommended sizes (all should be available):

  - **Large** – blade length: 115mm (+/- 5%), blade width: 35mm (+/- 5%)
  - **Medium** – blade length: 95mm (+/- 5%), blade width: 35mm (+/- 5%)
  - **Small** – blade length: 75mm (+/- 5%), blade width: 20mm (+/- 5%).

1.3.4. Pederson

Pederson specula are bivalve and self-retaining and are the narrower version of Graves specula. Therefore, they are typically used for smaller women and adolescents. They function by retracting both the anterior and posterior vaginal walls and are used to examine the vagina and cervix.

Pederson specula are bivalve and self-retaining and are the narrower version of Graves specula.

Because of the upper blade, no anterior vaginal wall retractor is needed, and screws keep the blades in place; thus, an assistant is not required and the healthcare provider can work hands-free. The blades also serve to protect the vaginal walls while performing any procedure; however, it has a limitation in that it restricts space in the vaginal cavity, and blades might mask lesions on the vaginal walls.

Pederson speculum minimum technical requirements:

- Lateral edges must be blunt;

- Material: must be biocompatible following ISO 10993-1, -5 and 10. If stainless steel, it must also follow ISO 7153-1; typical materials include austenitic stainless steel (non-quenched, non-magnetic steel), or biocompatible medical grade plastic (e.g. acrylic, non-PVC, non-latex).

- Single use specula are supplied as sterile;

- Recommended sizes (all should be available):

  - **Large** – blade length: 115mm (+/- 5%), blade width: 25mm (+/- 5%)
  - **Medium** – blade length: 95mm (+/- 5%), blade width: 22mm (+/- 5%)
  - **Small** – blade length: 75mm (+/- 5%), blade width: 13mm (+/- 5%).

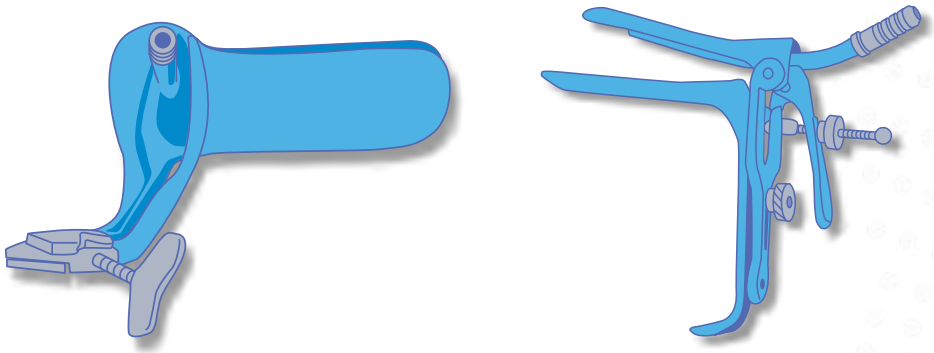
1.4. Operational considerations

1.4.1. Additional features

Two options that can facilitate a smooth workflow specifically for LLETZ procedures, but are not considered necessary, are in-built smoke extraction channels and/or insulation for the speculum. Figure 2 illustrates one each of Collins and Graves with both of these features.

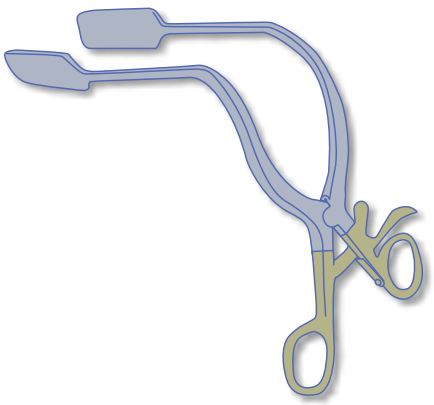
To note, insulated specula are more prone to wear and tear as a result of coating materials being subjected to requisite decontamination after each use. Hospital staff will have to examine coated specula very carefully for cuts, voids, cracks, tears, abrasions, etc. that can appear with frequent use.

Figure 5: Insulated speculum with in-built smoke extraction channel (L: Collins, R: Graves)



In addition, lateral vaginal specula (see Figure 3) are considered to be useful accessories, but are more costly relative to standard specula, and are considered to be beyond the scope of this guidance document.

Figure 6: Lateral vaginal speculum or retractor



1.4.2. How to use a speculum

As there are a wide variety of types, makes, and models of specula, it is important that the healthcare providers familiarize themselves with the particular device at hand, and that the selected speculum type suits both the examination and/or procedure type(s), and is appropriately sized for the patient.

Appropriate clinical training should be provided prior to using a speculum.

Appropriate clinical training should be provided prior to using a speculum. It is necessary to establish and/or maintain an on-going, competency-based capacity-building program to sustain clinical practice with all in-service programs, tools and resources, based on the standard clinical guidelines and in-country CMS pedagogy. Please refer to guidance provided in WHO's Comprehensive Cervical Cancer Control: a guide to essential practice.[1]

1.4.3. Decontamination and reprocessing

Health care-associated infections (HAI) are one of the most common adverse events in health care delivery. Not only do they have a significant impact on morbidity and mortality, but they also present an economic burden to health care facilities and countries. As part of a larger infection prevention and control (IPC) program[2], decontamination of instruments and medical devices play a critical role in HAI prevention.

The PAHO/WHO manual titled *Decontamination and reprocessing of medical devices for health-care facilities*[3] outlines the decontamination life cycle, which includes cleaning, disinfection and sterilization. Please refer to this manual for details on specific methods of decontamination, sterilization and reprocessing of medical devices. Always follow the device manufacturer's instructions for decontamination so as to not cause any damage and ensure proper decontamination.

Reusable specula should be cleaned and disinfected after each use and sterilized, as appropriate, between patients.

1.4.3.1. Health-care Waste Management

Knowledge about the potential for harm due to healthcare waste has become more important to governments, health care workers and civil society. Improper handling and disposal of healthcare facility waste is widely recognized as a source of avoidable infection. Therefore it is critical for healthcare facilities to appropriately manage disposal of healthcare waste, including but not limited to hazardous waste.

Hazardous waste includes sharps, infectious waste (contaminated with blood and other body fluids), pathological waste (such as human tissue) and chemical waste. For details on how to dispose of hazardous waste, please refer to facility and/or local guidelines and regulations and the WHO manual titled *Safe management of wastes from health-care activities*.[4]

Single-use specula and any consumables (swabs, cotton balls, gloves) used during examinations or procedures should be disposed of using the appropriate protocols for the healthcare centre.

1.4.3.2. Storage and packaging

Labelling on the primary packaging should include the name and/or trademark of the manufacturer and should adhere to the most current version of ISO 15223 – 1: *Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements*. Depending on the country, specific requirements for the information to be provided in the labelling may exist, such as the requirement for specific languages, warnings and regulatory conformity symbols.

As a minimum, the storage area should be clean and dust-free, dry, cool, well-lit, ventilated and vermin-proof.

As a minimum, the storage area should be clean and dust-free, dry, cool, well-lit, ventilated and vermin-proof. The device should be stored in its original packaging on a shelf or on in a storage cabinet.

In recognizing that environmental conditions in many LRS are quite varied and can be extreme, **it is the responsibility of the procurement body to ensure the expected storage conditions are within the manufacturer's storage recommendations for any specific device**. If the device will require that the storage environment be climate-controlled, appropriate temperature and humidity control systems, including monitoring, should be applied to avoid premature material disintegration.

However, in general, these devices should be able to withstand storage temperatures ranging from 15°C to 30°C, relative humidity ≤ 85% (non-condensing), and be protected from dripping water.

1.5. Quality Management Systems and post-market surveillance

A quality management system delineates a systematic approach to ensure ongoing quality of outputs. It is critical that all products are manfactured within a robust quality management system at the manufacturer. A QMS includes but is not limited to: standard operating procedures, documentation, design and manufacturing controls and third-party assessments. Maintenance of a QMS requires appropriate human resources and their management, infrastructure, timely and appropriate procurement, stock management, maintenance, and a rigorous pre- and in-service training curriculum.

Post-market surveillance is an obligation of the manufacturer in order to investigate and act on any adverse event and product failure and/or error. One of the most relevant sources of information to the post-market surveillance plan are the complaints made by end-users when an issue is detected. The field safety corrective actions, such as a recall or changes implemented to the product (including labelling), are notified by the manufacturer through a field safety notice to the National regulatory agencies / authorities (NRA), which will also conduct their own market surveillance activities and oversee the manufacturer's investigation incidents and complaints. WHO guidance on QMS and post-market surveillance for medical devices can be found in WHO Global Model Regulatory Framework for Medical Devices including in vitro diagnostic medical devices.[5]

1.6. Standards and regulatory compliance

There does not exist a specific international reference standard (e.g. ISO) for specula; however, the following standards categories apply for specific parts of the process:

- Medical device quality, performance, operations, and safety: ISO 13485, ISO 14971, ISO 15223-1 (See Chapter 1.8 and Annex 1)
- Biocompatibility: ISO 10993, all applicable parts (See Chapter 1.8 and Annex 1)
- Safety for non-cutting surgical instruments: ISO 7151 and ISO 7153-1
- For products supplied as sterile: ISO 11135, ISO 11137, ISO 11607, and ISO 17664.

It is important to observe medical device laws in the country of destination. In the absence of a regulatory agency, it is strongly recommended to consider which regulatory and/or normative body assessment was completed for each product prior to procurement decisions. The risk class depends mainly on the regulatory frameworks in each country and therefore, it may differ according to jurisdiction. For more details with regard to other regional regulatory requirements and applicable standards, see the specifications table in Chapter 1.7 and in Annex 1.

It is important to observe medical device laws in the country of destination.

1.7. Key tender/request for quotation specifications for a specula

Following are the key features that may be noted in a tender or request for quotation; see Annex 1 for detailed standardized WHO technical specifications.

Product description	Speculum opens vaginal canal and is often self-retaining, facilitates in visualizing the cervix for observation and to carry out any test, examination, or procedure.
Key product features	• Reusable specula made of biocompatible materials and resistance to decontamination, cleaning and disinfection methods, or • Single-use specula made of appropriate biocompatible materials • Bivalve and self-retaining to maintain an open vaginal canal • Available in a variety of sizes.
Operational requirements	• Temperature: 15 to 35°C • Relative humidity: ≤85% • (Storage temperature: 15 to 30°C, ≤85%, non-condensing).
Documentation requirements	• Instructions for use and service manuals to be provided • User language preference prioritized, otherwise English is mandatory.
Warranty	Minimum one year

Standards	Follow the active version of the standards below (or their national equivalent): • ISO 13485: Medical Devices - Quality Management Systems - Requirements for Regulatory Purposes; • ISO 14971: Medical Devices - Application of Risk Management to Medical Devices; • ISO 15223-1: Medical devices -- Symbols to be used with medical device labels, labelling and information to be supplied -- Part 1: General requirements. Safety and product standards: • ISO 7151: Surgical instruments -- Non-cutting, articulated instruments -- General requirements and test methods; • ISO 7153-1: Surgical instruments – Materials -- Part 1: Stainless steel; • ISO 10993-1: Biological evaluation of medical devices Part 1: Evaluation and testing within a risk management process; • ISO 10993-5: Biological evaluation of medical devices Part 5: Tests for in vitro cytotoxicity; • ISO 10993-10: Biological evaluation of medical devices Part 10: Tests for irritation and skin sensitization; • ISO 13402: Surgical and dental hand instruments -- Determination of resistance against autoclaving, corrosion and thermal exposure. For products supplied as sterile: • ISO 17664: Processing of health care products – Information to be provided by the medical manufacturer for the processing of medical devices; • ISO 11135: Sterilization of health-care products - Ethylene oxide; • ISO 11137: Sterilization of health care products – Radiation; • ISO 11607: Packaging for terminally sterilized medical devices.
Regulatory requirements	Compliance to (where applicable, but not limited to): • National Regulatory Authority requirements compliance • Approval by regulatory body of country of manufacturer (if applicable). And at least one of: • United States regulations: US FDA 510(k): » Device Class 1 for metal speculum » Device Class 2 for non-metal speculum. • European regulatory framework: » Regulation (EU) 2017/745 of the European Parliament and the Council; » Manufacturer must affix the CE marking and indicate the Notified Body number (when applicable) in the labelling and in the device, when possible. • Other regulatory body in an IMDRF founding member country such as Australia, Canada, or Japan.

Chapter 1 references

[1] IPC is a scientific approach encompassing epidemiology, social science and health system strengthening to provide a comprehensive approach to infection prevention control. The WHO has comprehensive guidelines on core components of IPC programmes: https://www.who.int/gpsc/core-components.pdf.

[2] World Health Organization. (2014). Comprehensive cervical cancer control: a guide to essential practice, 2nd ed. World Health Organization. http://www.who.int/iris/handle/10665/144785.

[3] World Health Organization and Pan American Health Organization. (2016). Decontamination and Reprocessing of Medical Devices for Health-care Facilities. https://www.who.int/infection-prevention/publications/decontamination/en/.

[4] World Health Organization. (2014). Safe management of wastes from health-care activities, 2nd ed. https://www.who.int/water_sanitation_health/publications/wastemanag/en/.

[5] World Health Organization. (2017). WHO Global Model Regulatory Framework for Medical Devices including In Vitro Diagnostics (IVDs). http://apps.who.int/medicinedocs/en/d/Js23213en.

Section 1 – Screening and Diagnostic Tools

Chapter 2: Technical guidance and specifications for HPV In Vitro Diagnostics

Brief description

HPV in vitro diagnostics (IVDs) using nucleic acid testing (NAT) technologies identify women at risk for cervical precancer. HPV NAT IVDs cover the range of manual methods to fully automated systems and the ability to test a single specimen or accommodate high throughput volumes. Specimen are either collected by a health care provider or self-collected before being appropriately prepared and tested on one of the flowing types of analysers:

- **Laboratory-based manual system:** Test kits will contain reagents that have to be handled i.e. mixed or pipetted. Laboratories will need to provide certain consumables (gloves, pipette tips) and other auxiliary equipment and items that are necessary but not provided (pipette, centrifuge, vortex, heating block, computer). Reagent grade running water and a reliable continuous power supply are generally required. Manual methods are more labour-intensive and therefore most appropriate for small to medium batched testing runs;

- **Laboratory-based automated analysers:** Both partially and fully automated systems are available. Most automated analysers are closed systems meaning that only reagents specified and supplied by the manufacturer may be used. There is minimal pre-analytical processing so that the operator need only follow software-guided instructions for loading reagents and samples. Consumables such as gloves, pipettes and pipette tips are still required as for manual methods. Also important is to have a laboratory information system. Reagent grade running water and a continuous, reliable power are required. Automated analysers may be more amenable to large batched testing runs for testing sites with high throughput;

- **Point of care or near patient testing:** There are both automated and manual systems in which HPV NAT IVDs are performed at or near to the point of care; automated systems use compact bench top devices, usually in primary care clinics or other health facilities without a laboratory. These IVDs may require limited pipetting of a single sample into a cartridge that is placed into the system or a simple manual intervention between amplification and detection modules. The remainder of the testing occurs without operator intervention. Continuous, reliable power is generally required. Point of care testing may allow for single visit "screen and treat" and multiple modules can be used to increase testing throughput.

2.1. Scope of chapter

This chapter specifies technical requirements for an HPV NAT IVD for cervical cancer screening programmes to detect HPV, a DNA virus.

Content herein focuses on present state of practice using up-to-date available technologies; however, authors are aware that innovations in manufacturing, healthcare facilities and practice will advance the field of cervical cancer screening, diagnostics and treatment. The specifications herein do not preclude appropriate upcoming products and/or technologies.

This chapter specifies technical requirements for an HPV NAT IVD for cervical cancer screening programmes to detect HPV, a DNA virus.

2.2. Background on HPV in vitro diagnostics

2.2.1. HPV Testing

HPV is a relatively small double stranded DNA virus that is present and accessible in infected exfoliated cell specimens, allowing detection by NAT IVDs.[1] NAT technologies have led to the development of HPV IVDs for screening that focus on the qualitative detection of the high-risk genotypes.[1,2] It is also known that HPV 16 and HPV 18 together are responsible for approximately 70% of all cervical cancers globally ; several HPV NAT IVDs have therefore been developed to specifically detect these most common oncogenic genotypes and in turn to identify those women at highest risk.

The majority of HPV NAT IVDs are DNA-based where primers and probes are used to detect specific segments of HPV DNA. More recently, HPV IVDs have been developed to detect mRNA transcripts coding for the E6/E7.[1,2] Among available commercial HPV NAT IVDs, results are generally reported out as "detected" or "not detected" for a pool of high-risk HPV genotypes; certain IVDs can also report out individual results in various combinations, for example: HPV 16 and 18; HPV 16, 18/45; HPV 16, 18, 45, 51, 52 with pooled results for 33/58, 56/59/66 and 35/39/68. Some HPV NAT IVDs that generate the individual genotype results require a reflex test run, while others are able to report out the individual results concurrently with the pooled result. When individual genotypes are reported out concurrently as an integrated step in the initial run, the time and resources needed for a second run are eliminated.

The majority of HPV NAT IVDs are DNA-based where primers and probes are used to detect specific segments of HPV DNA.

For quality control, some HPV NAT IVDs are designed with an internal gene control to confirm specimen adequacy and acceptable assay performance; this is considered an important aspect of the test since it can potentially identify false negative results. False positive results can be minimized by the inclusion of a negative control that is capable of detecting contamination.

Screening for HPV by NAT technologies involves three main steps: collecting the specimen, performing the test and interpreting the results. Each programme should procure HPV NAT systems based on their individual programme priorities. For some programmes, an HPV NAT IVD that can perform batched testing of specimens in less than four hours without the availability of reagent grade water or constant power supply is the optimal system, whereas for another programme, the optimal system may be an HPV NAT IVD performed at point of care that is able to provide results on individual specimens within a few hours and can be used to facilitate "screen and treat" in one clinic visit. For programmes with access to a laboratory, manual or automated systems can provide higher specimen throughput.

Screening for HPV by NAT technologies involves three main steps: collecting the specimen, performing the test and interpreting the results.

2.2.2. Specimen collection

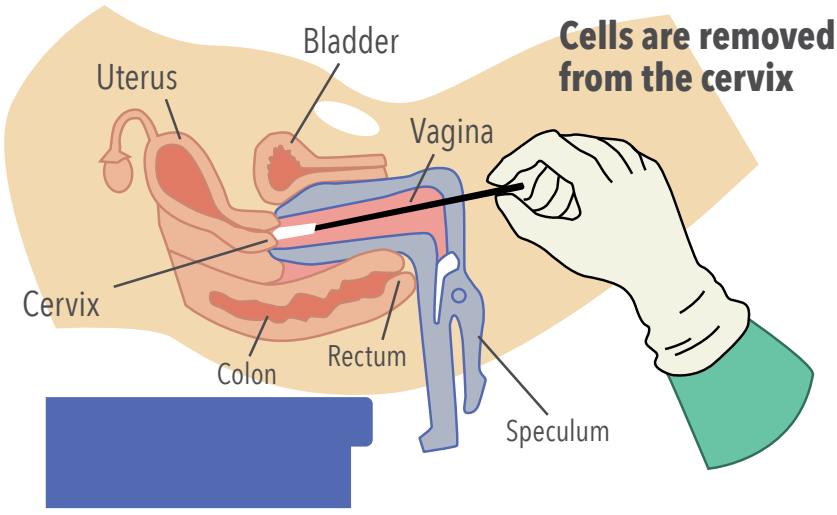
2.2.2.1. Healthcare-Provider Collected

To obtain a specimen for an HPV NAT IVD, a trained healthcare provider visualizes the cervix with a speculum[v] placed in the vagina and performs a scraping of cervical cells as shown in Figure 4. Various devices for specimen collection can be used and the manufacturer of the IVD will generally specify the appropriate collection device. The manufacturer's instructions for use should always be followed.

Cervical specimens collected by a healthcare provider are generally placed in a liquid transport medium that is specified by the manufacturer of the IVD.

[v] See section 1 chapter 1 on Speculum.

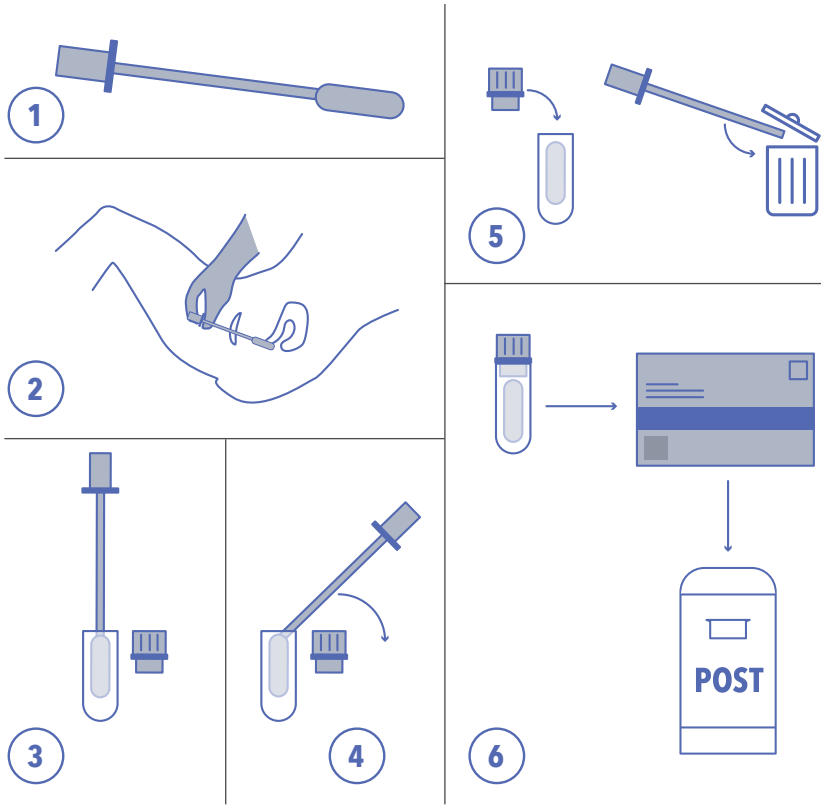
Figure 7: Health care provider collecting a specimen for HPV NAT by scraping the cervix.



2.2.2.2. Self-collected

One of the distinct advantages of HPV NAT IVDs over cytology in a cancer prevention programme is the option of using self-collected specimens rather than specimens collected in the clinic by trained healthcare providers. Unlike specimens for cytology testing that require collecting cells from the cervix under direct visualization, HPV specimens can be obtained from a self-collected vaginal swab, as shown in Figure 8.

Figure 8: Self-collection of a specimen for HPV NAT by swabbing the vagina.



Adapted from medical journals and Aprovix

Self-collection was first introduced in high-resource settings as a "last resort" for women who were not compliant with routine cervical cancer screening.

Self-collection was first introduced in high-resource settings as a "last resort" for women who were not compliant with routine cervical cancer screening. However, as some studies indicated that the clinical sensitivity for detecting CIN2 or greater was similar to provider (clinician)-collected sampling[4,5] or slightly inferior when signal amplification NAT HPV tests (as opposed to PCR-based tests) are used[5], self-collection became an attractive alternative in low resource settings. Studies have also indicated that the majority of women prefer self-collection, which can either be performed in their home or in the clinic under the guidance of trained healthcare providers.[6]

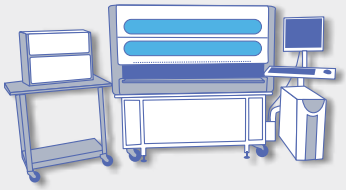
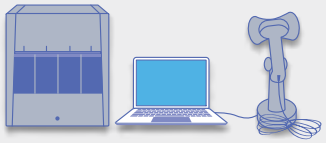
HPV NAT IVDs have been performed on self-collected specimens using a variety of collection devices (swabs, brushes, lavage). Various devices for specimen collection can be used and the manufacturer of the IVD will generally specify the appropriate collection device. The manufacturer's instructions for use should always be followed. Collected samples were originally placed in appropriate non-toxic transport media; however, more recent studies support the stability of transporting as a dry swab or transferring the sample to a card.[7] **Programmes need to determine how self-collection can be adapted to suit specific settings, including considerations for optimal collection device/transport media and transportation of the sample to where the test will be carried out.**

Various devices for specimen collection can be used and the manufacturer of the IVD will generally specify the appropriate collection device.

2.2.3. Performing HPV NAT IVDs

The commercially available HPV NAT IVDs span the spectrum of requiring significant manual pre-analytical, analytical and post-analytical steps to those where a fully automated system is utilized. The categories of IVDs are summarized in Table 2.

Table 2: Comparison of different HPV NAT IVDs

Testing Method	Manual	Automated	Point of Care or near patient testing
			
Manual steps	Maximum	Limited	Limited
Operator Qualifications	Experienced in laboratory procedures	Trained for specific automation	No laboratory experience needed; focused device training
Throughput	Small to moderate batch testing	High volume batch testing, but random access available	Single specimen, but can combine multiple modules to increase volume
Infrastructure Requirements	Vast majority of methods require reagent-grade water, continuous, reliable power supply. Requires appropriate chemical and biohazard waste management	Reagent-grade water, continuous, reliable power supply, significant laboratory footprint. Requires appropriate chemical and biohazard waste management	Continuous, reliable power supply. Requires appropriate chemical and biohazard waste management
Advantages	Lower initial investment	High throughput, limited operator involvement	Facilitates "screen and treat" programmes, no laboratory experience needed to operate
Limitations	Labour-intensive	High initial investment; large footprint	Low throughput (though moderately scalable to increase capacity)

The test kits for the manual test methods will contain reagents that require some preparation and involve procedures such as pipetting using a hand-held device, vortexing, heating, centrifugation and instrumentation that can detect the amplified target. These are moderately complex processes and require considerable hands-on-time performed by skilled and proficient operators.

Automated HPV NAT IVDs are generally performed in an analyser where reagents and uniquely identified specimens are loaded (either in the collection vial or as a pipetted aliquot into a secondary tube), software-guided testing choices are selected (type of specimen, number of specimens in run, result reporting format) and testing is then performed with minimal hands-on time required. The amplified target is detected within the system and a report is generated with results reported for various categories such as "detected", "not detected". Automated analysers have the advantage of higher throughput, but often involve batched testing, which may limit specimen flexibility. Newer automated, high throughput testing platforms are now available which enable random access and no longer require sample batching. The fully automated systems have specific requirements for instrument footprint (some are benchtop, others are free-standing), running reagent grade water, refrigeration and continuous power supply.

In addition, there are more recently-developed, simpler analysers for use at point of care, which consist of compact bench-top systems that require only pipetting of the sample into a cartridge that is then placed into the system for testing or very limited manual manipulation between amplification and detection units. An automatically-generated report of either detected/not detected is produced at the end of testing. This type of system can allow for random access single specimen testing and certain platforms can also be scaled up to offer multiple modules of the same analyser.

The test kits for the manual test methods will contain reagents that require some preparation and involve procedures such as pipetting using a hand-held device, vortexing, heating, centrifugation and instrumentation that can detect the amplified target.

2.2.4. Interpretation of Results by Healthcare Providers and Next Steps

Despite the high prevalence of HPV, the majority of infections will resolve without causing cervical cancer precursors. One of the key components of a cervical cancer prevention programme is to ensure that healthcare providers are adequately trained in the interpretation of the HPV NAT IVDs results, as well as in determining the next steps to be taken based on the results.

2.3. Complementary products necessary when using HPV IVDs

The products and equipment needed for HPV testing will vary depending on the method of collection (provider- or self-collection) and on the particular HPV NAT IVD that is used. Below is a listing of possible products; the manufacturers' instructions for use for a particular assay should be consulted for more specific guidance.

Table 3: Items that may be required but not provided to perform HPV testing

A. Specimen collection (pre-analytical step)

- Examination table with stirrups*
- Adjustable examination light* of at least 100W or 100W-LED equivalent, and/or a magnification lamp (white light spectrum only. Yellow, tungsten-based light sources should be avoided if possible
- Single-use powder free gloves
- Vaginal speculum (stainless steel or disposable plastic if no sterilization system available), various sizes*. (Chapter 1 for details on specula)
- Specimen collection device(s)
- Specimen transport medium
- Sterilization equipment (if using non-disposable specula). *

B. Test procedure (analytical step) (consult manufacturers' instructions for use for specific HPV NAT)

- Gloves
- Protective eyewear
- Specimen racks
- Pipettes (refer to manufacturer instructions for volumes required, but generally range from 0.5-2mL)
- Plugged (filtered) pipette tips
- Vortex
- Centrifuge
- Heating block
- Waste bag and safe disposal
- Disinfectant (refer to Chapter 9.1 for details).

*Provider-collected specimens only

2.4. Quality management systems and post-market surveillance

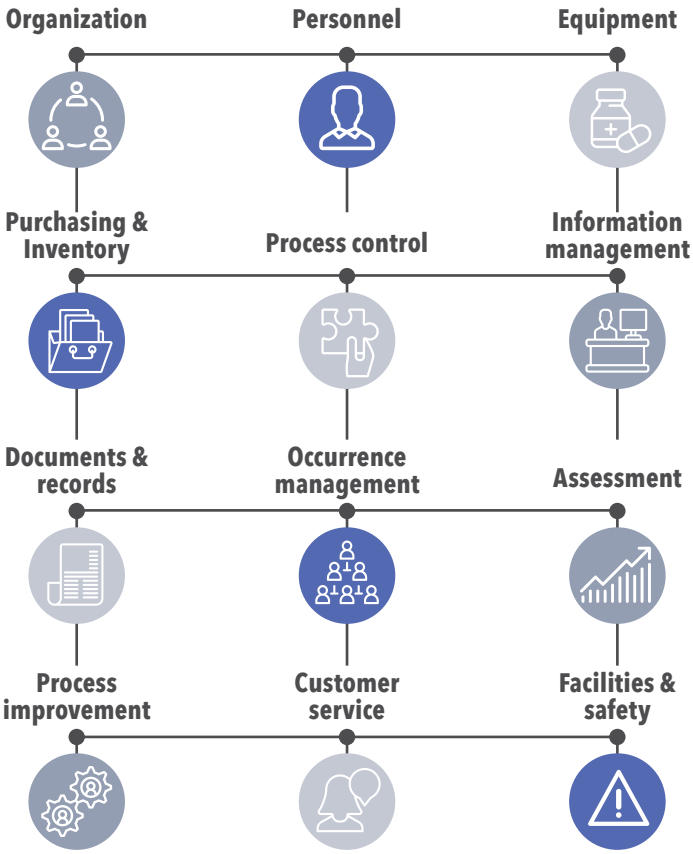
Health workers and laboratory technicians involved in specimen collection, screening and treatment need to be trained on the appropriate equipment requirements per the manufacturer's instructions for use. Instrument cleaning, calibration and proper storage are required.

A quality management system delineates a sytematic approach to ensure ongoing quality of outputs. It is critical that all facilities observe a quality management system comprising twelve key components (illustrated in Figure 6). Standard operating procedures, documentation and record-keeping, process control, third-party assessments are all key aspects of such a system. Additional requirements to maintain such a system include appropriate human resources and their management, infrastrucutre, timely and appropriate procurement, stock management, maintenance, and a rigorous pre- and in-service training curriculum.[8]

A quality management system delineates a sytematic approach to ensure ongoing quality of outputs.

Quality management systems are critical for ensuring the testing report that goes to the patient and the staff in charge of their care and treatment is accurate. Medical laboratories are encouraged to follow the most current version of *ISO 15189: Medical laboratories – Requirements for quality and competence to develop and operate under appropriate quality management systems.* [8] Please see WHO has guidance on quality management systems for medical laboratories via its Laboratory Quality Stepwise Implementation tool which can be found at the following link https://www.who.int/ihr/lyon/hls_lqsi/en/.

Figure 9: Twelve components of a quality management system[vi]



Post-market surveillance is an obligation of the medical device or IVD manufacturer to investigate and act on any adverse event and product failure and/or error (for example higher than expected rate of defective reagents or invalid results). For this purpose, the manufacturer must implement a post-market surveillance plan. One of the most relevant sources of information to the post-market surveillance plan are the complaints made by end-users when an issue is detected. The manufacturer should conduct a root cause analysis and determine whether the risk/benefit ratio is maintained. Any field safety corrective actions, such as a recall or changes implemented to the product (including labelling), are notified by the manufacturer through a field safety notice to the National regulatory agencies / authorities (NRA), which will also conduct their own market surveillance activities and oversee the manufacturer's investigation of complaints. WHO guidance on post-market surveillance for IVDs can be found in Post-Market Surveillance of In Vitro Diagnostics[8] and in the WHO Global Model Regulatory Framework.[9]

2.5. In vitro diagnostic performance

2.5.2. Clinical Performance

The sensitivity and specificity of an HPV IVD must be based on a clinically relevant endpoint to ensure that significant disease is not missed. For HPV NAT IVDs that are used as a screening assay in a cancer prevention programme, the sensitivity must be high enough to initially identify all women who are at risk of having or developing high grade precancerous lesions (CIN2 or greater), yet not too analytically sensitive so as to identify infection that is not likely to progress to disease. To optimize disease detection over transient HPV detection, clinical assays will generally select a cut-off for a "positive" (detected)/"negative" (not detected) result based on correlation to detection of CIN 2 or greater.

To ensure reliable clinical sensitivity and specificity for HPV detection, performance of an HPV NAT must undergo validation. Specific criteria have been established for validating an HPV NAT and details are described in Annex 2A. It is the ultimate responsibility of the programmes to determine the level of performance assessment that is appropriate for the setting; **however, it is not recommended that each country or screening programme conduct a performance assessment for the HPV NAT that is selected**. Rather, programmes can rely on assessment by the US Federal Drug Administration (FDA), Australian Therapeutic Goods Administration (TGA), Health Canada, Japan Ministry of Health and Welfare, European Commission, WHO Prequalification programme or country-specific regulatory agencies. Testing laboratories may also be able to conduct performance assessments according to their established procedures.

2.5.3. Analytical Performance

Analytical performance addresses analytical sensitivity, specificity, accuracy and linearity. Analytical sensitivity is determined by the limit of detection (LoD) of an HPV NAT, which is defined as the analyte concentration where 95% of test runs give positive results (at varying dilutions) when compared to an international reference material. Analytical specificity is determined by evaluating cross-reactivity with various interfering substances and concomitant infections. Precision confirms that the same HPV NAT results are obtained under varying testing conditions. More specific information regarding Analytical Performance can be found in Annex 2A.

2.5.4. Invalid rates

The invalid, or unreturnable rate, denotes results when HPV could not be measured, generally because of technical problems with the assay (such as a failed internal control or the absence of DNA). These rates are expected to be less than 5%; however, the actual rate in a clinical setting may initially be higher during the implementation of a new assay. Invalid rates must be reported by the manufacturer, and it is recommended for programmes to monitor these rates in order to identify trends as part of a post-market surveillance programme (see Chapter 2.4).

2.6. Operational Considerations

Additional procurement considerations are listed in the following subsections.

2.6.1. Equipment Maintenance

Information regarding maintenance can be found in the service manual for specific equipment and processes should be followed to ensure the continued safety and reliability of operation and to maintain warranty coverage. The corresponding service and maintenance package should be requested from the supplier or distributor before equipment is procured.

2.6.2. Storage and packaging

As a minimum, storage areas for IVDs should be clean and dust-free, dry, cool, well-lit, ventilated and vermin-proof. The device should be stored in its original packaging on a shelf or on in a storage cabinet. In recognizing that environmental conditions in many low resource settings are quite varied and can be extreme, **it is the responsibility of the procurement body to ensure the expected storage conditions are within the manufacturer's storage recommendations for any specific device**. If the device will require that the storage environment be climate-controlled, appropriate temperature and humidity control systems, including monitoring, should be applied to avoid premature product malfunction. In general, HPV NAT IVDs should be able to withstand storage temperatures ranging from 15°C to 30°C, relative humidity ≤ 60% (non-condensing), and be protected from dripping water.

2.6.2.1. Specimen collection, transport and storage

Specimens for HPV NAT IVDs are generally collected in media originally developed for liquid-based cytology testing. There are a variety of devices

for collecting exfoliated cervical cells for HPV NAT IVD testing. For provider-collected specimens these include the spatula (often used with the endocervical brush) and brush broom device; for self-collected specimens, swabs and lavage devices are also used. The manufacturers' instructions for use for the IVD should be consulted for information regarding the appropriate medium and the collection device(s) recommended, although programmes ultimately determine what is appropriate for their setting.

Specimens in collection medium can be shipped to testing sites without refrigeration. The manufacturers' instructions for use provide more specific information regarding transport and should be followed.

Specimens in collection medium can be shipped to testing sites without refrigeration.

Specimens in collection media are generally stable at 2-30°C for between 2 weeks to 6 months, although some products will fall outside this general stability timeframe. For situations where temperatures are >30°C, specimens should be processed as soon after collection as possible.

Specimens that have been partially processed may also be stored. Storage and sample transport information specific to a particular HPV NAT IVD can be found in the manufacturers' instructions for use.

2.6.2.2. Reagent storage

Reagent shelf life and conditions required for storage vary by product. Refer to the specific HPV NAT IVD manufacturers' instructions for use for guidance on shelf life and storage requirements. Consideration should be taken for how to best manage the supply chain and inventory of reagents and test kits, so as not to use expired product and minimize disposal due to storage past expiry date on the packaging label.

2.6.3. Health-care Waste Management

Knowledge about the potential for harm due to healthcare waste has become more important to governments, health care workers and civil society. Improper handling and disposal of healthcare facility waste is widely recognized as a source of avoidable infection; therefore, it is critical for healthcare facilities to appropriately manage disposal of healthcare waste, including but not limited to hazardous waste.

Hazardous waste includes sharps, infectious waste (contaminated with blood and other body fluids), pathological waste (such as human tissue) and chemical waste. For details on how to dispose of hazardous waste, please refer to facility and/or local guidelines and regulations and the WHO manual titled Safe management of wastes from health-care activities.[11]

Disposal of test kit contents must be in accordance with the manufacturer's instructions for use and local regulations. Used and unused reagents should be disposed of in accordance with country, federal, state, local and institutional waste regulations. Certain HPV NAT IVD contain toxic compounds and due care must be taken.

2.6.4. Decontamination and Reprocessing

Health care-associated infections (HAI) are one of the most common adverse events in health care delivery. Not only do they have a significant impact on morbidity and mortality, but they also present an economic burden to health care facilities and countries. As part of a larger infection prevention and control (IPC) program[ix], decontamination of instruments and medical devices plays a critical role in HAI prevention.

The PAHO/WHO manual titled Decontamination and reprocessing of medical devices for health-care facilities[12] outlines the decontamination life cycle, which includes cleaning, disinfection and sterilization. Please refer to this manual for details on specific methods of decontamination, sterilization and reprocessing of medical devices. Always follow the device manufacturer's instructions for decontamination so as to not cause any damage and ensure proper decontamination.

2.7. Standards and regulatory compliance

There are not available specific international reference standards (e.g. ISO) for HPV NAT IVDs; however, the following standards categories apply:

- Medical device quality, performance, operations, and safety: ISO 13485, ISO 14971 (See Chapter 2.8 and Annex 2B);
- In vitro diagnostic medical devices: ISSO 23640 and ISO 18113-1 (See Chapter 2.8 and Annex 2B).

With respect to regulatory approvals, products are most commonly assessed by one of the following bodies in the listed risk class:

Table 4: Regulatory authority/normative body and risk class for HPV IVDs.

Regulatory authority/Normative body	Risk class
European Union	Self-diagnostics or not included in list A or list B under the IVDD or Class C under the IVDR
US Food and Drug Administration	Class III
Health Canada	Class III
Therapeutic Goods Administration, Australia	Class 3
Ministry of Health, Labour and Welfare, Japan	Class III
World Health Organization Prequalification	Full prequalification assessment[13]

The stringency of the assessment, which includes evaluations of the QMS as well as analytical and clinical data to establish the performance characteristics of the IVD, will be dictated by the risk class and determines the design of studies and quantity of data required for dossier submission. It is important to observe all applicable local laws related to medical devices and their procurement. In the absence of a regulatory agency, it is recommended, though not binding, to consider which regulatory and/or normative body assessment was completed for each product prior to procurement decisions. The risk class depends mainly on the regulatory frameworks in each country and therefore, it may differ according to jurisdiction.

It is important to observe all applicable local laws related to medical devices and their procurement.

2.8. Key tender/request for quotation specifications for an HPV IVD

The following table outlines the key features that may be noted in a tender or request for quotation for the procurement of HPV IVDs. See Annex 2B for detailed standardised WHO technical specifications.

Product description	HPV NAT IVDs cover the range of manual methods to fully automated systems and the ability to test a single specimen or accommodate high throughput volumes. Specimens are either collected by a health care provider or self-collected before being appropriately prepared and tested on one of the flowing types of analysers: Laboratory-based manual system, Laboratory-based automated analysers or Point of care testing.
Key product features	• Minimum specimen throughput per hour must be provided; • At a minimum, HPV 16 or HPV 16 and 18 should be detected. Additional relevant genotypes to be detected are HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 (with 66, 68 acceptable but not preferable) as a pooled result; • Results must be presented as specific individual genotypes or as a pooled result • Individual targeted genotyping as a reflex test or concurrent (preferred) with pooled results; if reporting out individual genotypes, must have the ability to distinguish between genotypes.
Quality control	• Tests should include a positive control to confirm HPV amplification and a negative control to monitor for cross contamination; • Test systems should also use internal controls to confirm the presence of human cellular DNA and to rule out inhibitory substances.

Clinical evidence	See TSS-4: IVDs used for the detection of high-risk HPV types in cervical cancer screening for performance requirements.[14]
Components, accessories, consumables	HPV NAT IVDs will normally have the following essential components: 1. Specimen collection device and transportation media 2. Reagent kit(s) or cartridge 3. Analyser(s) for extraction, amplification and detection, separate or combined.
Operational requirements	• Test-run timing: » For manual test systems, the hands-on-time, the specimens per run and overall time must be specified; » For automated test systems, the specimens per run, total run time, hands-on-time and walk-away time must be specified; • Specimen volume: The required specimen volume for testing must be specified; • Storage and transport requirements: special indications, such as refrigeration or freeze, for reagents must be listed; • Stability: Requirements for stability prior to and during use; • Laboratory information systems compatibility: Inter-operability with laboratory information systems should be described; • The unit is suggested to be connected to a continuous, reliable power source; • Electrical source requirements (based on country/setting of use): » Amperage: _____. » Voltage: _____.. • Plug type: _____.
Documentation requirements	• Instructions for use and service manuals to be provided • User language preference prioritized, otherwise English is mandatory.
Warranty	Minimum 24 months.
Standards	Compliant with active version of the following standards (or equivalent): • ISO 13485: Medical devices–Quality management systems; • ISO 14971: Medical devices–Application of risk management to medical devices; • ISO 23640: In vitro diagnostic medical devices–Evaluation of stability of in vitro diagnostic reagents: ISO 18113-1: In vitro diagnostic medical devices -- Information supplied by the manufacturer (labelling) -- Part 1: Terms, definitions and general requirements.

Regulatory requirements	Careful consideration should be taken to ensure that the selected products have been assessed to an appropriate stringency level based on the risk classification for HPV NAT IVDs. Compliance to (where applicable, but not limited to): • NRA requirements compliance • Approval by regulatory body of country of manufacturer (if applicable). In the absence of a regulatory agency, it is recommended, to consider which regulatory and/or normative body assessment was completed for each product prior to procurement decisions, such as: • WHO Prequalification; • United States regulations: US FDA 510(k): Device Class III; • European regulatory framework: » Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 » Regulation (EU) 2017/746 of the European Parliament and the Council: Class C under the IVDR; » Manufacturer must indicate affix the CE marking and indicate the Notified Body number on the label. • Other regulatory bodies in an IMDRF founding member country such as Australia, Canada, or Japan.

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Section 1 – Screening and Diagnostic Tools

Chapter 3: Technical guidance and specifications for acetic acid for use in VIA

3.1. Scope of chapter

This chapter specifies preparation of acetic acid for visual assessment of the cervix. Content herein focuses on present state of practice using up-to-date available technologies; however, authors are aware that innovations in manufacturing, healthcare facilities and practice will advance the field of cervical cancer screening, diagnostics and treatment. The specifications herein do not preclude appropriate upcoming products and/or technologies.

Brief description

Visual inspection with acetic acid, or VIA, is a technique used for the detection of precancerous or cancerous lesions in the cervix, or cervical neoplasia. The application of dilute acetic acid on precancerous or cancerous lesions triggers whitening of these regions and is an effective low-cost method used to detect, triage and refer patients appropriately for subsequent treatment.

3.2. Background for visual inspection with acetic acid

Visual inspection with acetic acid (VIA) is a direct visual assessment of the cervix using a 3-5% acetic acid solution to visibly whiten cervical lesions , which temporarily produces what is known as an acetowhite lesion. This effect appears after one minute and may last 3-5 minutes in the case of CIN 2-3 and invasive cancer.[1]

Used since the early 1950s[2], VIA is now a widely-used visual screening technique for cervical neoplasia as it is low-cost, does not require laboratory infrastructure, and can provide immediate results. Furthermore, VIA is a key aspect of the "screen and treat" paradigm, where a patient can feasibly undergo treatment after VIA (or other screening technique in the paradigm) within a single visit. A single visit in which immediate treatment is performed when precancerous lesions are identified is especially important for low resource settings (LRS), where there is a high loss of follow-up after an initial visit to the health care centre.[3,4] It is important to note that due to the qualitative nature of this technique, sensitivity and specificity are quite variable. A meta-analysis has indicated sensitivity and specificity ranges of 66-96% and 64-98%, respectively, and noted that rigorous training was a commonality in higher values.[5] Therefore, VIA screening programs must include quality training and content inclusion in a continuing medical education (CME) program to ensure frequent refresher trainings. Proper training is required not only to ensure best clinical practice for the patient, but also for correct preparation and use of solutions, documentation, and interpretation of results.

3.3. Materials, equipment and accessories for acetic acid

3.3.1. Acetic acid solution

The recommended concentration is between 3-5% acetic acid by volume with distilled water.[6,7] Solutions of 5% acetic acid may be prepared by adding 5 ml of glacial acetic acid into 95 ml of distilled water.

The recommended concentration is between 3-5% acetic acid by volume with distilled water.

Acetic acid is the main ingredient of vinegar, however, the concentration of vinegar, varies from about 4-12% acetic acid[8] so caution should be taken when using an off the shelf product. In some countries, vinegar is not available. What is often sold in the market is a "vinegar substitute" that, in fact is acetic acid. If neither a 3-5% acetic acid solution nor vinegar is available, a pharmacist/chemist or local chemical supplier can make dilute 3-5% acetic acid solution using distilled water and glacial acetic acid (water-free acetic acid, 99.99% acetic acid).

The following formula can be used to calculate parts water necessary for a given starting concentration of acetic acid[9]:

$$\text{Total parts of water} = \frac{\text{(\% concentrate)}}{\text{(\% dilute)}} - 1$$

Example calculations:

1. How to prepare a 5% acetic acid solution from glacial acetic acid (100% acetic acid)

$$\text{Total parts of water} = \frac{100\%}{5\%} - 1 \longrightarrow \textbf{19 parts water to 1 part concentrate, by volume}$$

2. How to prepare a 5% acetic acid solution from a 25% aqueous acetic acid solution (by volume)

$$\text{Total parts of water} = \frac{25\%}{5\%} - 1 \longrightarrow \textbf{4 parts water to 1 part concentrate, by volume}$$

Process of making 5% acetic acid solution using glacial acetic acid (as an example):

1. Be sure to wear personal protective equipment: goggles, gloves, and lab coat when diluting acetic acid, especially if starting with caustic sources such as glacial acetic acid;

2. Work in a well-ventilated space, preferably with a fume hood;

3. On a clean work surface, place containers of source acetic acid (e.g. glacial acetic acid), water (distilled or boiled then cooled water), glass container with lid for final solution, graduated cylinder and syringe or small graduated cylinder;

4. To make 100 mL of 5% acetic acid solution from glacial acetic acid, using above ratio:

a. First measure 95 mL of water using a graduated cylinder and pour into clean container;

b. Next, measure 5 mL glacial acetic acid using a syringe or small graduated cylinder and pour into container after having already poured in the water.

5. Mix by closing the container and shake gently;

6. Label container with solution concentration;

7. If making fresh solutions from a mother solution, be sure to do so daily and dispose of any remaining dilutions at the end of the day.

Undiluted acid can cause severe chemical burn to human tissue. It is important to dilute the glacial acetic acid or higher concentration acetic acid to a maximum of 5% prior to application.

It is preferred to use distilled water so that the effect of acetic acid is consistent. Direct use of tap water or ground water could lead to reactions between the acetic acid and minerals and/or impurities in the water, resulting in the formation of acetate salts and a weaker acetic acid concentration.[10] In the absence of distilled water, tap water can be used but must be first boiled and then cooled.

It is preferred to use distilled water so that the effect of acetic acid is consistent.

3.3.2. Instruments and materials needed

In addition to the acetic acid itself, the following is a list of standard equipment needed in order to carry out a VIA exam.

Table 5: Items that may be required to perform VIA

- soap and water (or alcohol-based hand rub) for washing hands;
- a bright light source of at least 100W or 100W-LED equivalent, and/or a magnification lamp (white light spectrum only. Yellow, tungsten-based light sources should be avoided 48) to examine the cervix;
- a vaginal speculum, high-level disinfected (need not be sterile) – see Chapter 1;
- single-use examination gloves (need not be sterile);
- an examination table, preferably with knee crutches or leg rests or stirrups;
- cotton-tipped swabs;
- dilute acetic acid solution (3–5%) or white vinegar;
- Timer (clock, timer on mobile-phone).

3.4. Operational considerations

3.4.1. Acetic acid as used for VIA

The recommended concentration is between 3-5% acetic acid by volume with When using acetic acid as a medium for cervical screening by means of VIA, follow the guidance provided in section 3.3.1 for preparation of the solution. After a visual inspection of the illuminated cervix, the healthcare provider liberally applies the acetic acid solution to the cervix using a cotton swab. After one minute, the healthcare provider will again observe the illuminated cervix to ascertain whether or not any acetowhite lesions have formed. Though acetowhite lesions can last for 3-5 minutes, they often start to fade after two minutes.

For further details and guidance, please refer to WHO's Comprehensive Cervical Cancer Control: a guide to essential practice.[11]

3.4.2. Decontamination and reprocessing

Health care-associated infections (HAI) are one of the most common adverse events in health care delivery. Not only do they have a significant impact on morbidity and mortality, but they also present an economic burden to health care facilities and countries. As part of a larger infection prevention and control (IPC) program[12], decontamination of instruments and medical devices plays a critical role in HAI prevention.

The PAHO/WHO manual titled Decontamination and reprocessing of medical devices for health-care facilities[13] outlines the decontamination life cycle, which includes cleaning, disinfection and sterilization. Please refer to this manual for details on specific methods of decontamination, sterilization and reprocessing of medical devices. Always follow the device manufacturer's instructions for decontamination so as to not cause any damage and ensure proper decontamination.

Reusable instruments, including specula, should be cleaned and disinfected or sterilized where appropriate between patients and according to a standard protocol for the health facility. If a device appears damaged or no longer self-retains, it should immediately be taken out of service and replaced.

3.4.3. Health-care Waste Management

Knowledge about the potential for harm due to healthcare waste has become more important to governments, health care workers and civil society. Improper handling and disposal of healthcare facility waste is widely recognized as a source of avoidable infection; therefore it is critical for healthcare facilities to appropriately manage disposal of healthcare waste, including but not limited to hazardous waste.

Hazardous waste includes sharps, infectious waste (contaminated with blood and other body fluids), pathological waste (such as human tissue) and chemical waste. For details on how to dispose of hazardous waste, please refer to facility and/or local guidelines and regulations and the WHO manual titled Safe management of wastes from health-care activities.[14]

Any consumables (swabs, cotton balls, gloves) and single-use specula should be disposed of using the appropriate protocols for the health facility and according to manufacturer's instructions.

Prepared and unused dilute solutions left out during the day may have lower concentrations of acetic acid due to evaporation or may have been contaminated and should be discarded at the end of the day 48. These dilutions should be discarded at the end of the day in a safe manner and in accordance with ISO 14001: Environmental Systems Management.

3.4.4. Storage and packaging

Concentrated, starting or mother solution should be stored in its original and labelled container on a shelf or in a storage cabinet, separately from oxidizing materials and alkaline substances. Containers should be tightly sealed to avoid vapours from escaping. As a minimum, the storage area should be clean and dust-free, dry, cool, well lit, ventilated and vermin-proof.

Concentrated, starting or mother solution should be stored in its original and labelled container on a shelf or in a storage cabinet, separately from oxidizing materials and alkaline substances.

In recognizing that environmental conditions in many LRS are quite varied and can be extreme, **it is the responsibility of the procurement body to ensure the expected storage conditions are within the manufacturer's storage recommendations for any specific product**. If the product will require that the storage environment be climate-controlled, appropriate temperature and humidity control systems, including monitoring, should be applied to avoid premature disintegration.

However, in general, acetic acid should be able to withstand storage temperatures ranging from 15°C to 30°C, relative humidity ≤ 60% (non-condensing).

Diluted solutions of 3-5% concentration should be freshly prepared at the beginning of the day, and any remaining dilutions should be disposed of at the end of the day. Prior to each patient examination, a sufficient volume should be poured into a smaller container.

3.4.5. Software as a medical device to support screening and diagnosis of precancerous lesions.

New software packages are emerging that can facilitate remote training or confirmatory assessment using decision-assist mobile platform applications ("apps") or using systems of artificial intelligence (AI). In this context of cervical assessments, AI is intended to be used to assess a portfolio of images as part of a machine-learning based algorithm to classify the images to assist with the diagnosis of precancerous lesions. Whether or not the software uses AI, if it is "…intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device" then it is defined as software as a medical device (SaMD) by the IMDRF.[15] By this definition, software packages that facilitate diagnosis (including, but not limited to AI) are considered medical devices and must be treated as such from a regulatory, quality and procurement perspective. As these are innovative products, and currently under assessment, there is no further description of them in this publication, but they will be assessed in future revisions if the evidence is important to be considered.

New software packages are emerging that can facilitate remote training or confirmatory assessment using decision-assist mobile platform applications ("apps") or using systems of artificial intelligence (AI).

3.5. Quality management systems and post-market surveillance

The quality management system that underlies production of chemicals, such as for the production of acetic acid used for VIA, does not follow the same standard as for medical devices. Nevertheless, standards for acetic acid purity should come from the international pharmacopea or national equivalent.[16]

As VIA is a locally produced solution, the QMS, post market surveillance and medical devices regulations do not apply.

3.6. Standards and regulatory compliance

Standards for acetic acid purity, ensured concentration, and storage according to pharmacopoeia are listed in the specifications table in Chapter 3.7 and detailed specifications in Annex 3.

3.7. Key tender/request for quotation specifications for acetic acid for use with VIA

Following are the key features that may be noted in a tender or request for quotation; see Annex 3 for detailed standardized WHO technical specifications.

Product description	3-5% acetic acid is used for visual inspection with acetic acid (VIA), a technique used for the detection of precancerous or cancerous lesions in the cervix, or cervical neoplasia.
Key product features	The application of dilute acetic acid on precancerous or cancerous lesions triggers whitening of these regions as an effective low-cost method used to detect, triage and refer patients appropriately for subsequent treatment.
Components, accessories, consumables	If 5% solution is not readily available and dilutions are to be made, use: • Glacial acetic acid or other high concentration acetic acid solution • Personal protective equipment: goggles, gloves, and lab coat • Distilled or boiled water • Glass container with lid for 3-5% diluted solution • Graduated cylinder and syringe (or small graduated cylinder).
Operational requirements	Dilutions are to be made fresh and used daily under ambient conditions. Concentrated acetic acid should be stored in original closed container between 15°C to 30°C with relative humidity ≤ 60% (non-condensing). Must be stored separately from oxidizing materials and alkaline substances.
Standards	Compliant with active versions (or equivalent) of: • International Pharmacopoeia (WHO); and/or • European Pharmacopoeia; and/or • US Pharmacopeia. Globally Harmonized System of Classification and Labelling of Chemicals (GHS).

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Section 1 – Screening and Diagnostic Tools

Chapter 4: Technical guidance and specifications for colposcopes

4.1. Scope of chapter

This chapter specifies technical requirements for a colposcope, a device used to examine the lower genital tract epithelium, including tissues of the cervix, vulva, vagina, and anogenital areas.

Content herein focuses on present state of practice using up-to-date available technologies; however, authors are aware that innovations in manufacturing, healthcare facilities and practice will advance the field of cervical cancer screening, diagnostics and treatment. The specifications herein do not preclude appropriate upcoming products and/or technologies, which will be analysed in future revisions of this publication.

4.2. Background on the colposcope

Colposcopes aim to magnify and illuminate the cervix, across an area measuring approximately 20 to 30 mm in diameter, with enough distance between the colposcope lens and the cervix to accommodate the surgical instruments needed for the treatment. Historically, a colposcope contained 1) the colposcope head housing the optics; 2) the light source; and, 3) the body or stand. Over the years, whilst maintaining the original objective, modern colposcopes have leveraged advances in technology to facilitate visualization of the cervix. The use of a video camera and software allows the user to capture images and apply various coloured filters post-examination, which historically was achieved manually with light filters to provide green or blue light over the eyepieces during the examination. The use of video cameras also enables the recording of images and videos, magnification by the push of a button (whereas historically rough and fine focus adjustment knobs were used), and it has paved the way for colposcope miniaturization, making them portable.

Brief description

A colposcope is a low magnification, light-illuminated visualization instrument primarily used alongside screening tools for triaging, diagnosing and managing precancerous cervical lesions in women. It allows the examiner to view the epithelial tissues of the cervix and other anogenital areas. For purposes of cervical precancer assessment, it helps determine the transformation zone type and the grade of suspected epithelial abnormality. In addition, colposcopy facilitates and optimises biopsy and excisional treatment.

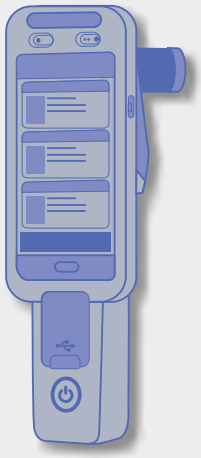
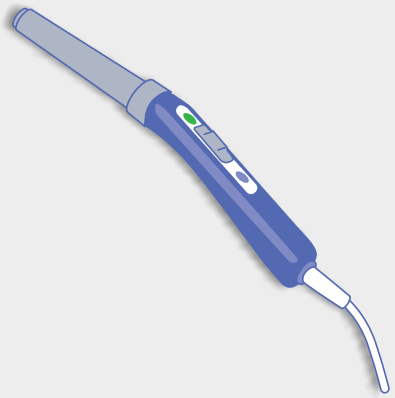
4.3. Types of colposcopes

Historically, binocular-type colposcopes were fully mechanical, and thus developed to comprise features that improved the optical ergonomics, including the use of convergent optical beam paths to avoid excess eye-strain, as well adjustable inter-pupillary distance, diopter adjustment, and removable eyecups. Features that improve overall workflow and support treatment procedures include an easily adjustable colposcope head with high freedom of movement (e.g. swing arm,) or adjustable base (e.g. good wheels, tilt stand, etc.) and option to lock the head in place for hands-free operation. Enhanced features, coupled with digital imagery, saw the advancement of digital or video colposcopes, which work with a degree of automation. Newer commercial designs of colposcopes incorporate traditional functions into far smaller packages, some of which use mobile platforms (e.g. mobile phones). [1,2] Table 6 describes these three different types, binocular, digital or video, and portable colposcopes, and compares their key technical features.[1,3]

Enhanced features, coupled with digital imagery, saw the advancement of digital or video colposcopes, which work with a degree of automation.

Table 6: Comparison table of types of colposcopes

Type	Binocular mounted colposcope	Digital or video mounted colposcopes
Image		
Brief description	Free-standing colposcopes provide a wide range of viewing angles. Such colposcopes can be mounted on pantographic arms, or single stand with height adjustment only. Power is only required for the light source.	These colposcopes are video cameras with LED lamps at the front of the optics. This is a digital lens system. A control panel at the back of the head is used for adjusting magnification, use of green filter, and image capture. These can be mounted on a height-adjustable stand.
Advantages	• Stereoscopic vision, useful for observing topography and vessel patterns of the cervix (depth of field, 3D); • Corrects for any near- or far-sightedness of the examiner.	• Can be handheld or mounted; • Autofocus of image if kept at a distance of 25–30 cm from the object; • Some models can record and store still or video images for future reference.
	• Hands-free once set-up and focused (and mounted if stand is available accessory).	
Limitations	• Heaviest, ranging from 10kg to 100kg with stand; • Restricted mobility – not portable; • Photo or video camera may be attached, though must be procured separately.	• Requires external monitor to see and interpret the two-dimensional images; • Requires different hand eye coordination compared to direct view with binocular colposcope.

Type	Portable colposcopes	
	Non-inserted	Vaginally inserted
Image		
Brief description	Portable colposcopes are lightweight and run on a battery. LED white light illuminates the cervix, green light filters may be applied during exam or on acquired image.	
	• Image displayed on mobile device.	• Image displayed on external screen.
Advantages	• Portable, <500g; • Battery operated (uses phone or laptop); • Low power requirements, draws off mobile phone/laptop • Can capture and store images.	
Limitations	• Mobile phone/laptop necessary for image viewing and capture must be procured separately; • May not work with all makes/models; • If optical zoom not featured, digital optics may be inferior; • Limited by mobile device sensor resolution.	
		• Invasive. Requires more stringent IPC measures (e.g. decontamination or single use sheaths).

When using a colposcope, the working distance, magnification and brightness are chosen by the clinician based on the patient anatomy, area of interest, and treatment procedures. Although not a feature unique to a colposcope, working distance is an important consideration to be made in procurement.

The colposcope should be operable from a standard working distance of 300 mm[4] (~12 inches), that is the lens at the front of the head is 300mm away from the surface of the cervix. This is usually fixed, although it may be variable to a degree to allow colposcopists to position themselves to the best advantage from the patient and other equipment for the procedure. This working distance also encompasses the length of the vagina, approximately 100 mm.[5] There are products on the market in the "portable" category that capture imagery internally and thus the notion of working distance does not apply.

When using a colposcope, the working distance, magnification and brightness are chosen by the clinician based on the patient anatomy, area of interest, and treatment procedures.

4.4. Equipment requirements

The following describes elements of a colposcope and considerations to be made in device selection.

Magnification: There shall be a range of optical magnification between 3x to 15x on the colposcope. This may be stepped magnification but it can be continuously variable. Greater magnification, between 20x to 30x, allows for closer inspection of fine vasculature.[5] When magnifying using both optical and digital zoom, ensure that final image resolution is at least 2 megapixels for clinical diagnosis.[6]

Illumination: Illumination is required for colposcopy to aid visualization at higher magnifications.[6] Light sources shall consist of good, even, full-spectrum visible light (white light), preferably halogen (15V/150W) or LED (20,000-35,000 LUX at 300mm working distance).

Colposcopes should have an illumination adjustment knob to change the intensity of light, a fan to cool the lamp bulbs (if halogen bulbs are used) , and facility for filters. The bulb should be easily changeable. Halogen lightbulbs are powerful and easily replaceable but generate heat. Light-emitting diode (LED) lamps are longer lasting and do not generate heat.[7]

Green light filters: Green light filters are used to visually enhance vascularization.[8] Deep red vasculature typically appears black under green light, which is particularly useful when assessing fine vessel changes. Filters may be used during examination or after examination, when processing images. Blue filters are also acceptable but not the preferred option.[8]

4.4.1. Additional requirements

The following detail some features to be considered; however, are not considered mandatory for colposcope functionality.

Mobility and portability: Size and manœuverability may be important if the colposcope is to be used in more than one room or clinic, or even in outreach. Therefore, the stand must be easily moved and may be placed in a fixed position during visualization.

Monitor display and quality: Most video colposcope manufacturers enable a connection between the colposcope and a computer. Specific software installed on the computer can capture and store images. Another option is to connect the colposcope directly to a LED TV or medical grade monitor using a HDMI, VGA or other video cable connection. This latter option avoids the cost of software, requires less hardware and thus maintenance. Either option may be chosen depending on the needs and budget of the health care centre.

Most video colposcope manufacturers enable a connection between the colposcope and a computer.

If indirect visualization is used and the image is displayed on an external screen, display quality such as resolution (minimum 2 megapixel), light intensity (luminance range 0.8-250 cd/m^2), and colour replication (standard red green blue, sRGB) are important due to the subjective nature of colposcope.[7]

Compatibility for use during treatments: When the target visualization is achieved, the colposcope should allow for continued use during treatment interventions (e.g., thermal ablation, cryotherapy or LLETZ). The colposcope head or mobile phone-based system may be attached to a weighted pantographic arm or a stand to facilitate hands-free operation.

4.4.2. Chemical agents

Visualization may be aided by applying chemicals such as normal saline, 3-5% acetic acid (see Chapter 2), or Lugol's solution (5g iodine + 10 gm potassium iodide + 100 ml distilled water)[4] to the cervix to highlight any precancerous lesions.

4.4.3. Power source/mains

Regardless of type of colposcope, there must be a reliable electrical power supply (220V or 120V, and 50 or 60 Hz, according to different national standards) accessible in the examination room or facility to allow for use and/or charging.

4.5. Operational considerations

4.5.1. How to use a colposcope

Before clinical application, it is important that the user of the colposcope familiarize themselves with the device: its mechanics for tension, magnification, focus, etc.; its electronics for light function; its accessories that facilitate functionality, such as filters; and, any other components.

Before clinical application, it is important that the user of the colposcope familiarize themselves with the device.

Setting up and operating a colposcope[7]:

1. Adjust the colposcope head to the appropriate working height of the clinician;

2. Turn on the observation light;

3. Locate controls for rough and fine focus adjustments, for binocular non-powered colposcopes, or zoom function, for video and mobile phone-based technologies;

4. Perform optical adjustments:

a. Center optics or camera on the cervix;

b. Adjust magnification and focus.

5. Locate the green filter switch or swing in or swing out green filter, as required;

6. Turn off the colposcope after use and stow away appropriately.

Appropriate clinical training should be provided in advance of using colposcopes. Furthermore, tele-medicine opportunities can be leveraged by digital capture and electronic sharing of an image. It is necessary to establish and/or maintain an on-going, competency-based capacity-building program to sustain clinical practice with all in-service programs, tools and resources, based on the standard clinical guidelines and local CMS pedagogy. Please refer to guidance provided in WHO's Comprehensive Cervical Cancer Control: a guide to essential practice.[9]

Appropriate clinical training should be provided in advance of using colposcopes.

4.5.2 Training tools

The WHO international Agency for Research on Cancer has recently developed the *Atlas of Colposcopy*[10] including training videos which can be seen at www.iarc.fr/media-centre/media-centre-iarc-news-atlas-colposcopy and https://screening.iarc.fr/colpochap.php?lang=1&chap=4 to demonstrate images for diagnostics using VIA, or other to treat cervical cancer.

4.5.3. Decontamination and reprocessing

Health care-associated infections (HAI) are one of the most common adverse events in healthcare delivery. Not only do they have a significant impact on morbidity and mortality, but they also present an economic burden to health care facilities and countries. As part of a larger infection prevention and control (IPC) program[11], decontamination of instruments and medical devices plays a critical role in HAI prevention.

The PAHO/WHO manual titled Decontamination and reprocessing of medical devices for health-care facilities[12] outlines the decontamination life cycle, which includes cleaning, disinfection and sterilization. Please refer to this manual for details on specific methods of decontamination, sterilization and reprocessing of medical devices. Always follow the device manufacturer's instructions for decontamination so as to not cause any damage and ensure proper decontamination.

Specific to colposcopes, it is important to not use harsh or corrosive cleaning agents on any part of the device as they can cause damage not only to the surface, but also to the mechanics. In addition to decontamination per the manufacturer's instructions for use and WHO guidelines, the following specific daily care requirements for the colposcope should include:

- Cleaning the lens(es) with alcohol, a watery soap solution, or any commercial lens cleaner
- Wiping the lens(es) with a soft, lint-free cloth.

Other tools and materials used in procedures where colposcopes are used (for example specula) should be cleaned and disinfected or sterilized, as appropriate, between patients.

4.5.4. Health-care Waste Management

Knowledge about the potential for harm due to healthcare waste has become more important to governments, health care workers and civil society. Improper handling and disposal of healthcare facility waste is widely recognized as a source of avoidable infection; therefore, it is critical for healthcare facilities to appropriately manage disposal of healthcare waste, including but not limited to hazardous waste. Hazardous waste includes sharps, infectious waste (contaminated with blood and other body fluids), pathological waste (such as human tissue) and chemical waste. For details on how to dispose of hazardous waste, please refer to facility and/or local guidelines and regulations and the WHO manual titled Safe management of wastes from health-care activities.[13]

Any consumables (swabs, cotton balls, gloves) should be disposed of using the appropriate protocols for the health facility.

4.5.5. Storage and packaging

Labelling on the primary packaging should include the name and/or trademark of the manufacturer and should adhere to the most current version of ISO 15223 – 1: Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied -- Part 1: General requirements. Depending on the country, specific requirements for the information to be provided on the label may exist, such as the requirement for specific languages, warnings and regulatory conformity symbols.

As a minimum, the storage area should be clean and dust-free, dry, cool, well-lit, ventilated and vermin-proof. The device should be stored in its original packaging on a shelf or on in a storage cabinet.

As a minimum, the storage area should be clean and dust-free, dry, cool, well-lit, ventilated and vermin-proof.

In recognizing that environmental conditions in many LRS are quite varied and can be extreme, **it is the responsibility of the procurement body to ensure the expected storage conditions are within the manufacturer's storage recommendations for any specific device**. If the device will require that the storage environment be climate-controlled, appropriate temperature and humidity control systems, including monitoring, should be applied to avoid malfunctioning.

However, in general, these devices should be able to withstand storage temperatures ranging from 15°C to 40°C, relative humidity ≤ 85% (non-condensing), and be protected from dripping water.

4.5.6. Maintenance and repair

Standard colposcopes, not in direct contact with the patient, require little maintenance. Besides care of the device through cleaning and disinfection with non-corrosive agents and soft cloths, the user should know basic maintenance (such as how to change a bulb). Other maintenance should not be required.

If a device appears damaged or does not function as expected (for example, if it will no longer illuminate, magnify the image or provide a clear and focused image), it should immediately be taken out of service for repair or replacement. Standard colposcopes may require replacement of worn parts including lamps, eyepiece rings, light guides and fuses. Follow the manufacturer's service manual, as instructions are specific to each colposcope model. Service manuals should be provided in the preferred language of the clinical technicians or engineers, or in English as a minimum. Procurers should ensure they procure colposcopes suited for the local power supply.

4.5.7. Software as a medical device

New software packages are emerging that can facilitate remote training or confirmatory assessment using decision-assist mobile platform applications ("apps") or artificial intelligence (AI). In this context of cervical assessments, AI is being used to assess a portfolio of images as part of a machine-learning based algorithm to classify the images to assist with the diagnosis of precancerous lesions. Whether or not the software uses AI, if it is "…intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device", then it is defined as a medical device (SaMD) by the IMDRF.[14] By this definition, software packages that facilitate diagnosis (including, but not limited to AI) are considered medical devices and must be treated as such from a regulatory, quality procurement and user perspective.

New software packages are emerging that can facilitate remote training or confirmatory assessment using decision-assist mobile platform applications ("apps") or artificial intelligence (AI).

4.6. Quality Management Systems and post-market surveillance

A quality management system delineates a systematic approach to ensure ongoing quality of outputs. It is critical that all products are manfactured within a robust quality management system at the manufacturer. A QMS includes but is not limited to: standard operating procedures, documentation, design and manufacturing controls and third-party assessments. Maintenance of a QMS requires appropriate human resources and their management, infrastrucutre, timely and appropriate procurement, stock management, maintenance, and a rigorous pre- and in-service training curriculum.

Post-market surveillance is an obligation of the medical device manufacturer in order to investigate and act on any adverse event and product failure and/or error. One of the most relevant sources of information to the post-market surveillance plan are the complaints made by end-users when an issue is detected. The manufacturer should conduct a root cause analysis and determine whether the risk/benefit ratio is maintained. In addition, sometime there are malfunctions or a deterioration in the characteristics and/or performance of the device that might lead to or might have led to the death. These situations are called incidents and the manufacturer must report them to the competent authorities as per vigilance reporting systems. The field safety corrective actions, such as a recall or changes implemented to the product (including labelling), are notified by the manufacturer through a field safety notice to the National regulatory agencies / authorities (NRA), which will also conduct their own market surveillance activities and oversee the manufacturer's investigation incidents and complaints. WHO guidance on QMS and post-market surveillance for medical devices can be found in WHO Global Model Regulatory Framework for Medical Devices including in vitro diagnostic medical devices.[15]

4.7. Standards and regulatory compliance

- Medical device quality, performance, operations, and safety: ISO 13485, ISO 14971, ISO 15223-1 (See Chapter 4.8 and Annex 4);
- Biocompatibility: ISO 10993, all applicable parts (See Chapter 4.8 and Annex 4).
- Electrical safety: IEC 60601, all applicable parts (See Chapter 4.8 and Annex 4); additionally,
- Endoscope general requirements: ISO 8600- parts 1, 3, 4, 5 and 6 (There is no specific standard for colposcopes but they are of the endoscopy family).

It is important to observe all applicable national laws and regulations related to medical devices manufacturing, procurement and/or use. In the absence of a medical devices regulatory agency, it is strongly recommended to consider which regulatory and/or normative body assessment was completed for each product prior to making a procurement decision. The risk class depends mainly on the regulatory framework of a country and therefore it may differ according to jurisdiction. For more details with regard to other regional regulations and standards, see the specifications table in Chapter 4.8 and in Annex 4.

It is important to observe all applicable national laws and regulations related to medical devices manufacturing, procurement and/or use.

4.8. Key tender/request for quotation specifications for a colposcope

Following are the key features that may be noted in a tender or request for quotation; see Annex 4 for detailed standardized WHO technical specifications.

Product description	A colposcope is a low magnification light-illuminated visualization instrument primarily used alongside screening tools for screening, diagnosing and managing precancerous cervical lesions in women. It allows the examiner to view the epithelial tissues of the cervix and other anogenital areas. For purposes of cervical precancer assessment, it helps determine the transformation zone type and the grade of suspected epithelial abnormality. In addition, colposcopy facilitates and optimises biopsy and excisional treatment.
Key product features	• **Magnification:** A range of optical magnification between 3x to 15x (either stepped or continuously variable); • **Illumination:** » Light sources shall be either halogen or LED to guarantee full-spectrum visible light (white light): * Halogen light: 15 V/150 W * LED: 20,000-35,000 LUX (at 300 mm working distance). » An illumination adjustment knob to change the intensity of light; » A fan to cool the bulbs (if halogen bulbs are used). • **Green light filters;** however, blue filters are also acceptable but not the preferred option.
Components, accessories, consumables	• Stand or mount to allow for hands-free operation • LED TV or medical grade monitor if not integrated (optional) • Single-use sheath (if using invasive portable model).
Operational requirements	• Temperature: 15°C to 35°C • Relative humidity: ≤85% • (Storage temperature: 15°C to 40°C, 85%, non-condensing) • Ingress protection rating: IPX2 • The unit is suggested to be connected to a reliable power source • Electrical source requirements (based on country/setting of use): » Amperage: _____ » Voltage: _____ » Plug type: _____.
Documentation requirements	• Instructions for use and service manuals to be provided • User language preference prioritized, otherwise English is mandatory.
Warranty	Minimum one year.

Standards

Following the active version of the standards below (or equivalent):

- ISO 13485: Medical Devices - Quality Management Systems - Requirements for Regulatory Purposes;
- ISO 14971: Medical Devices - Application of Risk Management to Medical Devices;
- ISO 15223-1: Medical devices -- Symbols to be used with medical device labels, labelling and information to be supplied -- Part 1: General requirements.

Safety & product standards:

- IEC 60601-1 - Medical electrical equipment - Part 1: General requirements for basic safety and essential performance;
- IEC 60601-1-2: Medical electrical equipment - Part 1-2 General requirements for basic safety and essential performance - Collateral Standard: Electromagnetic disturbances - Requirements and tests.

For vaginally-inserted colposcopes:

- Biocompatibility:
    - » ISO 10993-1: Biological evaluation of medical devices Part 1: Evaluation and testing within a risk management process;
    - » ISO 10993-5: Biological evaluation of medical devices Part 5: Tests for in vitro cytotoxicity;
    - » ISO 10993-10: Biological evaluation of medical devices Part 10: Tests for irritation and skin sensitization;
- Endoscopy (pertaining to inserted scope):
    - » ISO 8600-1: Endoscopes – Medical endoscopes and endotherapy devices – Part 1: General requirements;
    - » ISO 8600-3: Optics and optical instruments – Medical endoscopes and endoscopic accessories – Part 3: Determination of field of view and direction of view of endoscopes with optics;
    - » ISO 8600-4: Endoscopes – Medical endoscopes and endotherapy devices – Part 4: Determination of maximum width of insertion portion;
    - » ISO 8600-5: Optics and photonics – Medical endoscopes and endotherapy devices – Part 5: Determination of optical resolution of rigid endoscopes with optics;
    - » ISO 8600-6: Optics and photonics – Medical endoscopes and endotherapy devices – Part 6: vocabulary.

Regulations	Compliance with (where applicable, but not limited to): • National regulatory Authority requirements compliance; • Approval by regulatory body of country of manufacturer (if applicable). • Suggested, compliance with the legal requirements from at least one of the following regulatory frameworks: • United States regulations: US FDA Device Class II; • European regulatory framework: » Council Directive 93/42/EEC of 14 June 1993 on Medical Devices (Class IIa); » Regulation (EU) 2017/745 of the European Parliament and the Council; » Manufacturer must affix the CE marking and indicate the Notified Body number on the label and in the device, when possible. • Other regulatory body in an IMDRF founding member country such as Australia, Canada, or Japan.

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Section 2 – Treatment technologies

This section includes three technologies that can be used for the treatment of precancerous lesions. The selection of one technology over another, or using a mix of technologies would depend on several factors including, but not limited to: the nature of the cervical lesion, available healthcare workforce, level of training and specialty area of healthcare providers, availability of technical support, financial resources, supportive infrastructure (water, electricity, CO_2 and/or N_2O gas access), and other technological resources available. Table 7 presents the different technologies that can be used for treatment of precancerous lesions: thermal ablation, cryotherapy, and LEEP.

Table 7: Comparison overview of technologies to treat cervical lesions

	Thermal Ablation	Cryotherapy	LLETZ (LEEP)
Brief description	Destroys tissue by heating	Destroys tissue by freezing	Removes tissue by cutting, allowing for biopsy of removed tissue
Infrastructure requirements	Requires reliable power supply	Requires continuous reliable power supply (if using electrically cooled cryosurgery units)	Requires continuous, reliable power supply
Operator qualifications required	Basic	Skilled	High skill and specialized training required
Required accessories or consumables	N/A	Continued supply of medical gas or reservoir solution	Smoke evacuation device
Cost considerations	Initial equipment cost only, and maintenance costs	Ongoing cost of consumables, specially medical gas, and infrastructure requirements	Initial cost, plus maintenance, consumables and additional capital cost of smoke evacuation system
Advantages	Can be battery operated, enabling portability		Biopsy of lesion is possible. Electro Surgical Unit (ESU) can be used for other procedures
Limitations	Biopsy of lesion is not possible	Biopsy of lesion is not possible	• Operator qualifications and haemorrhage risk limit the use this procedure in lower level settings • Smoke evacuation device highly recommended

Each of these types of technologies will be further explained in the following chapters.

Chapter 5:
Technical guidance and specifications for thermal ablation devices

5.1. Scope of chapter

This chapter specifies technical requirements for a thermal ablation system, a device which uses heat to treat cervical intraepithelial neoplasia (CIN). Although thermal ablation has not been evaluated as widely as cryotherapy, it has been used effectively in some settings dating back to 1966[1,2,3] and has been deemed as effective as cryotherapy in treating all grades of CIN lesions. More recently, rechargeable, battery-driven portable devices have come onto the market, making the method more suitable for LRS.

Content herein focuses on present state of practice using up-to-date available technologies; however, authors are aware that innovations in manufacturing, healthcare facilities and practice will advance the field of cervical cancer screening, diagnostics and treatment. The specifications herein do not preclude appropriate upcoming products and/or technologies

Brief description

Thermal ablation devices use a heated probe tip to destroy cervical tissue with abnormal cell growth:

- The probe should be easily directed to the target tissue;
- Visual and/or audible cues communicate to the clinician when the target temperature has been reached and the appropriate treatment time has elapsed;
- The target temperature for treatment is 100°C;
- The probe tips should be round in shape, ranging from 8mm to 25mm in diameter, should not stick to cervical tissue, and be easy to decontaminate between patients;
- Units are AC or battery powered.

5.2. Background on thermal ablation devices

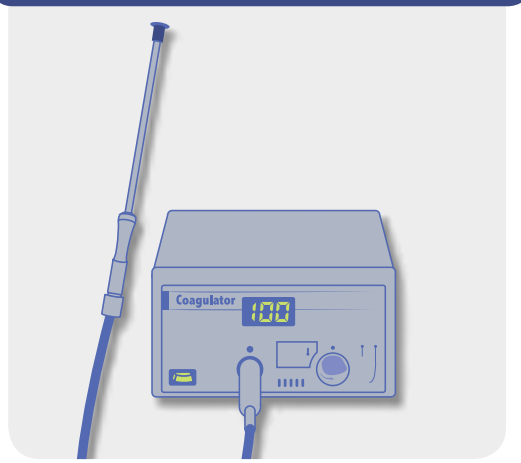
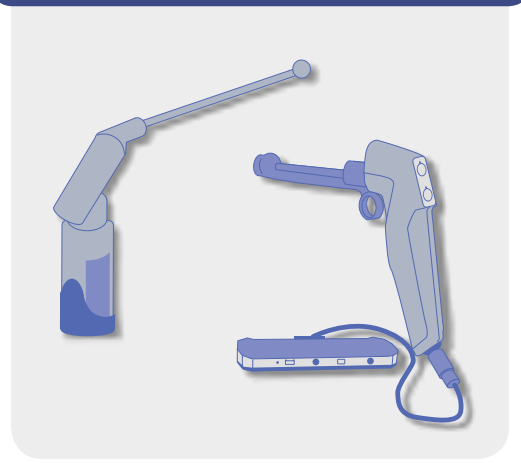
A thermal ablation device is a self-contained, electrically powered medical instrument designed to destroy tissue of the uterine cervix with low-grade heat. It may also be referred to as thermal coagulation or Semm cold coagulation, after the inventor of the device . The term "cold" has been used due to a treatment temperature of 100°C, which is lower than that used for standard clinical electrocautery (usually between 400-600°C).[4,5] At this treatment temperature, there is no charring or smoke plume to evacuate, an advantage if multiple applications are performed during a single treatment.[3,7] Thermal ablation is similar to cryotherapy (see Chapter 6), sharing the same intended use, albeit by a different mechanism.

Thermal ablation is appropriate for use in LRS because it is effective (documented effectiveness range between 87-97%[3]), has limited side-effects, is inexpensive compared with other treatment options, and is technically simpler to implement. It can be portable and does not require compressed gases. Treatment time recommended is 20-30 seconds per application, and it is common that up to 4 to 5 applications are necessary to cover the entire transformation zone.

5.3. Types of thermal ablation devices

There are generally two types of units, the handheld and the benchtop. Table 8 illustrates both, with descriptions of each model type.

Table 8: Comparison between benchtop and handheld thermal ablation devices

Type	Benchtop	Handheld
Image		
Brief description	Current benchtop models are no larger than 30 x 15 x 20 cm and weigh about 3.5 kg; thus, it can be transported but is not considered to be "portable". The probe including tip and shaft is attached to the handle, which is connected to the main unit by a cable.	Handheld thermal ablation devices, such as those that can be easily carried in a case or backpack (including accessories), comprise of a handle and a detachable probe, which has an integral tip that is applied to the lesion. Features may vary from one make to another, and parts are not interchangeable.
Product features	Stationary (~3.5 kg)	• The handle is fitted with one or more integrated controls located such that they can be operated with one hand; • The handle may have an integrated light source to aid in visualizing the cervix; • These are powered by a rechargeable and interchangeable battery and can treat at least 30 patients (minimum cumulative run-time of 1 hour on a single charge); back-up batteries should always be charged, ready for use.
Limitations	• Requires reliable electricity • Not portable.	• Procurement of back-up batteries required.

5.4. Equipment Requirements

The probe shaft and tip should be made from surgical-grade materials; the **probe shaft** should either itself be thermally-insulated or have a guard to prevent burns to the vaginal walls. If a protective sleeve is used over the probe, it needs to be cleaned and disinfected between patients. Illumination with a light source or from the thermal ablation unit itself is an advantage to workflow.

The depth of necrosis should be sufficient to destroy the tissue by ensuring the underlying tissue reaches a temperature of 100°C.[8,9] The device should prevent temperatures higher than that required for ablation and should have an automatic timer to control the duration of heat application.

The handle of either the benchtop or handheld unit shall be made of a material that can withstand routine cleaning. The probe (shaft and tip) should be removable to facilitate decontamination.

Environmental operating conditions for these units are from 5-40°C and relative humidity of ≤85%, non-condensing. Benchtop device should have grounding to prevent shock or leakage of electricity.

The depth of necrosis should be sufficient to destroy the tissue by ensuring the underlying tissue reaches a temperature of 100°C.

5.4.1. Probes

Probes shall be removable to allow for the interchange between various shapes and sizes, depending on need, as well as to facilitate decontamination. The following provides guidance on shape, size, material and other relevant details of the probes to be included or considered for procurement, regardless of whether benchtop or handheld units are being used:

Shape: The surface of the tip that contacts the cervix should be smooth with no sharp edges. A flat probe is always necessary to ensure full ablation of the transformation zone; however, nipple-shaped probes with an extrusion not exceeding 5 mm are very useful to anchor the probe to the centre of the cervix (see Figure 7). *(Note: conical tips or probes that extend into the endocervix should not be used for thermal ablation treatment of precancerous cervical lesions.)*

Dimensions: probe tip diameters may range from 8 mm to 25 mm, where common sizes are 8 mm, 12 mm, 16 mm, 19 mm and 25 mm (larger diameters are only suitable for use on large parous cervices and thus do not have as broad an application as smaller-sized probe tips). Multiple probe tip sizes should be available. The overall length of the probe with tip should be between 170 and 200 mm (see Figure 9).

Material: The surface of the probe should not easily adhere to the tissue. Probe tips may be coated with a non-stick material, such as polytetrafluoroethylene (PTFE) or polyether ether ketone (PEEK), which is non-cytotoxic and fit for in vitro use. The probe shaft should be rigid so that it cannot flex during normal use, and be thermally insulated to help prevent accidental burns to any tissue that it may come into contact with, such as the vaginal wall. All materials must be capable of routine decontamination (high-level disinfection, HLD, and sterilization – see Chapter 5.5.2.).

Probes shall be removable to allow for the interchange between various shapes and sizes, depending on need, as well as to facilitate decontamination.

Figure 10: Shapes for probe tips, not specific to thermal ablation (for illustrative purposes only)

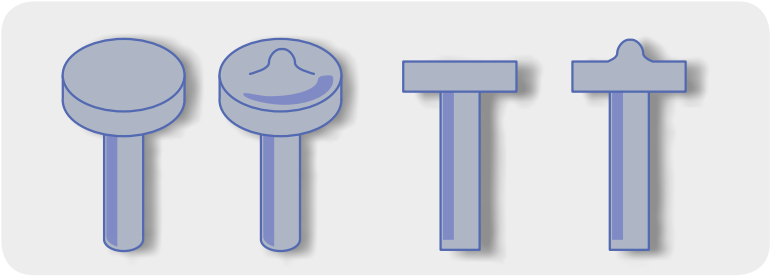
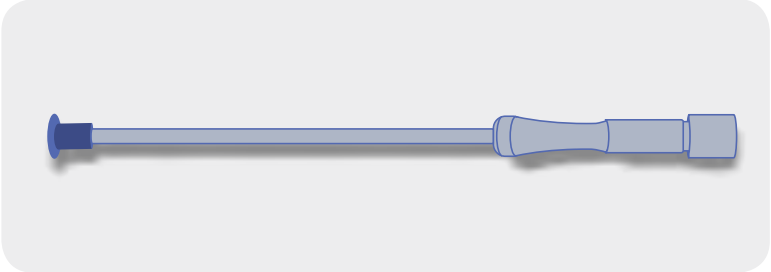


Figure 11: Image of probe-tip illustrating a nipple-tip extrusion

Figure 12: Image of integrated probe tip, shaft, and handle for a variety of probe tip shapes.



5.4.2. Additional Requirements

5.4.2.1. Accessories

The thermal ablation devices are used with a speculum for viewing and accessing the cervix[10] (see Chapter 1) and a light source (external or built-in) of at least 100W or 100W-LED equivalent, and/or a magnification lamp to improve visualization during the procedure. It is recommended that any such light source provide the white light spectrum, similar to daylight. Yellow, tungsten-based light sources should be avoided if possible.[11]

5.4.2.2. Power source/mains

Regardless of type of thermal ablation device, there must be a continuous, reliable electrical power supply (220V or 120V, and 50 or 60 Hz, according to different national standards) accessible in the exam room or facility to allow for use and/or charging.

For battery-powered devices, consideration should be given to how many patients need to be treated between charge cycles. A battery with a cumulative run-time of at least 1 hour should be capable of treating at least 30 patients, which should accommodate outreach activities such as mobile clinics. In addition, a back-up battery with the same capacity should be considered and should always be charged, ready for use.

For battery-powered devices, consideration should be given to how many patients need to be treated between charge cycles.

Should a device with battery power be procured, the user should have access to battery replacements as the batteries might not last the entire life span of the device. The user should refer to manufacturer guidelines for storage and usage instructions.

5.5. Operational considerations

Continued research into thermal ablation devices, standardized treatments (ideal probe size, timing of each ablation cycle to ensure the entire squamocolumnar junction (SCJ) zone is ablated) and other low-cost, effective, reliable, and quality treatment devices will aid the efforts to eventually eliminate cervical cancer.

5.5.1. How to use a thermal ablation device

It is important that the user be familiar with the thermal ablation instrument(s), and that the instructions for use are read prior to performing any treatments as there may be differences between products. When using a thermal ablation device:

1. Ensure the device will be used under optimal operating conditions, according to manufacturer's recommendations;

2. Select the appropriate device-specific probe with probe tip for the intended treatment and connect to the unit (benchtop models have cables, handheld units do not);

3. Set the probe to the required temperature (if applicable) and ensure probe tip is not in contact with any heat sensitive material when it is turned on;

4. Note that some probes must reach required temperature prior to vaginal insertion, whereas others are intended to reach the required temperature after vaginal insertion.

The following optional device functionalities will affect workflow; the user should be aware of which features their device has and prepare for their work accordingly:

- Automatic heating to a pre-set target temperature (100°C) with a single switch button can help workflow when treating many patients;

- Visual or audible cues to indicate how much time has elapsed in the treatment cycle (though use of a stopwatch is perfectly acceptable);

- Availability of extra, swappable and quick-charging batteries, if portable;

- Automatic shut-off at the end of a treatment cycle can help to conserve battery power between treatments.

Appropriate clinical training should be provided in advance of using thermal ablation units. It is necessary to establish and/or maintain an on-going, competency-based capacity-building program to sustain clinical practice with all in-service programs, tools and resources, based on the standard clinical guidelines and local CMS pedagogy. Please refer to guidance provided in the WHO guidelines for the use of thermal ablation for cervical pre-cancer lesions.[12]

It is important that the user be familiar with the thermal ablation instrument(s), and that the instructions for use are read prior to performing any treatments as there may be differences between products.

5.5.2. Decontamination and reprocessing

Health care-associated infections (HAI) are one of the most common adverse events in health care delivery. Not only do they have a significant impact on morbidity and mortality, but they also present an economic burden to health care facilities and countries. As part of a larger infection prevention and control (IPC) program[13], decontamination of instruments and medical devices plays a critical role in HAI prevention.

The PAHO/WHO manual titled Decontamination and reprocessing of medical devices for health-care facilities[14] outlines the decontamination life cycle, which includes cleaning, disinfection and sterilization. Please refer to this manual for details on specific methods of decontamination, sterilization and reprocessing of medical devices. Always follow the device manufacturer's instructions for decontamination so as to not cause any damage and ensure proper decontamination.

The probe shaft and tip form an integral unit; thus, it is decontaminated and reprocessed as one. Equipment and accessories in direct contact with the patient must be decontaminated according to manufacturer's instructions for use and local protocol. The rest of the device is to be cleaned and/or disinfected. Solutions for cleaning and disinfection need to be used according to the manufacturer's instructions as their specified disinfectant exposure time must be observed.

Other tools and materials used in thermal ablation (for example specula) should be cleaned and disinfected and sterilized, as appropriate, between patients.

5.5.3. Health-care Waste Management

Knowledge about the potential for harm due to healthcare waste has become more important to governments, health care workers and civil society. Improper handling and disposal of healthcare facility waste is widely recognized as a source of avoidable infection; therefore it is critical for healthcare facilities to appropriately manage disposal of healthcare waste, including, but not limited to, hazardous waste.

Hazardous waste includes sharps, infectious waste (contaminated with blood and other body fluids), pathological waste (such as human tissue) and chemical waste. For details on how to dispose of hazardous waste, please refer to facility and/or local guidelines and regulations and the WHO manual titled Safe management of wastes from health-care activities.[15]

Any consumables (swabs, cotton balls, gloves) should be disposed of using the appropriate protocols for the healthcare facility.

5.5.4. Storage and packaging

Labelling on the primary packaging should include the name and/or trademark of the manufacturer and should adhere to the most current version of ISO 15223 – 1: Medical devices -- Symbols to be used with medical device labels, labelling and information to be supplied -- Part 1: General requirements. Depending on the country, specific requirements for the information to be provided on the label may exist, such as the requirement for specific languages and warnings.

As a minimum, the storage area should be clean and dust-free, dry, cool, well-lit, ventilated and vermin-proof. The device should be stored in its original packaging on a shelf or on in a storage cabinet.

In recognizing that environmental conditions in many LRS are quite varied and can be extreme, **it is the responsibility of the procurement body to ensure the expected storage conditions are within the manufacturer's storage recommendations for any specific device**. If the device will require that the storage environment be climate-controlled, appropriate temperature and humidity control systems, including monitoring, should be applied to avoid premature material disintegration.

However, in general, these devices should be able to withstand storage temperatures ranging from 15°C to 40°C, relative humidity ≤ 60% (non-condensing), and be protected from dripping water.

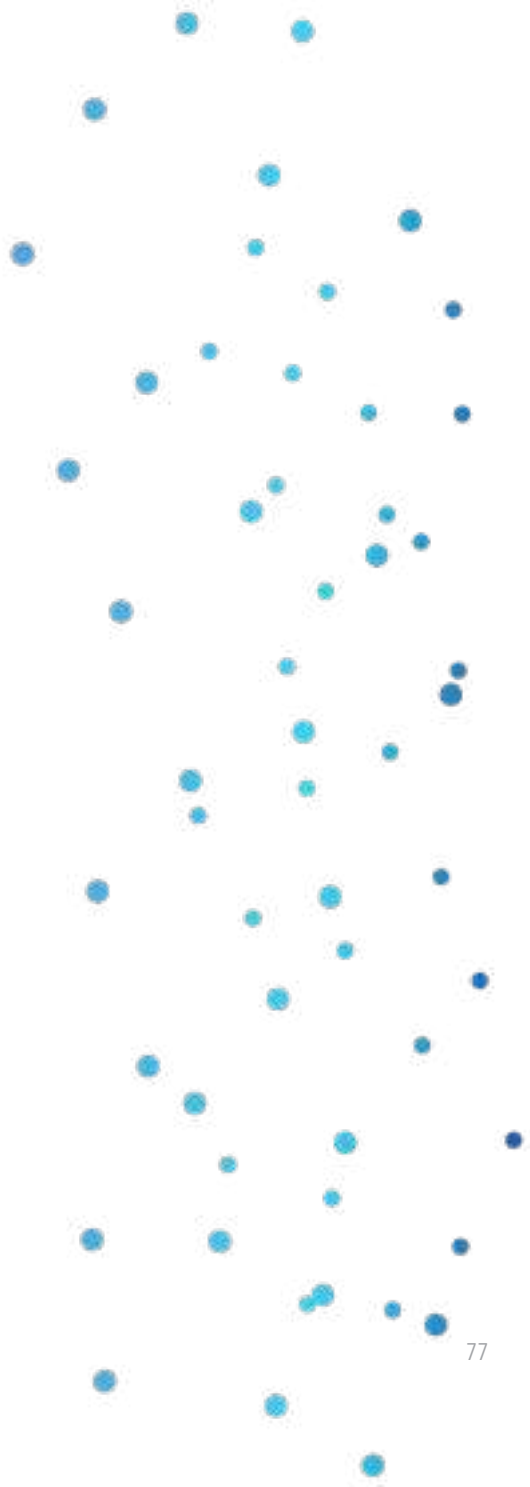
5.5.5. Maintenance

Depending on the unit, maintenance procedures will vary. Self-contained, portable devices shall have manufacture certification and contain microprocessors capable of internal checks to verify that the probe and handle are working properly. For benchtop models, daily functional tests should be conducted and it should be serviced on a regular basis for the service life of the device

Any requisite PPM, outlined in the service manuals, shall be duly carried out so as to prolong the use-life of the device. Any technical service as such, including PPM, shall be performed by the original equipment manufacturer or trained clinical engineering professionals.

If a device appears damaged or indicates a different visual cue during set-up or operation, it should immediately be taken out of service. Ensure coating covers probe tip and remains intact. Rechargeable batteries should be replaced and disposed of according to the manufacturer's instructions.

As a minimum, the storage area should be clean and dust-free, dry, cool, well-lit, ventilated and vermin-proof.



5.6. Quality Management Systems and post-market surveillance

A quality management system delineates a systematic approach to ensure ongoing quality of outputs. It is critical that all products are manfactured within a robust quality management system at the manufacturer. A QMS includes but is not limited to: standard operating procedures, documentation, design and manufacturing controls and third-party assessments. Maintenance of a QMS requires appropriate human resources and their management, infrastrucutre, timely and appropriate procurement, stock management, maintenance, and a rigorous pre- and in-service training curriculum.

Post-market surveillance is an obligation of the medical device manufacturer in order to investigate and act on any adverse event and product malfunction or failure. Post-market surveillance typically consists of complaint handling by end-users when an issue is detected. When information is made known to the product manufacturer, they must determine if the risks have increased and whether the benefits of the product outweigh the harms or risks. Any field safety corrective actions, such as a recall or change to the product (including labelling), are notified by the manufacturer through a field safety notice. National regulatory agencies / authorities (NRA) will also conduct their own market surveillance and oversee the manufacturer's investigation of complaints WHO guidance on QMS and post-market surveillance for medical devices can be found in WHO Global Model Regulatory Framework for Medical Devices including in vitro diagnostic medical devices.[16]

5.7. Standards and regulatory compliance

Thermal ablation devices are a type of medical devices so the following standards categories apply:

- Medical device quality, performance, operations, and safety: ISO 13485, ISO 14971, ISO 15223-1 (See Chapter 5.8 and Annex 5);
- Biocompatibility: ISO 10993, all applicable parts (See Chapter 5.8 and Annex 5);
- Electrical safety: IEC 60601, all applicable parts (See Chapter 5.8 and Annex 5);
- Secondary cells (batteries): IEC 62133, parts 1 and 2 – if applicable (See Chapter 5.8 and Annex 5).

It is important to observe all applicable local laws and regulations related to medical devices and their manufacturing, procurement and use. In the absence of a regulatory agency, it is strongly recommended to consider which regulatory and/or normative body assessment was completed for each product prior to procurement decisions. The risk class depends mainly on the regulatory framework of a country and therefore it may differ according to jurisdiction. For more details with regard to other regional regulations and standards, see the specifications table in Chapter 5.8 and in Annex 5.

It is important to observe all applicable local laws and regulations related to medical devices and their manufacturing, procurement and use.

5.8. Key tender/request for quotation specifications for a thermal ablation device

Following are the key features that may be noted in a tender or request for quotation; see Annex 5 for detailed standardized WHO technical specifications.

Product description	Thermal ablation devices use a heated probe tip to destroy cervical tissue with abnormal cell growth. They are available in benchtop console form or can be battery operated and portable.
Key product features	• Probe tip temperature controlled to reach 100°C • Visual and/or audible cues to ensure working temperature reached • Simple and easy to use, appropriate for all levels of care.
Components, accessories, consumables	• Minimum of 2 probe tips required: » One probe must be flat; » The second probe can be either flat or can have a gentle nipple extrusion not exceeding 5mm (so as to anchor in centre of cervix but not to ablate endocervix); » Probes should not have any sharp edges; » Varying diameters, ranging from 8 mm to 25 mm; » Biocompatible, material that will not adhere to cervix; » Reusable and thus decontamination is needed.
Operational requirements	• Temperature: 15-35°C; • Relative humidity: ≤85% (non-condensing); • Ingress protection: » Console: IP21 » Instrument cable, therapy probe: IPX7. • (Storage temperature: 15-30°C, storage relative humidity: ≤60%, non-condensing); • The unit is suggested to be connected to a reliable power source; • Electrical source requirements (based on country/setting of use): » Amperage: _____ » Voltage: _____ » Plug type: _____.

Documentation requirements	• Instructions for use and service manuals to be provided • User language preference prioritized, otherwise English is mandatory.
Warranty	Minimum one year
Standards	Following with active version of the standards listed below (or equivalent). General manufacturing: • ISO 13485: Medical Devices - Quality Management Systems - Requirements for Regulatory Purposes; • ISO 14971: Medical Devices - Application of Risk Management to Medical Devices; • ISO 15223-1: Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements. Safety & product standards: • IEC 60601-1 - Medical electrical equipment - Part 1: General requirements for basic safety and essential performance; • IEC 60601-1-2: Medical electrical equipment - Part 1-2 General requirements for basic safety and essential performance - Collateral Standard: Electromagnetic disturbances - Requirements and tests. Battery-operated only: • IEC 62133 - Secondary cells and batteries containing alkaline or other non-acid electrolytes – Safety requirements for portable sealed secondary cells: » Part 1: Nickel » Part 2: Lithium. Probe-specific requirements: • ISO 10993-1: Biological evaluation of medical devices Part 1: Evaluation and testing within a risk management process; • ISO 10993-5: Biological evaluation of medical devices Part 5: Tests for in vitro cytotoxicity; • ISO 10993-10: Biological evaluation of medical devices Part 10: Tests for irritation and skin sensitization.

Regulatory requirements	Compliance with (where applicable, but not limited to): • National regulatory agency requirements compliance • Approval by regulatory body of country of manufacturer (if applicable). • And at least one of: • United States regulations: US FDA Device Class II • European regulatory framework: » Council Directive 93/42/EEC of 14 June 1993 on Medical Devices; » Regulation (EU) 2017/745 of the European Parliament and the Council; » Manufacturer must affix the CE marking and indicate the Notified Body number (when applicable) on the label and in the device, when possible. • Other regulatory body in an IMDRF founding member country such as Australia, Canada, or Japan.

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[13] IPC is a scientific approach encompassing epidemiology, social science and health system strengthening to provide a comprehensive approach to infection prevention and control. The WHO has comprehensive guidelines on core components of IPC programmes: https://www.who.int/gpsc/core-components.pdf

[14] World Health Organization and Pan American Health Organization (2016). Decontamination and Reprocessing of Medical Devices for Health-care Facilities. https://www.who.int/infection-prevention/publications/decontamination/en/.

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Section 2 – Treatment technologies

Chapter 6: Technical guidance and specifications for a cryosurgical unit

Brief description

A cryosurgical unit includes cooled cryoprobe and accessories, intended to destroy cervical tissue with abnormal cells by applying an extremely cold probe to the tissue:

- The cryotip should be round in shape and 17-23 mm in diameter, the overall length of the cryoshaft and cryotip assembly should be between 170 and 200 mm;
- Temperature at probe edge is capable of reaching -20 °C or even colder.

Two types of cryosurgical units are discussed in this chapter:

Gas:

- The cryosystem includes hand-held unit (comprise of cryotip, shaft, trigger and handle), connector/pressure gauge assembly (hose, pressure release valve, pressure gauge, exhaust port and connector to the cylinder), and gas supply;
- It can be part of a console or stand-alone;
- A closed system probe should be used, in which the cryogen flows to and circulates in the probe head;
- Carbon dioxide (CO_2) or nitrous oxide (N_2O) are commonly used.

Electric:

- The cryosystem includes cryotips, a hand-held device, pen cores and a Stirling cooler to cool the tip;
- Units are hand-held with a cooling console/base unit;
- It can be AC or battery powered.

Note to reader:

WHO's Comprehensive Cervical Cancer Control: a guide to essential practice,[1] coupled with this chapter, are intended to serve as the clinical and technical guidance for cryotherapy.

WHO technical specifications for Cryosurgical equipment for the treatment of precancerous cervical lesions and prevention of cervical cancer has been replaced with the present document.

WHO IARC has developed training material:[2] https://screening.iarc.fr/elearningifcpc.php

6.1. Scope of chapter

This chapter defines technical requirements for a cryosurgical unit that delivers cryotherapy to treat cervical intraepithelial neoplasia (CIN).

Content herein focuses on present state of practice using up-to-date available technologies; however, authors are aware that innovations in manufacturing, healthcare facilities and practice will advance the field of cervical cancer screening, diagnostics and treatment. The specifications herein do not preclude appropriate upcoming products and/or technologies

This chapter defines technical requirements for a cryosurgical unit that delivers cryotherapy to treat cervical intraepithelial neoplasia (CIN).

6.2. Background for cryotherapy

Cryotherapy, an ablative therapy used since 1967, uses extremely low temperatures to freeze and destroy abnormal tissue for the destruction of cervical intraepithelial neoplasia (CIN).[3] It is also known as cryocautery, cryosurgery, or simply "cryo". It is a relatively simple procedure appropriate for use in LRS because it is easy to learn, the device is portable, and the treatment is considered to be very safe and effective, with success rates between 85-94%,[4] and with minimal risk of excessive bleeding or significant pain.[5] Cryotherapy is similar to thermal ablation (see Chapter 5), sharing the same intended use, albeit by a different mechanism.

It functions by freezing the identified abnormal area(s) of the cervix by applying a highly cooled probe, causing cryonecrosis of epithelial cells due to intracellular fluid crystallization and consequent irreversible membrane rupture.[6]

The application of cryotherapy takes only a few minutes, and although usually causes some lower abdominal discomfort and uterine cramping, the side effects are considered both minimal and tolerable.

Cryotherapy systems can be cooled by either pressurized gas (CO_2 or N_2O) or super-cooled from an electrical power supply. Systems cooled by pressurized gas require the reliable acquisition, safe transportation and safe handling of a medical gas.[84] For electric based systems, a continuous, reliable power source is required as well as an ethanol-based medium to prevent the probe core from freezing to the wall of the unit.

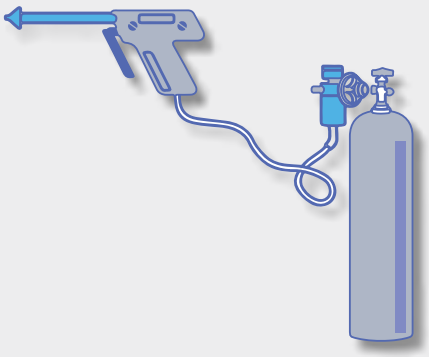
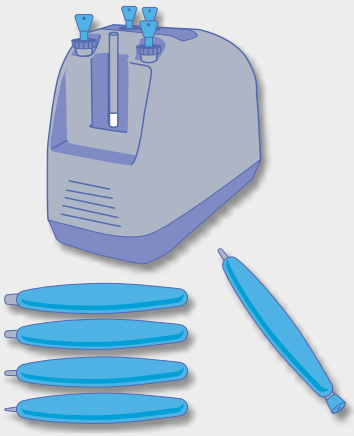
Cryotherapy is usually performed on an outpatient basis and can be performed at all levels of the health system by adequately trained healthcare providers.[1]

Cryotherapy systems can be cooled by either pressurized gas (CO_2 or N_2O) or super-cooled from an electrical power supply.

6.3. Types of cryotherapy units

6.3.1 Different types of cryosurgical units

Table 9: Comparison between gas and electrically cooled cryotherapy units

Type	Gas cooled	Electrically cooled
Image		
Brief description	Gas-based cryosurgical equipment is relatively ubiquitous and is available from many manufacturers. The cryosystem includes cryotips, hand-held device, connector/pressure gauge assembly (hose, pressure release valve, pressure gauge, exhaust port and connector to the cylinder), and gas supply. This is a closed system probe in which the cryogen flows to and circulates in the probe head and exhausted back down the shaft.	Electric systems are designed to provide cryotherapy without the use of compressed gas. There is a cooler in the base that cools a core using electricity. The core is then removed from the base and inserted into the probe head for use. A variety of reusable tips are available for use.
Advantages	Comes in various sizes to fit different clinical needs. Available in most markets. Widely used, lots of evidence and clinical guidelines available.	No gas required and therefore no medical gas supply chain required.
Limitations	Gas supply requires local supply chain and can be harmful to users (particularly N_2O).	Requires continuous, reliable electricity. Newer technology compared to gas-cooled, and therefore not as ubiquitous. May require continuous supply of reservoir solution (ethanol-based) to coat cores prior to cooling.

6.4. Equipment requirements

All cryosurgical equipment should be capable of reaching and maintaining a cryotip temperature below - 50°C at the centre and below -20°C around the side edges of the cryotip.

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6.4.1. Hand-held unit

The hand-held part is typically gun shaped, with the cryoshaft connecting the probe tips, which can be attached to and removed from the handle, and subsequently, the gas or electricity supply mechanism. It shall be made of a material that withstands routine decontamination. One or more integrated triggers and other controls on the handle of the unit should allow for temperature regulation to control the freezing-thawing cycle that takes place in the cryotip.

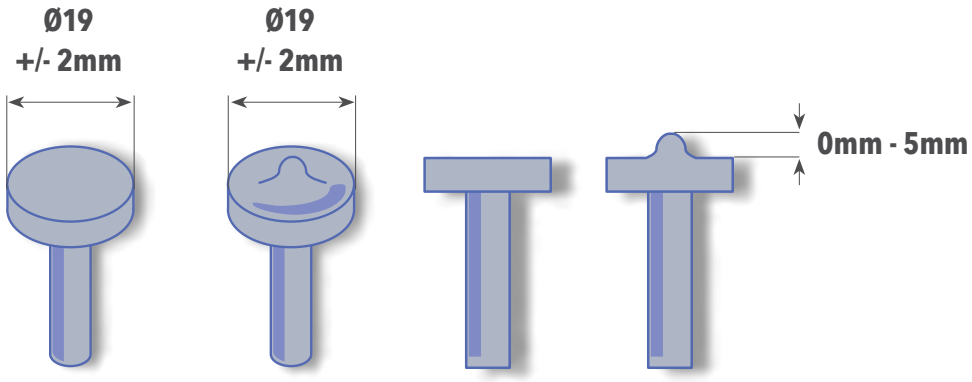
If temperature regulation is part of the hand-held device, as with gas-cooled systems, the device should be designed to give the user sensory feedback indicating its "on" or "off" status, as well as with a latching mechanism to allow the user to lock the trigger in the ON position. The controls are located such that they can be operated with just one hand.

6.4.2. Cryoprobe

The cryoprobe consists of cryotip and the cryoshaft. The cryotip is removable to allow for the interchange between various tip shapes and sizes, depending on need, as well as to facilitate cleaning and disinfection. The following provides guidance on shape, size, material and other relevant details of the cryoprobes to be included or considered for procurement, regardless of type of cryotherapy unit being used:

Shape: The surface of the tip that contacts the cervix should be smooth with no sharp edges. A flat probe is always necessary to ensure full ablation of the transformation zone; however, nipple-shaped probes with an extrusion not exceeding 5 mm are very useful to anchor the probe to the centre of the cervix (see Figure 10). *(Note: conical tips or probes that extend into the endocervix should not be used for cryotherapy of precancerous cervical lesions.)*

Figure 13: Illustrations of suggested cryotips and dimensions



Dimensions: The cryotip should have a 17-23 mm diameter (larger diameters are only suitable for use on large parous cervices and thus do not have as broad an application as smaller-sized probe tips). Multiple probe tip sizes should be available. The overall length of the cryoshaft and cryotip assembly should be between 170 and 200 mm.

Materials: the cryotip shall be made from surgical-grade materials to allow for direct contact with human tissue (must be non-cytotoxic, see Chapter 6.7 standards and regulations), and to facilitate the repetitive decontamination without compromising its integrity.

Due to the risk of damaging surrounding tissue, safety features to protect the vagina upon entry and exit of the cooled probe tip are recommended. The probe shaft should either itself be a non-thermal conductor or must have a guard to prevent burns to the vaginal walls. The shaft should be rigid so that it does not flex during normal use.

Specific to gas-based units, in addition to potential challenges associated with the sourcing, delivery, storage, and handling of liquid nitrogen in LRS, **only closed systems, which use a compressed gas-based cryogen flowing through the shaft in a hollow tube and is exhausted back through the hand-held device, are recommended for precancerous cervical lesions.**

Due to the risk of damaging surrounding tissue. Safety features to protect the vagina upon entry and exit of the cooled probe tip are recommended.

6.4.3. Additional Requirements

6.4.3.1. Accessories - all

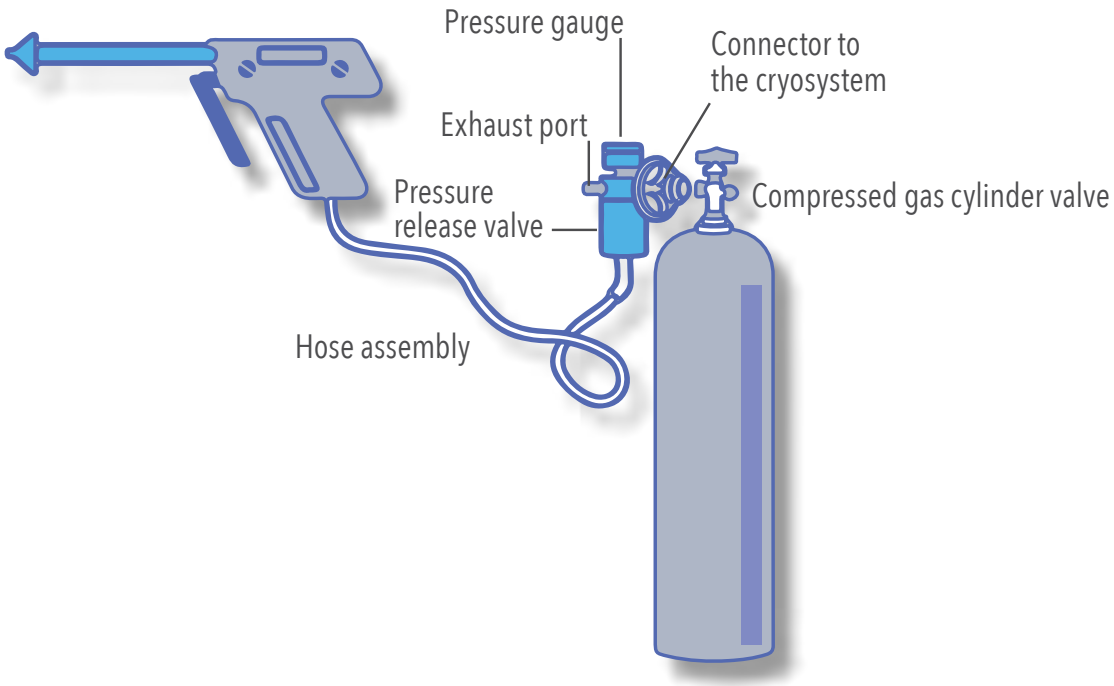
Cryotherapy units are used with a speculum for viewing and accessing the cervix[6] (see Chapter 1) and a light source (external or built-in) of at least 100W or 100W-LED equivalent, and/or a magnification lamp to improve visualization during the procedure. It is recommended that any such light source provide the white light spectrum, similar to daylight. Yellow, tungsten-based light sources should be avoided if possible.[8]

It is recommended that any such light source provide the white light spectrum, similar to daylight.

6.4.3.2 Requirements for gas-based units

Connector/Pressure gauge assembly: A hose assembly connects the hand unit to a connector/pressure gauge assembly that connects to the high-pressure gas cylinder. It comprises a high pressure hose to facilitate gas flow to the unit, as well as to return used gas to the assembly to be vented through an exhaust port (venting of the gas within the handset is not acceptable) – see Figure 11 below.

Figure 14: Hose and connector/pressure gauge assembly used in cryotherapy



The hose shall be rated for a pressure of at least 13,790 kPa (2000 psi), or twice the maximum gas cylinder pressure, with a minimum length of 150 cm to allow sufficient free movement of the clinician while operating the device. Returned gas is depleted into the air through the exhaust port (see Figure 11).

The gas connector permits the system to connect directly to the compressed gas cylinder. It is made of metal and should be rated for use with pressurized gases. It must be compatible with the cylinder valve fitting available locally (e.g. pin-index or bullnose) where the equipment is to be used.

The gas connector permits the system to connect directly to the compressed gas cylinder.

A pressure gauge indicates the pressure within the cylinder. It may be colour-coded to indicate the safe working range for the device.

A pressure relief valve protects the device, the user, and the patient from potentially excessive tank output pressure. The valve has an internal rupture disk, which bursts at a set pressure, preventing the device from over-pressurization.

A pressure regulator, silencer, temperature sensor and active defrosting function may or may not be incorporated into the unit. For the pressure regulator, it is important to ensure that local gas suppliers have cylinders that are fitted with accessories compatible with the device connector assembly.

Gases Carbon Dioxide (CO_2) and Nitrous Oxide (N_2O): Either CO_2 or N_2O are suitable to be used in cryotherapy; the choice of gas must be made at the time of purchase based on local availability and clinical preference, to ensure proper fittings (as each gas has its unique valve fitting assembly). Most manufacturers offer the option of using either.

Both CO_2 and N_2O have temperature and pressure ratings at which the gas liquefies; see Table 10 (their critical point):

Table 10: Critical points of CO_2 and N_2O

Gas	Critical Temperature	Critical Pressure
CO_2	31.2 °C	7378 kPa (1070.1 psi)
N_2O	36.4 °C	7245 kPa (1050.8 psi)

At normal room temperature, and under high pressure (as realized in cylinders), both gases will be in liquid form. At typical storage temperatures (20 °C to 30 °C), the pressure in a CO_2 cylinder will vary between 5860 – 7170 kPa (850 – 1040 psi); and 5060 – 6315 kPa (734 – 916 psi) for a N_2O cylinder. As temperature increases, so will the pressure of the contents. **Under high temperature conditions (i.e. >30 °C), the pressure may become too high for use with some types of cryosurgical equipment. In this case, the cylinder has to cool to below 30 °C before it can be used. Ideally, appropriate storage should be made available for these gases.**

It is recommended that if N_2O gas is to be used with cryotherapy units, gas-scavenging facilities should be used during N_2O-generated cryotherapy. Users should contact the supplier to request information on scavenging the N_2O exhaust, including the proper size and type of exhaust hose for equipment that has a N_2O scavenging port.[9] In LRS where scavenging facilities are not available, the procedure room must be well ventilated to allow for natural dissipation. It is recommended that users consider the substitution of CO_2, which is less hazardous.

A consistent gas supply in LRS might prove challenging. Medical-grade gases should be used to ensure that the quality of the gas is of an acceptable level for use with medical equipment, and that the gas will not damage the equipment. CO_2 is preferred by WHO guidelines where both gases are available. CO_2 is often cheaper and more readily available.

Gas cylinders: Gas pressure in CO_2 or N^2O cylinders are typically 5515-6895 kPa (800-1000 psi). In addition to analogue number readings, the gauges used on cryosurgical equipment are commonly colour-coded to indicate acceptable operational ranges (red: critical, yellow: low, green: acceptable operating pressure).

Different standards, regulations, and requirements apply to gases and gas cylinders depending upon country, region and application. Cylinders are normally made of steel but can be made of aluminium or carbon composites. They come in a wide range of sizes; for NO_2, from 450-18,000 L gas, for CO2, from 450-3,600 L gas.[7] It is best to opt for the largest cylinder size available subject to practical considerations relating to storage and handling on site.

Some manufacturers will provide an empty gas cylinder with the equipment package; however, it is essential to confirm with a local gas supplier prior to purchase if they have the correct fittings to be able to refill the cylinder. Additionally, it is advisable to check with the local gas supplier what the differences would be in refilling your own cylinder, as opposed to leasing one of theirs in a cylinder 'swap-out'.

The cylinder must be standing upright to deliver gas. The safety rules for the cylinder must be followed. Safe transport and storage of compressed gases can be difficult. It is important to follow local regulations regarding transport, supply and use of compressed gas cylinders.

6.4.3.3 Electricity-based cryotherapy units: Power Supply

If using electrically cooled cryosurgical units, there must be a continuous, reliable electrical power supply (220V or 120V, and 50 or 60 Hz, according to different national standards) accessible in the exam room to allow for use by cooling and maintaining cores at required temperatures.

For treatment, when cores have reached the required temperature, they are removed from the base unit and are then placed into the handheld unit to cool the cryotip. At this point, they will no longer be continuously cooled. Once the cryotip makes contact with the tissue, the core will start to warm. It is important that the user be familiar with the amount of time the cryotip will remain cold enough for effective ablation, and to know when to insert a new, adequately cooled core to complete the procedure.

6.5. Operational considerations

6.5.1. How cryotherapy is used

Cryotherapy is indicated as an option for the treatment of cervical precancerous lesions; the success rate of cryotherapy is quite high for low-grade disease.[10] It can be performed at the first assessment visit following "screen and treat" protocol or after a diagnostic biopsy. WHO recommends the double freezing method, which comprises a 3-minute freeze, 5-minute thaw, 3-minute freeze cycle in preference to single-freeze therapy.

Cryotherapy is indicated as an option for the treatment of cervical precancerous lesions; the success rate of cryotherapy is quite high for low-grade disease.

During usage, units scheduled for use with CO_2 should be able to reach temperatures at least as low as – 68°C; N_2O units should be able to reach temperatures at least as low as -89°C; and, electrically cooled systems should be able to reach lows of between -110°C to -105°C. With these temperatures, the temperature at the probe's edge will be capable of reaching < -20°C, a requisite for successful therapy. These figures have been summarized in Table 11:

Table 11: Cryo equipment temperature[83]

Cooling method	Temperature of central tissue	Temperature at probe edge	Temperature of central tissue	Temperature at edge of tissue
CO_2	< -68°C	-20°C	-68°C	About -20°C
N_2O	< -89°C	-20°C	-89°C	About -20°C
Cores, electricity	-110°C to -105°C	-20°C	• -80°C at time = 0 • -50°C at ~2 min. The core is not being cooled continuously during treatment cycle. Core exchange is required.	About -20°C
Conditional on: • **Contact between probe head and epithelium being completely uniform** • **Maintenance of gas system pressure at >40 kg/cm² to achieve required temperature.**				

(adapted from IARC's technical publication Colposcopy and Treatment of Cervical Precancer)

For cryotherapy, all equipment should be specific for the intended purpose of treating precancerous cervical lesions. Instructions for use and service manuals outlining the basic operation of all components shall accompany each unit. These shall cover assembling the equipment, risk of use, and required maintenance.

Appropriate clinical training should be provided in advance of using cryotherapy equipment. It is necessary to establish and/or maintain an on-going, competency-based capacity-building programme to sustain clinical practice with all in-service programmes, tools and resources, based on the standard clinical guidelines and local CMS pedagogy.

Appropriate clinical training should be provided in advance of using cryotherapy equipment.

Please consult WHO's Comprehensive Cervical Cancer Control: a guide to essential practice[11] and the WHO Guidelines for screening and treatment of precancerous lesions for cervical cancer prevention[11] for guidance on the proper preparation for and procedure of cryotherapy, and Colposcopy and treatment of cervical intraepithelial neoplasia: a beginners manual.[12]

IARC, has developed some Training packages Specifically chapter 12 explains the Treatment of cervical intraepithelial neoplasia by cryotherapy. It can be seen at[2] https://screening.iarc.fr/colpochap.php?lang=1&chap=12.php

6.5.2. Decontamination and Reprocessing

Healthcare-associated infections (HAI) are one of the most common adverse events in healthcare delivery. Not only do they have a significant impact on morbidity and mortality, but they also present an economic burden to healthcare facilities and countries. As part of a larger infection prevention and control (IPC) programme,[13] decontamination of instruments and medical devices plays a critical role in HAI prevention.

The PAHO/WHO manual titled Decontamination and reprocessing of medical devices for healthcare facilities[14] outlines the decontamination life cycle, which includes cleaning, disinfection and sterilization. Please refer to this manual for details on specific methods of decontamination, sterilization and reprocessing of medical devices. Always follow the device manufacturer's instructions for decontamination so as not to cause any damage and ensure proper decontamination.

Equipment and accessories in direct contact with the patient must be decontaminated, cleaned, and then either sterilized or disinfected, using a high-level disinfectant (HLD). The rest of the device is to be cleaned and/or disinfected; solutions for cleaning and disinfection need to be used according to the manufacturer's instructions as their specified disinfectant exposure time must be observed.

Other tools and materials used in cryotherapy (for example specula) should be cleaned and disinfected between patients.

6.5.3. Health-care Waste Management

Knowledge about the potential for harm due to healthcare waste has become more important to governments, healthcare workers and civil society. Improper handling and disposal of healthcare facility waste is widely recognized as a source of avoidable infection; therefore it is critical for healthcare facilities to appropriately manage the disposal of healthcare waste, including but not limited to hazardous waste.

Hazardous waste includes sharps, infectious waste (contaminated with blood and other body fluids), pathological waste (such as human tissue) and chemical waste. For details on how to dispose of hazardous waste, please refer to facility and/or local guidelines and regulations and the WHO manual titled Safe management of wastes from healthcare activities.[15]

Any consumables (swabs, cotton balls, gloves) should be disposed of using the appropriate protocols for the healthcare facility.

6.5.4. Storage and Packaging

Labelling on the primary packaging should include the name and/or trademark of the manufacturer and should adhere to the most current version of ISO 15223 – 1: Medical devices -- Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements. Depending on the country, specific requirements for the information to be provided on the label may exist, such as the requirement for specific languages and warnings.

As a minimum, the storage area should be clean and dust-free, dry, cool, well-lit, ventilated and vermin-proof. The device should be stored in its original packaging on a shelf or on in a storage cabinet.

In recognizing that environmental conditions in many LRS are quite varied and can be extreme, **it is the responsibility of the procurement body to ensure the expected storage conditions are within the manufacturer's storage recommendations for any specific device.** If the device will require that the storage environment be climate-controlled, appropriate temperature and humidity control systems, including monitoring, should be applied to avoid premature material disintegration.

However, in general, these devices should be able to withstand storage temperatures ranging from 15°C to 40°C, relative humidity ≤ 85% (non-condensing) for gas-based systems, and ≤60% (non-condensing) for electrically cooled systems, both should be protected from dripping water.

6.5.5. Maintenance

Essential spare parts and consumables such as, cryo-tips, reservoir solution (for the electrically cooled cryocores), the hose assembly, O-ring and Bodok seals (sealing washers) (for gas-based systems) should be purchased from the original equipment manufacturer (OEM) and adequate inventory shall be maintained by ordering replacements in a timely manner.

Planned preventative maintenance (PPM) schedules are important to follow per the manufacturer's service manual, especially for gas-based systems. Annual general equipment inspections should be performed routinely by the clinical engineering staff to detect any impending problems, such as cracked gauge faces, dry-rotted tubing and hoses, if any leaks are discovered, O-rings or washers in the joint are to be replaced. For the handheld units, maintenance should be performed regularly based on manufacturer's recommendation. Lack of maintenance can affect the performance of the device.

Specific to gas-based systems, cylinders must be stored appropriately and below 30°C, clearly identified from other gases, and when used, done so in well-ventilated areas. It is very important to check all connections and joints for leaks after turning on the cylinder valve. If a cylinder falls over or if the valve is otherwise damaged or broken, it can turn the cylinder into a dangerous projectile because of contents under pressure, which can cause extensive damage, serious injury and even death.[16]

The cylinders themselves must undergo hydrostatic testing every 10 years;[17] the purchaser of gases should ensure that their supplier carries out the requisite maintenance of equipment. Such maintenance tasks require specialized personnel and are not recommended to be performed in the hospital due to safety concerns.

Planned preventative maintenance (PPM) schedules are important to follow per the manufacturer's service manual, especially for gas-based systems.

6.6. Quality Management Systems and post-market surveillance

A quality management system delineates a systematic approach to ensure ongoing quality of outputs. It is critical that all products are manfactured within a robust quality management system at the manufacturer. A QMS includes but is not limited to: standard operating procedures, documentation, design and manufacturing controls and third-party assessments. Maintenance of a QMS requires appropriate human resources and their management, infrastrucutre, timely and appropriate procurement, stock management, maintenance, and a rigorous pre- and in-service training curriculum.

Post-market surveillance is an obligation of the medical device manufacturer in order to investigate and act on any adverse event and product malfunction or failure. Post-market surveillance typically consists of complaint handling by end-users when an issue is detected. When information is made known to the product manufacturer, they must determine if the risks have increased and whether the benefits of the product outweigh the harms or risks. Any field safety corrective actions, such as a recall or change to the product (including labelling), are notified by the manufacturer through a field safety notice. National regulatory agencies / authorities (NRA) will also conduct their own market surveillance and oversee the manufacturer's investigation of complaints. WHO guidance on QMS and post-market surveillance for medical devices can be found in WHO Global Model Regulatory Framework for Medical Devices including in vitro diagnostic medical devices.[18]

6.7. Standards and regulatory compliance

A specific international reference standard (e.g. ISO) does not exist for cryosurgical units; however, the following standards categories apply:

- Medical device quality, performance, operations, and safety: ISO 13485, ISO 14971, ISO 15223-1 (See Chapter 6.8 and Annex 6)
- Biocompatibility: ISO 10993, all applicable parts (See Chapter 6.8 and Annex 6)
- Electrical safety: IEC 60601, all applicable parts (See Chapter 6.8 and Annex 6)
- High-pressure gases: ISO 21969, all applicable parts, (See Chapter 6.8 and Annex 6)

It is important to observe all applicable local laws related to medical devices and their procurement. In the absence of a regulatory agency, it is strongly recommended to consider which regulatory and/or normative body assessment was completed for each product prior to procurement decisions. The risk class depends mainly on the regulatory framework of a country and therefore it may differ according to jurisdiction. For more details regarding other regional regulations and standards, see the specifications table in Chapter 6.8 and in Annex 6.

It is important to observe all applicable local laws related to medical devices and their procurement.

6.8. Key tender/request for quotation specifications for a cryotherapy device

Following are the key features that may be noted in a tender or request for quotation; detailed standardized WHO technical specifications can be found in Annex 6.

Product description	A cryosurgical unit, either a console or hand-held, is used to destroy cervical tissue with abnormal cell growth. It comprises a gas or electrically-cooled cryoprobe, capable of reaching temperatures colder than -68°C.
Key product features	• Cryosystems include a hand-held unit with use-specific cryotips: » Minimum of 2 cryotips are required: * One cryotip must be flat; * The second cryotip can be either flat or can have a gentle nipple extrusion not exceeding 5mm (so as to anchor in centre of cervix but not to ablate endocervix); * Cryotip diameters ranging from 17 mm to 23 mm; * Biocompatible, material that will not adhere to cervix; * Reusable and thus de-contaminable. • The overall length of the cryoshaft and cryotip assembly should be between 170 and 200 mm; • Temperature at probe edge shall be capable of reaching less than -20 °C; • If gas-cooled, either carbon dioxide (CO_2) or nitrous oxide (N_2O) is used; • If electrically-cooled, an ethanol-based solution and electricity are necessary.
Components, accessories, consumables	For gas systems: • cryosystems include a hand-held unit (comprising a cryotip, shaft, trigger and handle), connector/pressure gauge assembly (hose, pressure release valve, pressure gauge, exhaust port and connector to the cylinder), and gas supply. For electric systems: cryotips, a hand-held device, all requisite accessories to cool the tip.

Operational requirements	• Temperature: 10-40°C; • Relative humidity: ≤85%, non-condensing; • (Storage temperature: -20 to +60°C or greater (?), storage relative humidity: 0-80%, non-condensing); • Electrically-cooled cryosystems require reliable electrical power supply (based on country/ setting of use): » Amperage: _____ » Voltage: _____ » Plug type: _____ .
Documentation requirements	• Instructions for use and service manuals to be provided. • User language preference prioritized, otherwise English is mandatory.
Warranty	Minimum one year
Standards	Following with active version of the standards listed below (or equivalent): General manufacturing: • ISO 13485: Medical Devices - Quality Management Systems - Requirements for Regulatory Purposes; • ISO 14971: Medical Devices - Application of Risk Management to Medical Devices; • ISO 15223-1: Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements. Safety and product standards for *electrically-cooled systems*: • IEC 60601-1 - Medical electrical equipment - Part 1: General requirements for basic safety and essential performance; • IEC 60601-1-2: Medical electrical equipment - Part 1-2 General requirements for basic safety and essential performance - Collateral Standard: Electromagnetic disturbances - Requirements and tests. Safety and product standards for *gas-based systems*: • ISO 21969 High-pressure flexible connections for use with medical gas systems. Probe-specific requirements: • ISO 10993-1: Biological evaluation of medical devices Part 1: Evaluation and testing within a risk management process; • ISO 10993-5: Biological evaluation of medical devices Part 5: Tests for in vitro cytotoxicity; • ISO 10993-10: Biological evaluation of medical devices Part 10: Tests for irritation and skin sensitization.

Regulations	Compliance with (where applicable, but not limited to): • Local national regulatory agency requirements compliance • Approval by regulatory body of country of manufacturer (if applicable). And at least one of: • United States regulations: US FDA : Device Class II • European regulatory framework: » Council Directive 93/42/EEC of 14 June 1993 on Medical Devices (Class IIb); » Regulation (EU) 2017/745 of the European Parliament and the Council; » Manufacturer must affix the CE marking and indicate the Notified Body number on the label and in the device, when possible. • Other regulatory body in an IMDRF founding member country such as Australia, Canada, or Japan.

Chapter 6 references

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[12] https://screening.iarc.fr/colpochap.php?lang=1&chap=12.php.

[13] IPC is a scientific approach encompassing epidemiology, social science and health system strengthening to provide a comprehensive approach to infection prevention and control. The WHO has comprehensive guidelines on core components of IPC programmes: https://www.who.int/gpsc/core-components.pdf.

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Section 2 – Treatment technologies

Chapter 7: Technical guidance and specifications for ESUs used in LLETZ

Brief description

The LLETZ, or LEEP, can use typical ESUs; General requirements of an ESU:

- Minimum 1 monopolar handpiece port, 1 monopolar return electrode port (with alarm for poor contact quality), 1 bipolar outlet;
- Different and adjustable current modes: coagulation mode (up to 80 W / 150 Ω), cutting mode (up to 110 - 200 W / 300 -400 Ω), and blended current mode;
- Hand or foot switch to activate different electrodes or settings.

LLETZ-specific minimum requirement: 1 monopolar outlet, 1 monopolar return electrode; blended current option, and must cover the following power output ranges that can be selected by the user:

- coagulation 30 - 50 W
- cutting 30 - 50 W.

Electrodes: wired, in various sizes and shapes; comes with a minimum: ball electrode (3mm or 5mm), square loop electrode (smaller size), semicircular loop electrode (larger size); and, a ground plate.

ESUs are powered by electricity. It is recommended to use a continuous power supply along with voltage stabilization to avoid interruption during treatment. Battery powered ESUs are available, can be portable, and appropriate for use in rural settings with appropriately qualified staff.

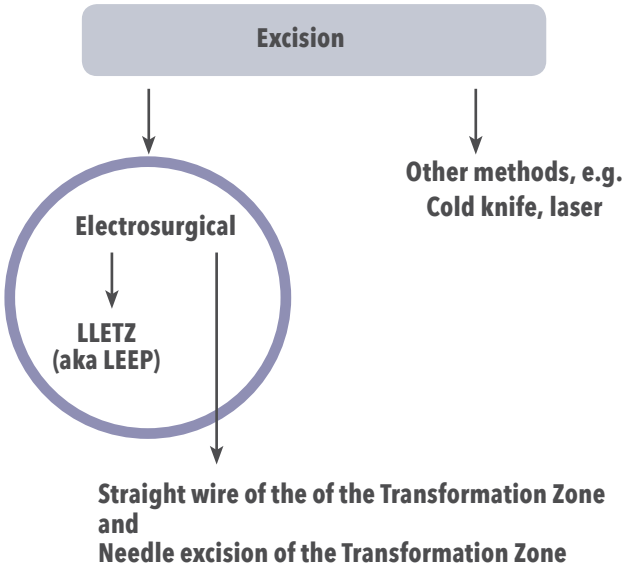
7.1. Scope of chapter

This chapter defines technical specifications for an electrosurgical unit (ESU) for Large Loop Excision of the Transformation Zone (LLETZ), also known as Loop Electrosurgical Excision Procedure (LEEP), and provides details for other important equipment to perform a successful LLETZ procedure.

Content herein focuses on present state of practice using up-to-date available technologies; however, authors are aware that innovations in manufacturing, healthcare facilities and practice will advance the field of cervical cancer screening, diagnostics and treatment. The specifications herein do not preclude appropriate upcoming products and/or technologies

Content herein focuses on present state of practice using up-to-date available technologies.

(adapted from algorithm provided by W. Prendiville)



7.2. Background for ESU and LLETZ

The passage of electricity to and through tissue produces heat. Faraday discovered that at a very high frequency (> 100 kHz), doing so does not contract muscle tissue. ESUs were subsequently developed to perform the safe passage of electricity through the human body in controlled circuits, and to use the localized point-of-contact effect – the heat – for medical purposes. Electrosurgery has been used for more than a century, for many types of surgical procedures, for both cutting and coagulating tissue. The technology's haemostatic effect makes ESUs useful for procedures on organs rife with capillary beds such as the liver, spleen, thyroid, and the lungs.[1]

The passage of electricity to and through tissue produces heat. Faraday discovered that at a very high frequency (> 100 kHz), doing so does not contract muscle tissue.

There are two types of output modes for clinical use: monopolar and bipolar. The prefixes mono- and bi- refer to the number of active electrodes. In monopolar electrosurgery, an active electrode carries current to the tissue, which is then spread through the body, then collected and returned to the ESU by a ground/neutral plate electrode.[2] In bipolar mode, both electrodes are high-density power and are situated across from each other. Bipolar electrosurgery is primarily used to coagulate tissue.

ESUs are programmed to deliver power in watts, defined as the rate which energy is used and commercially billed to the users.

LLETZ was developed in Bristol, United Kingdom, in 1986 using a low-voltage across a loop of thin wire, usually blending diathermy currents to enable both cutting and coagulation, under local anaesthesia. The process is also known as LEEP.[3] LLETZ is the removal of abnormal areas from the cervix, using a loop made of thin wire heated with electricity. It may be performed at the first patient visit after screening, and has been well recognized as a standard practice to treat CIN. The procedure can be performed on an outpatient basis and usually takes 10-15 minutes; however, a patient should stay in-facility for a few hours if at risk of bleeding.

Table 12 lists equipment and supplies required by highly skilled personnel to perform a successful LLETZ.

Table 12: Required equipment to perform a LLETZ procedure

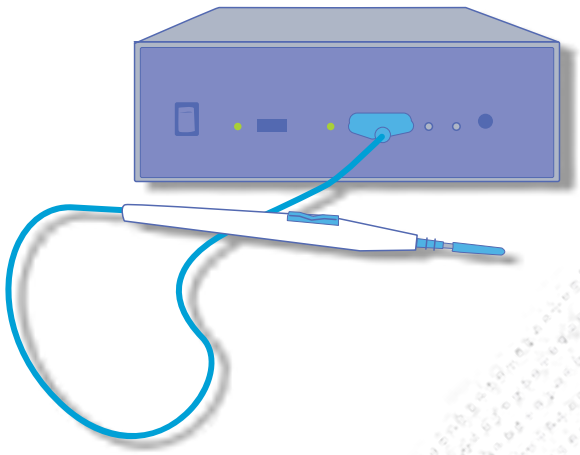
- Electrosurgical unit:
  - » Current generator
  - » Electrode(s)
- Colposcope
- Speculum, preferably with side retractors
- Smoke evacuation device
- Forceps
- 5 ml syringes with a long 23-27-gauge needle (such as dental or spinal needle)
- Suture kit: Needles, sutures, and other requisite material
- Specimen containers
- Medical adhesive

7.2.1. Electrosurgical unit

An ESU converts low-frequency alternating current (AC) into higher voltage radiofrequency (RF) output. It has a broad application and is commonly used in many different surgeries, including dermatological, gynaecological and cardiac procedures, among many others.

A general, non-LLETZ-specific ESU has been described herein should the healthcare facility wish to use a the device for other types of surgical procedures. However, because LLETZ only requires some functionalities provided by an ESU, the minimum device requirements for a successful LLETZ are specified to ensure that these are covered by the device functionality. For example, LLETZ only requires monopolar electrosurgery, and the requisite current is lower than that used for some other procedures.

Figure 15: Image of a standard ESU



7.2.1.1. General ESU

This Chapter discusses the basic mechanism and specifications of ESU used in health care facilities.

This Chapter discusses the basic mechanism and specifications of ESU used in health care facilities.

The face of an ESU is a control panel for adjusting and displaying settings, including the main power switch (ON/OFF), a power indication light, electrode (monopolar, bipolar and ground plate) ports, mode selection (mono- or bipolar), operating mode selection (RF for coagulation or cutting), and blended operating mode (if option available). There may be other indications, including: low battery light, charging indication, charger input, and ground plate displace warning light in more advanced or portable equipment. The ESU is usually operated by a foot pedal (the user activates the electrode by foot), allowing full freedom of hands with the electrodes themselves to carry out the procedure.

It is crucial for the ESU to be able to generate current at a RF range from 200,000 -500,000 Hz, which will allow for desired thermal effects without muscle contraction or nerve stimulation.

There are two main current modes: coagulation and cutting. In the coagulation mode, an interrupted or low-current (up to 80 W) /high-voltage waveform is generated. This output denatures the protein and leads to a homogenous thermal coagulum. During cutting mode, a high-current (up to 110-200 W) /low-voltage waveform is generated. This output rapidly vaporizes the tissue and produces a clean incision with haemostasis or minimal bleeding.[4]

There is usually a 'blend current' option to generate a current combining both types of current, in a variety of combinations (e.g., blend 1, blend 2, blend 3) that can be set by the user.

Some ESUs have a resistance recognition system, a contact quality monitor (CQM) in the ground plate circuitry in order to support clinicians when poor contact with the ground plate (return electrode) is detected; some CQMs can cut the electric current if there is no longer good contact between the ground plate and patient body. Typically, these ground plates are split, where an even flow of current is necessary through both (which will indicate good contact) to enable electricity to pass around the circuit. An alarm in all CQMs warns the operator if contact is poor.[5]

7.2.1.2. Minimal requirement of ESU to be used for LLETZ procedures

There are some specific requirements of standard ESUs that are necessary for a successful LLETZ, namely monopolar mode, the option for blended current, and a CQM.

There are some specific requirements of standard ESUs that are necessary for a successful LLETZ, namely monopolar mode, the option for blended current, and a CQM.

For LLETZ, electrical current passes from the ESU through an electrode (a loop) to the tissue, and then through the body to the return electrode (ground plate) and ultimately back to the ESU. Hence, the unit must have the monopolar mode with one hand piece port and one return (ground plate) electrode port as a minimum.

LLETZ uses 30-50 watts of coagulation and cutting, hence the ESU must be able to cover that range. A blended current option is highly recommended as it is usually used in the procedure with about 20% coagulation and 80% cutting for optimal effect.[6] Blended current enables the simultaneous cutting through tissue and achieving relative haemostasis of the stromal vessels, without inflicting significant damage on the biopsy specimen or the cervical wound left behind.

For patient safety and to decrease burn risk, it is recommended to have a CQM with an in-built alarm.

7.2.2. Electrodes

Two different types of electrodes are used for LLETZ: a hand-piece electrode and a ground plate (return electrode).

7.2.2.1. Hand-piece electrode

Electrodes are usually made of stainless steel or tungsten wire. Loops of different sizes and shapes are used for taking diagnostic biopsies. At a minimum, two loop sizes (specific sizes determined by the manufacturer, generally one small and one large), as well as a ball electrode (see Figure 13) are required, for example:

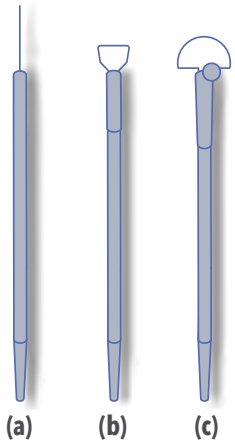
Electrodes are usually made of stainless steel or tungsten wire.

- Small electrode: 15mm x 5 mm deep, generally used for small lesions in nulliparous women;
- Larger electrode: 20mm x 8 mm deep, generally used for larger lesions and multiparous women;
- Ball electrodes: 3mm or 5mm, generally used to achieve haemostasis after excision of the transformation zone or to seal a biopsy site.

Electrodes can be single-use or reusable. For more details, refer to WHO guideline Comprehensive Cervical Cancer Control: a guide to essential practice for more procedure instructions.[7]

Proper decontamination is required for reusable electrodes after each use. See Chapter 7.5.2.

Figure 16: Different types and sizes of el ectrodes

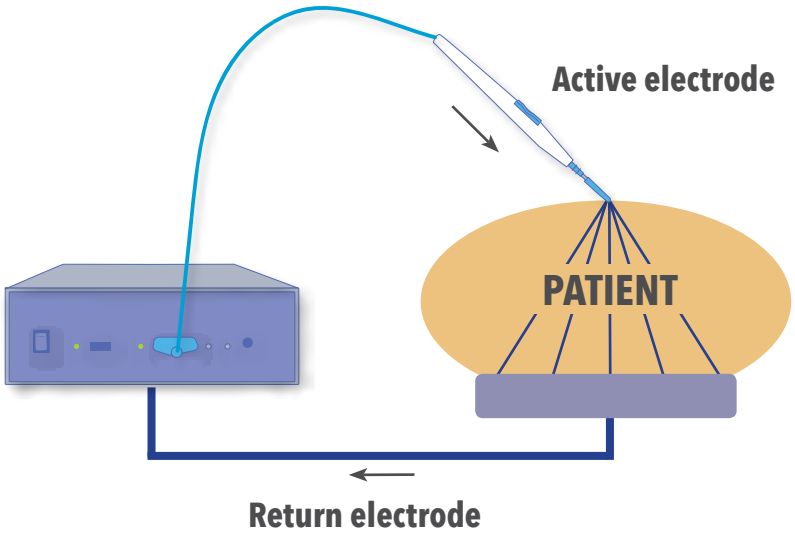


(a) ball electrode
(b) square loop electrode
(c) semicircular loop electrode

7.2.2.2. Ground plate (Return electrode)

Ground plate (also known as neutral electrode, return electrode, or dispersive pad) is the electrode that attaches to the patient and functions by closing the circuit, returning the current back to the ESU. The ground plate itself is usually affixed with a medical adhesive, and the plate is usually reusable. The ground plate should be positioned relatively close to the point of contact; for LLETZ, a convenient and appropriate position is under the patient's buttocks (see Figure 14). It ensures complete contact and reduces the risk of burn injury.

Figure 17: Illustration of the electrical current flowing in a monopolar ESU



7.3. Other equipment used in LLETZ

Other equipment used in LLETZ are briefly discussed here, including power supply and smoke evacuation device. Colposcopes are discussed in Chapter 4 (specifications Annex 4), and specula in Chapter 1. In addition, the use of a light source of at least 100W or 100W-LED equivalent, and/or a magnification lamp should be used to improve visualization during the procedure. It is recommended that any such light source provide the white light spectrum, similar to daylight. Yellow, tungsten-based light sources should be avoided if possible.[8]

Other equipment used in LLETZ are briefly discussed here, including power supply and smoke evacuation device.

7.3.1. Power supply

Consideration of power supply is important when using ESUs. To ensure patient safety, it is important to connect the ESU unit to a continuous, reliable power supply. In addition to the mains or generator, an uninterruptible power supply (UPS) can act as a holdover power source to complete a procedure in the event of a power loss.

Some manufacturers equip ESUs with a battery to increase its portability. Procurement of such devices does not preclude the need for electricity for charging. In addition, there are several other factors to be considered for battery powered ESUs to meet contextual need, including battery specifications (cell type, capacity, voltage), charge and discharge specifications, service life (how many approximate charge cycles), safety features and reliability.[9]

If a device with battery power is procured, the user should have access to battery replacements as the batteries might not last the entire life span of the device. The user should refer to manufacturer's instructions regarding storage and operation instructions.

7.3.2. Smoke evacuation

Electrosurgery produces harmful chemical and biological by-products in the vaporized tissue plume, which can be carcinogenic.[10] Thus, this vaporized tissue plume should be evacuated for all procedures by using a smoke evacuation system. Depending on the amount of plume that may be produced during the procedure, or depending on facility infrastructure and available resources, there are different systems that can be used.

Electrosurgery produces harmful chemical and biological by-products in the vaporized tissue plume, which can be carcinogenic .

During LLETZ, a dense smoke plume is created within the confined space of the vaginal canal. In addition to the aforementioned carcinogenic potential that can be harmful to clinicians, this plume blocks visual sight of the cervix, which could impede work. It is strongly recommended to use a smoke evacuator or a simple suction device. Some ESUs have smoke evacuators built into the system, providing an integrated clinical flow; however, these units are more expensive. If simple suction is used, the suction tubing is usually attached to the speculum to keep the operative area clear by evacuating the smoke to external and internal filters.[11]

Health facilities should choose the smoke evacuation system based on local needs and budget.

7.4. Handling and use

7.4.1. General safety precautions when using ESUs

In some cases, the current can cause local burns; any metal jewellery worn by the patient must be removed prior to an ESU procedure.[106] It is important to check for implanted electrical devices (IEDs) prior to electrosurgery. IEDs, such as cardiac pacemakers, ventricular assist devices, and neurologic stimulators, can be interrupted or damaged by the current generated by ESUs. It is recommended to avoid monopolar electrosurgery on patients with IEDs. For patients with an IED who require electrosurgery, the IED-related expert (such as cardiologist or neurologist, etc.) must be consulted prior to procedure, the electrode should be applied as far as possible from the IED, the use of capacity-coupled return electrodes should be avoided, and good contact of the ground plate is to be ensured.

Do not use the device in the presence of flammable anaesthetics or oxidizing gases (such as nitrous oxide or oxygen) or in close proximity to volatile solvents (such as ether or alcohol), as an explosion may occur.

Do not place instruments near or in contact with flammable materials (such as gauze or surgical drapes).

7.4.2. Additional safety precautions for LLETZ

LLETZ uses monopolar electrosurgery and therefore needs a ground plate for the electricity to return to the ESU after achieving its effect at the point of contact between the loop and the tissue. If there is poor ground plate contact, an injury can occur if the current finds an easier pathway to return to ground. Examples of such sites are the metal stirrups of some gynaecological couches, jewellery, or other metal body adornments. However, if the ground plate is large and in good contact with the skin, the aforementioned is unlikely to cause injury.

During the procedure, it is possible to injure the vaginal wall and tissues immediately adjacent to it. The loop should be moved slowly through the cervix underneath the transformation zone; it should not bend during the process. If it does that means the operator is pushing it too quickly, and the electrosurgical effect changes from fulgurative to desiccative.

It is not recommended to use insulated specula as a poorly insulated speculum is likely to cause more damage than an uninsulated speculum.

7.5. Operational considerations

7.5.1. How ESUs are used for LLETZ

All equipment should be fit for the intended purpose of treating precancerous cervical lesions. Each unit should be accompanied by training materials specifying basic operation of all components, assembling the equipment, risk of use, and maintenance.

All equipment should be fit for the intended purpose of treating precancerous cervical lesions.

Appropriate clinical training should be provided in advance of using ESUs. Clinical guidelines on the use of equipment are available in the WHO's WHO's Comprehensive Cervical Cancer Control: a guide to essential practice.[7]

Training videos have been developed by WHO IARC , the related to this content is: Colposcopy and treatment of cervical intraepithelial neoplasia, a beginners manual, specifically Chapter 14. Treatment of cervical intraepithelial neoplasia by Loop Electrosurgical Excision Procedure (LEEP), which can be viewed at: https://screening.iarc.fr/colpochap.php?lang=1&chap=13.php

7.5.2. Decontamination and reprocessing

Health care-associated infections (HAI) are one of the most common adverse events in health care delivery. Not only do they have a significant impact on morbidity and mortality, but they also present an economic burden to health care facilities and countries. As part of a larger infection prevention and control (IPC) programme[13], decontamination of instruments and medical devices plays a critical role in HAI prevention.

The PAHO/WHO manual titled Decontamination and reprocessing of medical devices for health-care facilities[14] outlines the decontamination life cycle, which includes cleaning, disinfection and sterilization. Please refer to this manual for details on specific methods of decontamination, sterilization and reprocessing of medical devices. Always follow the device manufacturer's instructions for decontamination so as not to cause any damage and ensure proper decontamination.

Proper sterilization and post-sterilization handling are required for all electrodes for infection prevention and control. All equipment and accessories in direct contact with the patient must be decontaminated, cleaned, and then either sterilized or disinfected, using a high-level disinfectant (HLD). The rest of the device is to be cleaned and/or disinfected; solutions for cleaning and disinfection need to be used according to the manufacturer's instructions as their specified disinfectant exposure time must be observed. Other tools and materials used for LLETZ (for example specula) should be cleaned and disinfected between patients.

7.5.3. Health-care Waste Management

Knowledge about the potential for harm due to healthcare waste has become more important to governments, health care workers and civil society. Improper handling and disposal of healthcare facility waste is widely recognized as a source of avoidable infection; therefore it is critical for healthcare facilities to appropriately manage disposal of healthcare waste, including but not limited to hazardous waste.

Hazardous waste includes sharps, infectious waste (contaminated with blood and other body fluids), pathological waste (such as human tissue) and chemical waste. For details on how to dispose of hazardous waste, please refer to facility and/or local guidelines and regulations and the WHO manual titled Safe management of wastes from health-care activities.[15]

Any consumables (swabs, cotton balls, gloves) should be disposed of using the appropriate protocols for the healthcare facility.

7.5.4. Storage and Packaging

Labelling on the primary packaging should include the name and/or trademark of the manufacturer and should adhere to the most current version of ISO 15223–1: Medical devices -- Symbols to be used with medical device labels, labelling and information to be supplied -- Part 1: General requirements. Depending on the country, specific requirements for the information to be provided on the label may exist, such as the requirement for specific languages and warnings.

As a minimum, the storage area should be clean and dust-free, dry, cool, well-lit, ventilated and vermin-proof. The device should be stored in its original packaging on a shelf or on in a storage cabinet.

In recognizing that environmental conditions in many LRS are quite varied and can be extreme, **it is the responsibility of the procurement body to ensure the expected storage conditions are within the manufacturer's storage recommendations for any specific device**. If the device will require that the storage environment be climate-controlled, appropriate temperature and humidity control systems, including monitoring, should be applied to avoid premature material disintegration.

However, in general, these devices should be able to withstand storage temperatures ranging from 15°C to 40°C, relative humidity ≤ 60% (non-condensing), and be protected from dripping water.

7.5.5. Maintenance

There are PPM requirements for ESU devices. Typical maintenance includes checking integrity of mounts, plug, cord and external circuits; verification of the connection of dispersive electrodes, proper operation of controls and switches; checking for any current leakage from chassis or electrodes; verify and document output waveform characteristics on the ESU analyser (if possible). These activities should be outlined in the service manual and shall be carried out by clinical engineering professionals. Suppliers should provide a warranty of at least two years.

7.6. Quality Management Systems and post-market surveillance

A quality management system delineates a systematic approach to ensure ongoing quality of outputs. It is critical that all products are manfactured within a robust quality management system at the manufacturer. A QMS includes but is not limited to: standard operating procedures, documentation, design and manufacturing controls and third-party assessments. Maintenance of a QMS requires appropriate human resources and their management, infrastrucutre, timely and appropriate procurement, stock management, maintenance, and a rigorous pre- and in-service training curriculum.

Post-market surveillance is an obligation of the manufacturer in order to investigate and act on any adverse event and product failure and/or error. One of the most relevant sources of information to the post-market surveillance plan are the complaints made by end-users when an issue is detected. The field safety corrective actions, such as a recall or changes implemented to the product (including labelling), are notified by the manufacturer through a field safety notice to the National regulatory agencies / authorities (NRA), which will also conduct their own market surveillance activities and oversee the manufacturer's investigation incidents and complaints. WHO guidance on QMS and post-market surveillance for medical devices can be found in WHO Global Model Regulatory Framework for Medical Devices including in vitro diagnostic medical devices.[16]

7.7. Standards and regulatory compliance

There do not exist specific industry reference standards (e.g. ISO) for electrosurgical units (ESUs); however, the following standards categories apply:

- Medical device quality, performance, operations, and safety: ISO 13485, ISO 14971, ISO 15223-1 (See Chapter 7.8 and Annex 7);
- Biocompatibility: ISO 10993, all applicable parts (See Chapter 7.8 and Annex 7);
- Electrical safety: IEC 60601, all applicable parts (See Chapter 7.8 and Annex 7);
- Secondary cells (batteries): IEC 62133, parts 1 and 2 – if applicable (See Chapter 7.8 and Annex 7).

It is important to observe all applicable local laws related to medical devices and their procurement. In absence of a regulatory agency, it is strongly recommended to consider which regulatory and/or normative body assessment was completed for each product prior to procurement decisions The risk class depends mainly on the regulatory frameworkof a country and therefore, it may differ according to jurisdiction. For more details with regard to other regional regulations and standards, see the specifications table in Chapter 7.8 and in Annex 7.

7.8. Key tender/request for quotation specifications for an ESU for LLETZ

Following are the key features that may be noted in a tender or request for quotation; detailed standardized WHO technical specifications can be found in Annex 7.

Product description	Electrosurgical units (ESUs) are used to carry out LLETZ (LEEP) procedures with the safe passage of electricity at a high frequency to and through tissue for both cutting (with wire electrodes) and coagulating (with ball electrodes). ESUs require highly-trained clinicians and are meant for use at higher-level health facilities.
Key product features	• Control panel for adjusting and displaying power settings; • Hand or foot switch to activate different electrodes or settings; • Minimum 1 monopolar handpiece port, 1 monopolar return electrode port (with alarm when poor contact quality), 1 bipolar outlet (bipolar not required for LLETZ); • Radiofrequency range from 200,000 Hz to 5,000,000 Hz. General ESU Modes: • coagulation mode: up to 80 W / 150 Ω • cutting mode: up to 110 - 200 W / 300 -400 Ω • blended current mode optional. LLETZ-specific setting: • blended current option mandatory • coagulation: 30 - 50 W settings available • cutting: 30 - 50 W settings available.
Components, accessories, consumables	Electrode: wired, various sizes and shapes, at a minimum has: • electrode (3-5mm ball) • square loop electrode (smaller) • semicircular loop electrode (larger); and • return electrode (typically a pad). A contact quality monitor (CQM) as an added feature, with either alarm or current shut-off, is highly recommended for patient safety.

Operational requirements	• Temperature: 5-40°C; • Relative humidity: ≤85% non-condensing; • The unit is suggested to be connected to a continuous, reliable power source (leverage surgical ward UPS); • Electrical source requirements (based on country/setting of use): » Amperage: _____ » Voltage: _____ » Plug type: _____ .
Documentation requirements	• Instructions for use and service manuals to be provided • User language preference prioritized, otherwise English is mandatory.
Warranty	Minimum one year.
Standards	Compliant with active version of the following standards (or equivalent): General • ISO 13485: Medical Devices - Quality Management Systems; • ISO 14971: Medical Devices - Application of Risk Management to Medical Devices; • ISO 15223-1: Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied; Specific • ISO 10993-1: Biological evaluation of medical devices Part 1: Evaluation and testing within a risk management process; • ISO 10993-5: Biological evaluation of medical devices Part 5: Tests for in vitro cytotoxicity; • ISO 10993-10: Biological evaluation of medical devices Part 10: Tests for irritation and skin sensitization; • ISO 13402: Surgical and dental hand instruments -- Determination of resistance against autoclaving, corrosion and thermal exposure. Safety and product standards: • IEC 60601-1 - Medical electrical equipment - Part 1: General requirements for basic safety and essential performance; • IEC 60601-1-2: Medical electrical equipment - Part 1-2 General requirements for basic safety and essential performance - Collateral Standard: Electromagnetic disturbances - Requirements and tests; • IEC 60601-2-2: Medical electrical equipment – Part 2-2: Particular requirements for the basic safety and essential performance of high frequency surgical equipment and high frequency surgical accessories. If battery-powered: • IEC 62133: Secondary cells and batteries containing alkaline or other non-acid electrolytes – Safety requirements for portable sealed secondary cells: » Part 1: Nickel » Part 2: Lithium.

Regulations	Compliance to (where applicable, but not limited to): • NRA requirements compliance • Approval by regulatory body of country of manufacturer (if applicable). • And at least one of: • United States regulations: US FDA 510(k): Device Class 2; • European regulatory framework: » Council Directive 93/42/EEC of 14 June 1993 on Medical Devices (Class IIb); » Regulation (EU) 2017/745 of the European Parliament and the Council; » Manufacturer must affix the CE marking and indicate the Notified Body number on the label and in the device. • Other regulatory body in an IMDRF founding member country such as Australia, Canada, or Japan.

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Section 3 – Procurement Guidance and further research

Chapter 8: Procurement guidance for medical devices

There are a number of medical devices and IVDs (devices, herein) on the market for the diagnosis and treatment of precancerous lesions for the prevention of cervical cancer, but not all of them are procured appropriately to match need of identified use-case.

Thus, key specifications that can be included in a tender in order to help managers and procurement personnel to purchase the correct product are described in each corresponding chapter; however, care should be taken to adapt contents to suit the needs of the end users if necessary.

In addition to outlining specifications, a request for supplemental information is also useful to include in a tender/request for quotation to aid in the decision making. Such information includes, but is not be limited to, the following:

- lead-time from receipt of contract/purchase order;
- method of shipment;
- shipping route;
- INCOTERMS (See details in Chapter 8.3);
- shipment/delivery costs, if applicable;
- weight and dimension of shipment;
- validity of quotation;
- payment terms;
- general and any special terms and conditions that will appear on the contract and/or the purchase order;
- evidence of ISO compliance when applicable;
- copy of regulatory approvals/clearances (e.g. US FDA, CE, or other acceptable SRAs; and,
- copy of proof of registration in the country of import.

Once a tender is awarded, it is important that the purchaser to obtain necessary documents in order to facilitate the movement of commodities or devices and to clear customs in an expeditious manner as possible. The following information and documentation should be obtained, as a minimum, in advance:

- delivery date;
- copy of the certificate of origin;
- copy of the certificate of conformity;
- commercial invoice;
- final transportation documents (waybill).

It is also important to note that countries who have not historically regulated medical devices are moving in this direction It is becoming increasingly common for aspects of regulation to be in place, and very likely that both the device manufacturer as well as make and model of specific devices must be registered in order for importation to take place.

In the absence of a registered product/manufacturer, an importer can often work with the Ministry of Health to apply for an import waiver. However, import waivers are usually only issued on a per shipment basis, thus it is important to also work with manufacturers to ensure that they apply to the local regulatory authority (or body responsible) in order to become registered for future procurements. In some countries, the registration process can take from one to three years; the earlier the manufacturer applies, the better, to ensure entrance of the shipment to the recipient country.

8.1. Nomenclature

The nomenclature, or naming system, of medical devices is used to generically identify medical devices and related health products. Nomenclature is a crosscutting system that can support medical devices at all levels: manufacturers, regulators, in procurement, and for final users in hospitals (stock management, post-market feedback loops, etc.).

Having a nomenclature system in place for medical devices can help to facilitate their management and regulation by standardizing terms, facilitating clear communication across all levels. With over 10,000 types of commercialized medical devices available, procurement decisions are often complicated by the lack of standardization of description of functionality of devices.

There are three main components to nomenclature: classification, nomenclature, and coding. If appropriately developed, these collective aspects of nomenclature can overcome linguistic barriers.

Classification or categorization is the grouping of all products in a logical, hierarchical manner. Devices share properties, enabling relationships, and it is important that these are appropriately mapped out by considering function, applications, operation principles, type of use, material and other properties, etc.

Nomenclature is the term given to and description of a type of product. This follows the classification and associated set of rules and criteria. It is important that these are clear, concise, and generic so as to avoid confusion and maintain agnosticism.

Coding is the process of assigning a unique identifier, or code, to each term of the classification and nomenclature system. Coding supports classification, such that hierarchy and relationships are evident in any type of medical device code.

A robust, well-utilized nomenclature system can simplify asset management in facilities: functional inventories, product availability, and the monitoring and evaluation of devices. Further, nomenclature can accelerate the regulatory process, support registration for market approval, and enhance post-market surveillance by tracking usage and enabling follow-up.

Globally, there are multiple classification, coding, and nomenclature systems which are often proprietary. To date, most international organizations and even UN agencies use varying systems. These systems are non-harmonized, which makes it very difficult to cross-map, thus rendering the full potential of such a system unachievable. Multiple, parallel systems complicate standards and regulatory processes, add unnecessary layers or challenges in procurement and supply, make for inefficient stock-keeping for and thus maintenance of devices more disorganized, hinder the reporting of adverse events and associated recalls related to faulty medical devices or malfunctions.

Globally, there are multiple classification, coding, and nomenclature systems which are often proprietary.

WHO has been working to develop the International classification, coding and nomenclature system of Medical Devices which leverages WHO's International Classification of Disease hierarchy, relationship, and classification platform (Active at time of publication: ICD-11). A code for each of the devices in this book will be found in this nomenclature, which will be further developed in the near future. The benefit is that this new WHO nomenclature will be open source and can be used by manufacturers, regulators, procurers, and even inventories in hospitals free of charge.

8.2. Incoterms

There are standard International Commercial Terms, known widely as "Incoterms®", which have been developed and trademarked by the International Chamber of Commerce (ICC). Incoterms are a suite of pre-defined terms, widely used in global commercial transactions. The use of Incoterms is encouraged by trade councils, courts, and international lawyers as they take into consideration international commercial law, and help to simplify the movement of goods in what is otherwise a very grey area.

With any international procurement, Incoterms can help to delineate tasks borne by seller and buyer with respect to transaction obligations (e.g. transport and delivery), and with whom lie risks and costs at every step of the way, including highlighting at which point the responsibility shifts from seller to buyer. Using Incoterms helps to clarify, for example, who is paying customs clearance charges, import duties and taxes, final delivery costs, etc.

As the terms themselves are so widely known and accepted, they are regularly incorporated into a purchase order and subsequently a sales contract; however, they are not themselves a contract, they do not themselves determine prices, currency rates, or override any local law.

There are standard International Commercial Terms, known widely as "Incoterms®", which have been developed and trademarked by the International Chamber of Commerce (ICC).

At time of publication, current terms were Incoterms 2010; however, ICC has already started drafting Incoterms 2020. For further information, please visit the ICC's website where Incoterms 2010 rules can be found, along with detailed guidance: https://iccwbo.org/resources-for-business/incoterms-rules/

8.3. Donations

Donations of medical equipment can be very helpful in bridging inequity between technologies produced by the global healthcare innovation community and users in low resource settings. However, if poorly executed, donations can turn into a burden for the recipient, wasting an enormous amount of money, human resources and time.

Donations must be seen as a standard procurement. The only deviation relates to the initial financial transaction, where cost is borne by the donor. Factors that will enable a successful medical donation include, but are not limited to:

- A partnership between donor and recipient
- An understanding of and appreciation for the challenges of the recipient's context
- Inventory to identify gaps in priority medical equipment so as to not procure blindly.

The recipient can then better plan for:

- Short- and longer-term integration of new equipment such as:
    - » Immediate need for infrastructure to support donations
    - » Needs for necessary accessories, spare parts and consumables
    - » Capacity building programs for end-users and clinical engineering staff.

- Tracking and monitoring of donations for:
    - » Follow-up issues as they relate to safety (post-market surveillance)
    - » Quantification of impact of donations.

For more information, please refer to WHO's Medical device donations: considerations for solicitation and provision.

Section 3 – Procurement Guidance and further research

Chapter 9: For further research

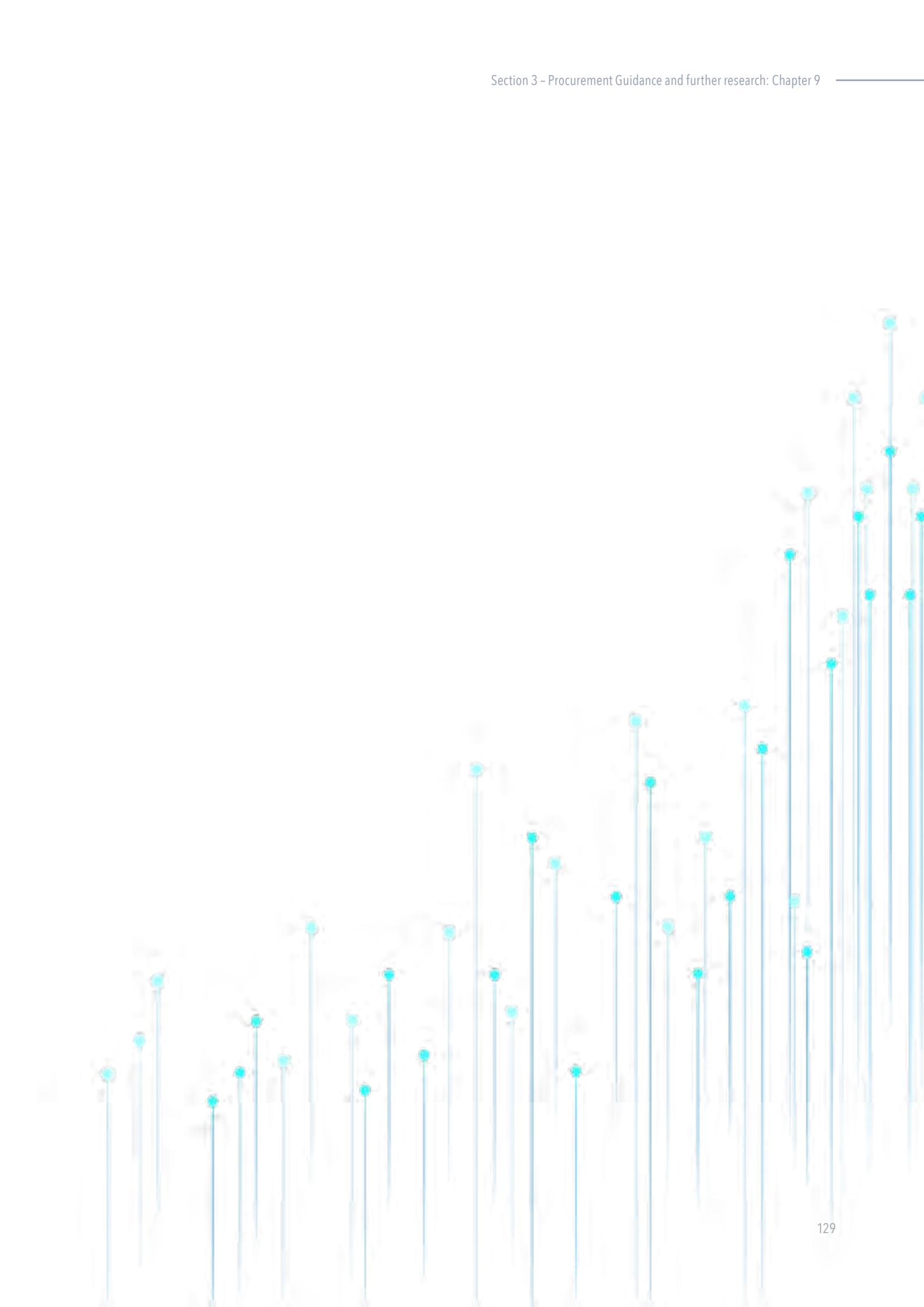
Technical specifications play a vital role in procuring affordable, high quality and appropriate medical devices and IVDs (devices, herein) for the diagnosis and treatment of precancerous lesions for the prevention of invasive cervical cancer. Stakeholder collaboration can ensure that the most effective and robust equipment is available. In collaboration with PATH and the Clinton Health Access Initiative (CHAI), WHO has gathered internal and external experts to determine and develop technical specifications. The challenges faced during this process were:

- discrepancies among existing standards and professional association guidelines
- lack of international standards for certain health technologies
- making unbiased optimal recommendations in a smaller market with limited vendors.

Some manufacturers from low-income countries find it difficult to comply with ISO, one of the most used international standards, as they are not publicly available and are not free of charge. It is difficult for manufacturers in these countries to make affordable devices for health facilities in low-resource settings while following these standards. However, quality and safety must never be sacrificed in order to lower development costs. Thus, careful consideration should be given when deciding not to apply a specific standard.

Quality and safety must never be sacrificed in order to lower development costs.

Research of innovative applications using medical devices plus artificial intelligence to support diagnostics and the appropriate methods to assess, regulate and use these devices remains a challenge and further studies need to be conducted.



Section 4

Annexes: technical specifications

Annex 1
Technical Specifications for specula for "screen & treat"

MEDICAL DEVICE SPECIFICATION (including information on the following where relevant/appropriate, but not limited to)			
i	**Version No.**	**1**	
ii	**Date of initial version**	**December 2019**	
iii	**Date of last modification**		
iv	**Date of publication**	**February 2020**	
v	**Completed / submitted by**	**WHO**	
NAME, CATEGORY AND CODING			
1	WHO Category / Code	Speculum, vaginal: XD9478	Speculum, vaginal, reusable: XD1KF1
2	Generic name	Speculum, vaginal	
3	Specific type or variation (optional)	Vaginal speculum, bivalved	
12	Keywords (optional)	surgical, gynaecology, vaginal exam	

PURPOSE OF USE		
14	Clinical or other purpose	A vaginal speculum is a device intended to open the vaginal canal to enable a healthcare provider to visually inspect the cervix and collect vaginal or cervical specimens and/or perform surgical operations in a woman's lower genital tract.
15	Level of use (if relevant)	Hospital, clinic, or health post
16	Clinical department/ward (if relevant)	Family medicine; gynaecology; obstetrics; outpatient clinic; outreach.
17	Overview of functional requirements	Bivalved vaginal specula have two blades that are self-retaining to facilitate visualization of the cervix for observation, testing, or to carry out a procedure.

TECHNICAL CHARACTERISTICS		
18	Detailed requirements	• Specify: reusable or single-use • Bivalved and self-retaining to maintain an open vaginal canal • To be available in a variety of sizes (large, medium, small, AND narrow e.g. Pedersen) • Type to be specified based on user preference or availability Example types and sizes: Collins: o Large – blade length: 110mm (+/- 5%), blade width: 40mm (+/- 5%). o Medium – blade length: 100mm(+/- 5%), blade width: 35mm (+/- 5%). o Small – blade length: 85mm(+/- 5%), blade width: 30mm (+/- 5%). Cusco: o Large – blade length: 11.5cm (+/- 5%), blade width: 3.5cm (+/- 5%). o Medium – blade length: 9.5cm (+/- 5%), blade width: 3.5cm (+/- 5%). o Small – blade length: 7.5cm (+/- 5%), blade width: 2cm (+/- 5%). Graves: o Large – blade length: 115mm (+/- 5%), blade width: 35mm (+/- 5%). o Medium – blade length: 95mm(+/- 5%), blade width: 35mm (+/- 5%). o Small – blade length: 75mm(+/- 5%), blade width: 20mm (+/- 5%). Pederson (narrower version of graves): o Large – blade length: 115mm (+/- 5%), blade width: 25mm (+/- 5%). o Medium – blade length: 95mm(+/- 5%), blade width: 22mm (+/- 5%). o Small – blade length: 75mm(+/- 5%), blade width: 13mm (+/- 5%). * More sizes and types available (e.g. larger, smaller, wider)
19	Displayed parameters	N/A
20	User adjustable settings	N/A
PHYSICAL/CHEMICAL CHARACTERISTICS		
21	Components (if relevant)	N/A
22	Mobility, portability (if relevant)	N/A

23	Raw Materials (if relevant)	Reusable: metal alloys (typically non-quenched, non-magnetic, austenitic stainless steel) and shall be autoclavable.	Single-use: high-strength plastic (for example acrylics) and are supplied as sterile.
PHYSICAL/CHEMICAL CHARACTERISTICS			
24	Electrical, water and/or gas supply (if relevant)	N/A	
ACCESSORIES, CONSUMABLES, SPARE PARTS, OTHER COMPONENTS			
25	Accessories (if relevant)	N/A	
26	Sterilization process for accessories (if relevant)	N/A	
27	Consumables / reagents (if relevant)	N/A	
28	Spare parts (if relevant)	N/A	
29	Other components (if relevant)	N/A	
ACCESSORIES, CONSUMABLES, SPARE PARTS, OTHER COMPONENTS			
30	Sterility status on delivery (if relevant)	Reusable: N/A	Single-use: sterile
31	Shelf life (if relevant)	N/A	

32	Transportation and storage (if relevant)	Storage area should be clean and dust-free, dry, cool, well-lit, ventilated and vermin-proof. Store device in original packaging on a shelf or on in a storage cabinet. Devices should be able to withstand storage temperatures ranging from 15°C to 30°C, relative humidity ≤ 85% (non-condensing), and be protected from dripping water.
33	Labelling (if relevant)	Labelling on the primary packaging should include the name and/or trademark of the manufacturer and should adhere to the most current version of ISO 15223 – 1: Medical devices -- Symbols to be used with medical device labels, labelling and information to be supplied -- Part 1: General requirements.
ENVIRONMENTAL REQUIREMENTS		
34	Context-dependent requirements	Environmental conditions vary globally and can be extreme; however, the following are tenable: - Operating temperature: 15°C to 35°C - Operating relative humidity: ≤ 85%, non-condensing It is the responsibility of the procurement body to ensure that the manufacturer's recommended operation and storage conditions are respected. If the device requires that the operating and/or storage environment be climate-controlled, appropriate temperature and humidity control systems, including monitoring, should be applied to avoid premature material disintegration and/or device failure.
TRAINING, INSTALLATION AND UTILISATION		
35	Pre-installation requirements (if relevant)	N/A
36	Requirements for commissioning (if relevant)	N/A
37	Training of user/s (if relevant)	Clinical staff training in vaginal examinations and gynaecological procedures.
38	User care (if relevant)	N/A
WARRANTY AND MAINTENANCE		
39	Warranty	One year

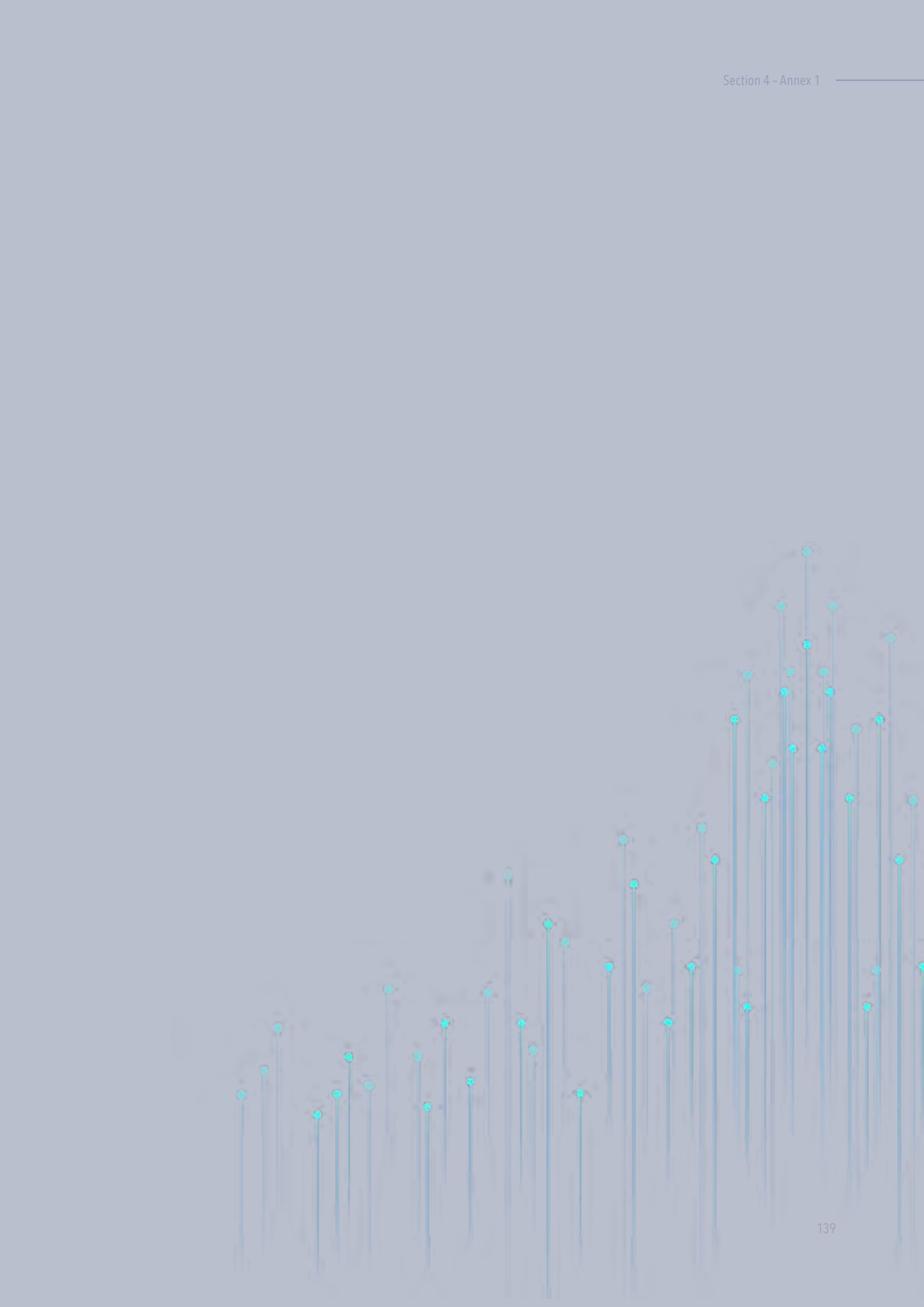
40	Maintenance tasks	N/A	
41	Type of service contract	N/A	
42	Spare parts availability post-warranty	N/A	
43	Software / Hardware upgrade availability	N/A	
DOCUMENTATION			
44	Documentation requirements	• Instructions for use and service manuals to be provided (including procedures for decontamination). • User language preference prioritized, English is mandatory. • Contact details of manufacturer, supplier and local agent.	
DECOMMISSIONING			
45	Estimated Life Span	N/A	
SAFETY AND STANDARDS			
46	Risk Classification	US FDA: Device Class 1 for metal speculum EU: Class I	US FDA: Device Class 2 for non-metal speculum EU: Class I
47	Regulatory Approval / Certification	Compliance to (where applicable, but not limited to): • National Regulatory Agency/Authority (NRA) requirements compliance • Approval by regulatory body of country of manufacturer (if applicable) And at least one of: • FDA 510k clearance (US FDA) • CE mark (EU), with indication of Notifying Body (when applicable) • Other regulatory body in an IMDRF founding member country such as Australia, Canada, or Japan.	

<table>
<tr><td rowspan="2">48</td><td rowspan="2">International standards</td><td colspan="2">Compliant with active version of the following standards (or equivalent):</td></tr>
<tr><td>For reusable products:

• ISO 7153-1: Surgical instruments – Materials -- Part 1: Stainless steel
• ISO 13402: Surgical and dental hand instruments -- Determination of resistance against autoclaving, corrosion and thermal exposure.</td><td>For singe-use products, supplied as sterile:

• ISO 17664: Processing of health care products – Information to be provided by the medical manufacturer for the processing of medical devices
• ISO 11135: Sterilization of health-care products - Ethylene oxide
• ISO 11137: Sterilization of health care products - Radiation
• ISO 11607: Packaging for terminally sterilized medical devices</td></tr>
<tr><td>49</td><td>Reginal / Local Standards</td><td colspan="2">Country-specific and regional standards may apply</td></tr>
<tr><td>50</td><td>Regulations</td><td colspan="2">US regulations:
21 CFR part 820 Quality System Regulation
21 CFR part 878.1800 - Speculum and accessories.

EU regulations:
European Commission Regulation (EU) No. 2017/745 (replacing 93/42/EEC) "</td></tr>
</table>



Annex 2A
Clinical and analytical performance details for HPV NAT IVDs

Clinical Performance

The sensitivity and specificity of an HPV IVD must be based on a clinically relevant endpoint to ensure that significant disease is not missed and also that transient HPV infection is not detected resulting in over-management of women with HPV detectable results. For HPV NAT IVDs that are used as a screening assay in a cancer prevention programme, the sensitivity must be high enough to initially identify all women who are at risk of having or developing high grade precancerous lesions (CIN2 or greater), yet not too analytically sensitive to identify infection that is not likely to progress to disease. To optimize disease detection over transient HPV detection, clinical assays will generally select a cut-off for a "positive"/"negative" result based on detection of CIN 2 or greater. This cut-off may not be the same as the analytical limit of detection (LoD).

To ensure reliable clinical performance, performance criteria have been developed for the validation of an HPV NAT. The most widely accepted criteria require favourable comparison to an HPV NAT IVD designated as the standard comparator. The HPV NAT IVD designated as the standard comparator should demonstrate superior sensitivity to cytology for the detection of precancerous lesions and should have met stringent regulatory standards from multiple regulatory agencies,[1] as well as approval by at least one of the founding members of IMDRF (International Medical Devices Regulators Forum). [2]

HPV NATs under consideration for use in screening programmes should have been validated by independent studies using the following criteria for clinical sensitivity and clinical specificity:

Table 13: Clinical sensitivity and specificity criteria

Performance Parameter	Sample Specification	Performance
Sensitivity	At least 60 cervical specimens from a population-based screening cohort of women ≥30 years with histologically confirmed CIN2 or greater	At least 90% of the sensitivity of the standard comparator for detection of CIN2 or greater
Specificity	At least 100 cervical specimens from a population-based screening cohort of women ≥30 years with histologic confirmation of no CIN2 or greater present	At least 98% of the specificity of the standard comparator for detection of CIN2

These criteria require that a candidate IVD must be evaluated for the performance parameters of sensitivity, specificity and intra- and inter-laboratory reproducibility. For sensitivity, clinical performance has been set to at least 90% of that of the standard comparator test for detection of CIN2 or greater in women ≥30 years. In addition, the candidate IVD should have a clinical specificity for CIN2 or greater of at least 98% of that of the standard comparator in women ≥30 years of age.

The criteria for an HPV NAT also specify that the specimens originate from a population-based screening cohort. For the sensitivity assessment, it is estimated that at least 60 cervical specimens derived from women with histologically confirmed CIN2 or greater should be tested. To confirm non-inferiority of specificity, specimens obtained from at least 100 women with histologic confirmation that CIN2 or greater is not present are required.

Analytical Performance

Unlike clinical performance, there are no accepted criteria for analytical performance of HPV NAT IVDs. A range of analytical sensitivities (expressed as LoD) can be considered, but it should be noted that the sensitivity will depend on the HPV genotype detected, the various technologies that are used in the IVDs, and the characteristics of the specific IVD. Analytical sensitivity or limit of detection is generally expressed as viral copies per reaction or per millilitre:

Table 14: Analytical sensitivity criteria

	Copies/reaction	Copies/ml
Range of Analytic Sensitivity[3]	24-7500	50-5000
Performance Parameter	Sample Specification	Performance

Alternatively, the analytical sensitivity or detection limit for NAT assays shall be expressed by the 95 % positive cut-off value. This is the analyte concentration where 95 % of test runs give positive results following serial dilutions of an international reference material, for example a WHO standard or calibrated reference material[112].

Analytic specificity is determined by evaluating an HPV NAT IVD for cross-reactivity with a panel of bacteria, fungi and viruses, including those commonly found in the female urogenital tract; the low-risk HPV genotypes are also included to ensure that a detectable HPV result will not lead to over-management/treatment of women who do not have one of the high-risk genotypes. Specificity is further confirmed by assessing the effects of endogenous (leukocytes, whole blood, cervical mucous) and exogenous (contraceptive and feminine hygiene products) interfering substances that can be found in cervical specimens. The manufacturer's instructions for use provide

information on both the microorganisms and interfering substances that have been evaluated.

Intra- and inter-laboratory reproducibility is addressed by demonstrating an agreement with a lower confidence bound not less than 87%. It is recommended that at least 500 specimens be evaluated, at least 30% of which tested positive in a reference laboratory using a clinically validated assay.

Table 15: Intra- and inter-laboratory reproducibility criteria

Intra- and Inter-Laboratory Reproducibility[5]	At least 500 samples 30% of which tested positive for HPV in a reference laboratory using a clinically validated assay	Lower bound of agreement not less than 87%

References

[1] World Health Organization (2018). Technical Specifications Series for submission to WHO Prequalification – Diagnostic Assessment. TSS-4: In vitro diagnostic medical devices (IVDs) used for the detection of high-risk human papillomavirus (HPV) genotypes in cervical cancer screening. Geneva, Switzerland: World Health Organization. http://apps.who.int/iris/bitstream/handle/10665/272282/9789241513814-eng.pdf?ua=1

[2] Founding members of IMDRF include Australia, Canada, European Union, Japan and USA.

[3] Burd, E. (2016). Human Papillomavirus laboratory testing: the changing paradigm. Clinical Microbiology Reviews; 29: 291-319.

[4] Decision of 3 February 2009 amending Decision 2002/364/EC on common technical specifications for in vitro-diagnostic medical device (notified under document number C(2009) 565)). https://eur-lex.europa.eu/eli/dec/2009/108(1)/oj

[5] Meijer CJ, Berkhof J, Castle PE, H et al. Guidelines for human papillomavirus DNA test requirements for primary cervical cancer screening in women 30 years and older. Int J Cancer. 2009; 124: 516-520.

Annex 2B
Technical Specifications for HPV NAT IVDs

In Vitro Diagnostic Medical Device (IVD) SPECIFICATION (including information on the following where relevant/appropriate, but not limited to)		
i	**Version No.**	**1**
ii	**Date of initial version**	**December 2019**
iii	**Date of last modification**	
iv	**Date of publication**	**February 2020**
v	**Completed / submitted by**	**WHO**
NAME, CATEGORY AND CODING		
1	WHO Category / Code	Under development
2	Generic name	HPV NAT to be used at point of care
3	Specific type or variation (optional)	n/a
INTENDED USE		
14	Test purpose	For screening. To detect nucleic acid for high-risk HPV genotypes including HPV 16 and HPV 18.
15	Specific disorder/condition or risk factor of interest	Certain subtypes of HPV as the causative agent of cervical and other anogenital carcinomas.

16	Testing population	Females over 30 years of age at risk of cervical cancer
17	Level of the health system	IVDs for use at point of care should be able to be used in settings without laboratory infrastructure, e.g. no or intermittant electricity, no reagent grade water, no specialised specimen collection available, no specialised laboratory staff available. Level I, Level II, Level III, Level IV health facilities.
18	Intended user	Specimen collection - trained healthcare worker or self test procedure - trained healthcare worker
PERFORMANCE CHARACTERISTICS		
19	Clinical sensitivity	See TSS-4: IVDs used for the detection of high-risk HPV types in cervical cancer screening for performance requirements
21	Analytical sensitivity	
22	Clinical specificity	
23	Invalid/unreturnable rate	
OPERATIONAL CHARACTERISTICS		
24	Detection type	Qualitative detection of DNA with PV gene target (L1, E1 ORF).

25	Genotype detection	Relevant genotypes to be detected are HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 (with 66, 68 acceptable but not preferable) as optional pooled result. Detection of HPV 16 or HPV 16 and 18 is required at a minimum. Individual targeted genotyping as a reflex test or concurrent (preferred) with pooled results; if reporting out individual genotypes, must have the ability to distinguish between genotypes.
26	Specimen type	Cervical or vaginal, generally using device and specimen transport medium validated and supplied by the manufacturer of IVD. The required specimen volume for testing must be specified.
27	Specimen throughput	For IVDs used at POC, throughput varies based on product design, but is usually no more than 8 specimens per 8 hour shift per operator.
28	Time to first results (including hands-on time)	Specimens per run, total run time, hands-on-time and walk-away time must be specified.
29	Displayed parameters	HPV 16 detected/not detected HPV 18 detected/not detected HPV 16 or 18 detected/not detected Pooled result, if performed
30	Internal quality control	Essential, amplification control Desirable, positive and negative controls Desirable, sample adequacy control (human housekeeping gene)
31	Compatibility with external quality control material	Desirable (e.g. SeraCare, Acrometrix, Bio-rad)
32	Shelf life upon manufacture (months)	Shelf-life must be specified.
33	Guaranteed shelf life upon delivery	Must have a minimum of 80% of the guaranteed shelf life at the time of delivery, where guaranteed shelf life may be less than shelf life upon manufacture. Note: the guaranteed shelf life is highly dependent on INCOTERMs as stipulated in procurement contracts.

34	Stability of reagents (temperature and humidity)	Transport (room temperature; 17 to 27 °C) Storage (2 to 30 °C) On-board (2 to 30 °C). Manufacturer must provide duration for on-board stability. In-use (2 to 30 °C)
35	Stability for specimen collection media	Transport (room temperature; 17 to 27 °C) Storage (2 to 30 °C) In-use (2 to 30 °C)
36	Stability for controls/calibrators	Transport (room temperature; 17 to 27 °C) Storage (2 to 30 °C) On-board (2 to 30 °C). Manufacturer must provide duration for on-board stability. In-use (2 to 30 °C)
37	Operating conditions for analysers (temperature and humidity)	Manufacturer must provide required operating conditions for the IVD (temperature and humidity)
PHYSICAL/CHEMICAL CHARACTERISTICS		
38	Components(if relevant)	HPV NAT IVDs will normally have the following essential components: 1. Specimen collection device and transportation media 2. Reagent kit(s) or cartridge 3. Analyser(s) for extraction, amplification and detection, separate or combined.
39	Footprint (cubic m3)	No more than size of average room.
40	Weight (kg) and volume	Must be able to be placed on a non-reinforced table or else come with own stand.
INFRASTRUCTURE REQUIREMENTS		
41	Electricity	Constant electrical supply required with access to an uninterrupted power supply (UPS), or battery powered.
42	Water (reagent grade)	Required/not required
43	Refrigeration or cold chain	No cold chain for IVDs used at POC.

ACCESSORIES, CONSUMABLES, SPARE PARTS, OTHER COMPONENTS		
44	Consumables / reagents (if relevant)	HPV NATs come in different designs and therefore requirements are dependent on manufacturer specifications. HPV NATs will normally require the following consumables for each test: 1. Specimen collection device 2. Reagents contained within a test kit or a cartridge
45	Items required but not provided	Specimen collection devices and transport media Specimen racks Bleach 70% ethanol Paper towel Powder-free gloves Pipettes and plugged pipette tips Waste disposal For provider-collected specimens, an exam table with stirrups, adjustable exam light and vaginal speculum are also required.
46	Other auxiliary laboratory equipment	Vortex
LABELLING		
47	Instructions for use	IFU submitted must relate to regulatory version registered for sale and use in country of supply.
48	Certificate of analysis	Must be submitted with each consignment of reagents shipped.
ENVIRONMENTAL AND BIOSAFETY REQUIREMENTS		
49	Hazardous classification	Hazardous goods classification, including material safety data sheet (MSDS)
50	Disposal requirements	Biohazard receptacles are required for disposal of any biological specimen, including amplified genetic material contained within test kits, cartridges, or collection devices.
TRAINING, INSTALLATION AND UTILISATION		
51	Installation and calibration	Any substantive calibration to be conducted by the supplier (should not be separately charged). Only minimal calibration to be conducted by testing provider.

52	Training of users	Pre-service and in-service
WARRANTY AND MAINTENANCE		
53	Warranty	Minimum 24 months.
54	Preventive maintenance	Expected minimal maintenance to be conducted by testing provider should be stated. Frequency of servicing based on fixed time periods or based on the number of tests the instrument processes.
55	Corrective maintenance	Major fixes and/or replacements, the response and resolution times are governed by the service level agreement.
56	Type of service contract	Must cover labour, repair, spare parts, loaner instrument, shipping and logistics costs, and training
57	Spare parts availability, post-warranty	To be covered in service level agreement.
DECOMMISSIONING		
58	Estimated Life Span	No less than 2 years.
QUALITY AND REGISTRATION		
59	Global regulatory approvals	Careful consideration should be taken to ensure that the selected products have been assessed to an appropriate stringency level based on the risk classification for HPV NAT IVDs.
60	Free sale certificate	Provide valid certification for export from country of origin
61	WHO prequalification status	Desirable. Provide valid WHO PQ Public Report and current WHO list of prequalified IVDs.
62	International standards	Compliant with active version of the following standards (or equivalent):
63	National registration	Essential. Provide valid certification.

64	Post-market surveillance	Essential, respond to customer complaints in timely manner and notify NRA for serious and moderate adverse events according to their timelines.
65	Field safety corrective actions	Essential, inform affected customers of any FSCA (such as recall or change in labelling) in a timely manner and notify NRA for all FSCA.
64	Replacement of defective product	Desirable, depending on root cause of issue.

In Vitro Diagnostic Medical Device (IVD) SPECIFICATION		
i	**Version No.**	**1**
ii	**Date of initial version**	**December 2019**
iii	**Date of last modification**	
iv	**Date of publication**	**February 2020**
v	**Completed / submitted by**	**WHO**
NAME, CATEGORY AND CODING		
1	WHO Category / Code	Under development
2	Generic name	HPV NAT to be used in laboratory setting.
3	Specific type or variation (optional)	n/a
INTENDED USE		
14	Test purpose	For screening. To detect nucleic acid for high-risk HPV genotypes including HPV 16 and HPV 18, or for the detection of mRNA transcripts coding for E6/E7.
15	Specific disorder/condition or risk factor of interest	Certain subtypes of HPV as the causative agent of cervical and other anogenital carcinomas.
16	Testing population	Females over 30 years of age at risk of cervical cancer
17	Level of the heallth system	IVDs for use in laboratory settings, e.g. with stable or intermittent electricity, reagent grade water, specialised specimen collection and processing available, specialised laboratory staff available. Level II, Level III, Level IV health facilities
18	Intended user	Specimen collection - trained healthcare worker or self Test procedure - trained laboratory technician for laboratory-based IVDs

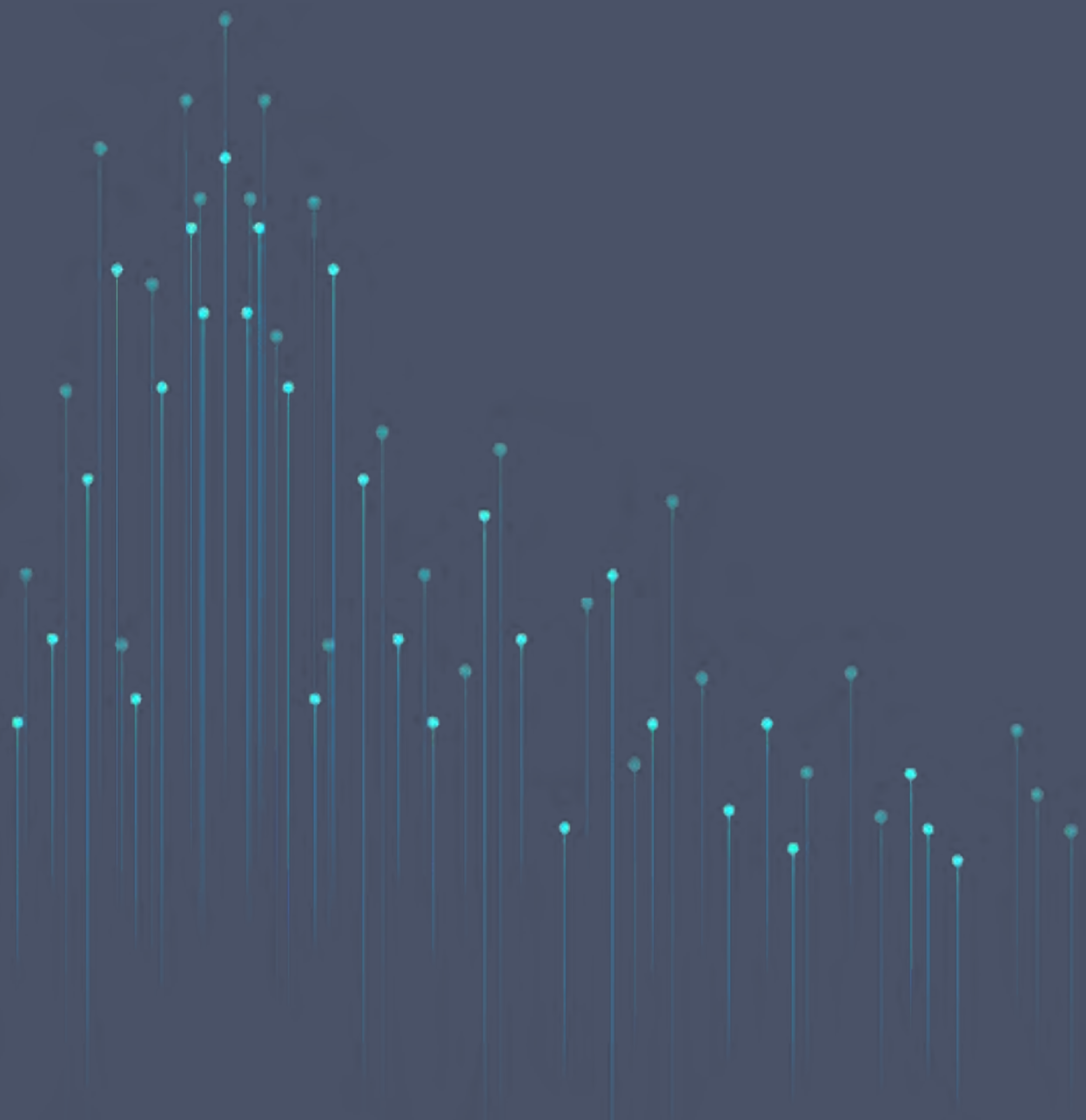
PERFORMANCE CHARACTERISTICS		
19	Clinical sensitivity	See TSS-4: IVDs used for the detection of high-risk HPV types in cervical cancer screening for performance requirements
21	Analytical sensitivity	
22	Clinical specificity	
23	Invalid/unreturnable rate	
OPERATIONAL CHARACTERISTICS		
24	Detection type	Qualitative detection of DNA or RNA with HPV gene target (L1, E6, E7, E1 ORF).
25	Genotype detection	Relevant genotypes to be detected are HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 with 66, 68 optional as pooled result. Detection of HPV 16 or HPV 16 and 18 is required at a minimum. Individual targeted genotyping as a reflex test or concurrent (preferred) with pooled results; if reporting out individual genotypes, must have the ability to distinguish between genotypes.
26	Specimen type	Cervical or vaginal, generally using device and specimen transport medium validated and supplied by the manufacturer of IVD. The required specimen volume for testing must be specified.
27	Specimen throughput	For laboratory-based IVDs, throughput is usually no more than 94 specimens per run per operator.
28	Time to first results (including hands-on time required)	For manual test systems, the hands-on-time, the specimens per run and overall time must be specified. For automated test systems, the specimens per run, total run time, hands-on-time and walk-away time must be specified.
29	Displayed parameters	HPV 16 detected/not detected HPV 18 detected/not detected HPV 16 or 18 detected/not detected Pooled result, if performed

30	Internal quality control	Essential, amplification control Desirable, positive and negative controls Desirable, sample adequacy control (human housekeeping gene)
31	Compatibility with external quality control material	Desirable (e.g. SeraCare, Acrometrix, Bio-rad)
32	Shelf life upon manufacture (months)	
33	Guaranteed shelf life upon delivery	Reagents must have a minimum of 80% of the guaranteed shelf-life at the time of delivery, where guaranteed shelf-life may be less than shelf-life upon manufacture. Note: the guaranteed shelf-life is highly dependent on INCOTERMs as stipulated in procurement contracts.
34	Stability of reagents (temperature and humidity)	Transport (room temperature; 17 to 27 °C) Storage (2 to 30 °C) On-board (2 to 30 °C). Manufacturer must provide duration for on-board stability. In-use (2 to 30 °C)
35	Stability for specimen collection media	Transport (room temperature) Storage (2 to 30 °C) In-use (2 to 30 °C)
36	Stability for controls/calibrators	Transport (room temperature) Storage (2 to 30 °C) On-board (2 to 30 °C). Manufacturer must provide duration for on-board stability. In-use (2 to 30 °C)
37	Operating conditions for analysers (temperature and humidity)	Manufacturer must provide required operating conditions for the IVD (temperature and humidity)
PHYSICAL/CHEMICAL CHARACTERISTICS		
38	Components(if relevant)	HPV NAT IVDs will normally have the following essential components: 1. Specimen collection device and transportation media 2. Reagent kit(s) or cartridge 3. Analyzer(s) for extraction, amplification and detection, separate or combined.

39	Footprint (cubic m3)	Varies based on throughput and product design.
40	Weight (kg) and volume	Must be able to be placed on a non-reinforced table or else come with own stand.
INFRASTRUCTURE REQUIREMENTS		
41	Electricity	Constant electrical supply required with access to an uninterrupted power supply (UPS). Desirable to have battery operation option in case of power outage to finish the in-process run.
42	Water (reagent grade)	Required/not required.
43	Refrigeration or cold chain	2 to 8 °C
ACCESSORIES, CONSUMABLES, SPARE PARTS, OTHER COMPONENTS		
44	Consumables / reagents (if relevant)	HPV NATs come in different designs and therefore requirements are dependent on manufacturer specfications. HPV NATs will normally require the following consummables for each test: 1. Specimen collection device 2. Reagents contained within a test kit or a cartridge
45	Items required but not provided	Specimen collection devices and transport media Specimen racks Bleach 70% ethanol Paper towel Powder-free gloves Pipettes and plugged pipette tips Waste disposal For provider-collected specimens, an exam table with stirrups, adjustable exam light and vaginal speculum are also required.
46	Other auxiliary laboratory equipment	Vortex
LABELLING		
47	Instructions for use	IFU submitted must relate to regulatory version registered for sale and use in country of supply.
48	Certificate of analysis	Must be submitted with each consignment of reagents shipped.

ENVIRONMENTAL AND BIOSAFETY REQUIREMENTS		
49	Hazardous classification	Hazardous goods classification, including material safety data sheet (MSDS)
50	Disposal requirements	Biohazard receptacles are required for disposal of any biological specimen, including amplified genetic material contained within test kits, cartridges, or collection devices.
TRAINING, INSTALLATION AND UTILISATION		
51	Installation and calibration	Any substantive calibration to be conducted by the supplier (should not be seperately charged). Only minimal calibration to be conducted by testing provider.
52	Training of users	Pre-service and in-service
WARRANTY AND MAINTENANCE		
53	Warranty	Minimum 24 months.
54	Preventive maintenance	Expected minimal maintenance to be conducted by testing provider should be stated. Frequency of servicing based on fixed time periods or based on the number of tests the instrument processes.
55	Corrective maintenance	Major fixes and/or replacements, the response and resolution times are governed by the service level agreement.
56	Type of service contract	Must cover labour, repair, spare parts, loaner instrument, shipping and logistics costs, and training
57	Spare parts availability, post-warranty	To be covered in service level agreement.

DECOMMISSIONING		
58	Estimated Life Span	No less than 2 years.
QUALITY AND REGISTRATION		
59	Global regulatory approvals	Careful consideration should be taken to ensure that the selected products have been assessed to an appropriate stringency level based on the risk classification for HPV NAT IVDs.
60	Free sale certificate	Provide valid certification for export from country of origin
61	WHO prequalification status	Desirable. Provide valid WHO PQ Public Report and current WHO list of prequalified IVDs.
62	International standards	Compliant with active version of the following standards (or equivalent): • ISO 13485: Medical devices–Quality management systems (must provide certification) • ISO 14971: Medical devices–Application of risk management to medical devices • ISO 23640: In vitro diagnostic medical devices–Evaluation of stability of in vitro diagnostic reagents • ISO 18113-1: In vitro diagnostic medical devices -- Information supplied by the manufacturer (labelling) -- Part 1: Terms, definitions and general requirements
63	National registration	Essential. Provide valid certification.
64	Post-market surveillance	Essential, respond to customer complaints in timely manner and notify NRA for serious and moderate adverse events according to their timelines.
65	Field safety corrective actions	Essential, inform affected customers of any FSCA (such as recall or change in labelling) in a timely manner and notify NRA for all FSCA.
66	Replacement of defective product	Desirable, depending on root cause of issue.



Annex 3
Technical Specifications for Acetic Acid for VIA

MEDICAL DEVICE SPECIFICATION		
i	**Version No.**	**1**
ii	**Date of initial version**	**December 2019**
iii	**Date of last modification**	
iv	**Date of publication**	**February 2020**
v	**Completed / submitted by**	**WHO**
NAME, CATEGORY AND CODING		
1	WHO Category / Code	N/A
2	Generic name	Acetic acid
3	Specific type or variation (optional)	Glacial acetic acid
10	Alternative name/s (optional)	Glacial acetic acid; Methanecarboxylic acid; Ethanoic acid; Vinegar acid; glacial/ alcohol of vinegar; carboxylic acid C2; ethanoic acid; ethylic acid; methanecarboxylic acid; pyroligneous acid.

11	Alternative code/s (optional)	CAS No : 64-19-7; Formula : $C_2H_4O_2$ UN 2789, class 8: Acetic acid, glacial or Acetic acid solution, with more than 80 percent acid, by mass UN 2790, class 8: Acetic acid solution, not less than 50 percent but not more than 80 percent acid, by mass or Acetic acid solution, with more than 10 percent and less than 50 percent acid, by mass IUPAC Name: acetic acid MDL Number: MFCD00036152;
12	Keywords (optional)	Acetic Acid
PURPOSE OF USE		
14	Clinical or other purpose	Visual inspection with acetic acid (VIA) is a direct visual assessment of the cervix using a 3-5% acetic acid solution to visibly whiten cervical lesions, which temporarily produces what is known as an acetowhite lesion.
15	Level of use (if relevant)	Hospital, clinic, or health post
16	Clinical department/ward (if relevant)	Family medicine; gynaecology; obstetrics; outpatient clinic; outreach.
17	Overview of functional requirements	Acetic acid solution shall be 3-5%, by volume, acetic acid in a solution of distilled water.

TECHNICAL CHARACTERISTICS		
18	Detailed requirements	• 3-5% Acetic acid solution required • Dilutions to be made, with distilled water, to 3-5% Acetic acid by volume. • If diluting from a higher concentration, to be made fresh daily: - Use only under a chemical fume hood. - Use explosion-proof equipment. - Keep away from open flames, hot surfaces and sources of ignition. - Do not breathe vapours or spray mist. - Avoid contact with eyes. - Avoid direct contact with skin. - Avoid spilling on clothing. - Take precautionary measures against static discharges. • Unused dilutions to be discarded at the end of the day
19	Displayed parameters	N/A
20	User adjustable settings	N/A
PHYSICAL/CHEMICAL CHARACTERISTICS		
21	Components (if relevant)	Acetic Acid, distilled water
22	Mobility, portability (if relevant)	N/A
23	Raw Materials (if relevant)	Glacial acid, or higher than 5% acetic acid to be diluted with distilled water to 3-5% acetic acid, by volume.
UTILITY REQUIREMENTS		
24	Electrical, water and/or gas supply (if relevant)	N/A

ACCESSORIES, CONSUMABLES, SPARE PARTS, OTHER COMPONENTS		
25	Accessories (if relevant)	If diluting glacial (water-free) or high-percentage acetic acid, use: gloves, goggles, apron, graduated cylinder, syringe/small cylinder, storage container with lid, and distilled water. Speculum Light
26	Sterilization process for accessories (if relevant)	N/A
27	Consumables / reagents (if relevant)	N/A
28	Spare parts (if relevant)	N/A
29	Other components (if relevant)	N/A
PACKAGING		
30	Sterility status on delivery (if relevant)	N/A
31	Shelf life (if relevant)	• Solutions in original packaging to respect indicated storage conditions and best-before date. • Dilutions: one day (due to potential for evaporation or contamination).

32	Transportation and storage (if relevant)	**Storage area:** - Clean, dust-free, dry, cool, out of direct sunlight, well-lit, ventilated (floor level) and vermin-proof. - Fireproof, frost-proof store-room in detached building. - Keep store-room locked. - Provide for a tub to collect spills. - Provide the tank with earthing. **Storage:** - Keep concentrated, starting or mother solution in original packaging on a shelf or in a storage cabinet. - Keep containers labelled and tightly closed - Keep away from open flames, hot surfaces and sources of ignition or flammables area. - Store separately from oxidizing materials and alkaline substances. - acetic acid should be able to withstand storage temperatures ranging from 15°C to 30°C, relative humidity ≤ 60% (non-condensing). Packaging materials: suitable materials are aluminium and glass. MATERIAL TO AVOID: steel, iron, zinc, lead, copper, and bronze.
33	Labelling (if relevant)	Globally Harmonized System of Classification and Labelling of Chemicals (GHS) or equivalent. Labelling on the primary packaging should include the name and/or trademark of the manufacturer and should adhere to the most current version of ISO 15223 – 1: Medical devices -- Symbols to be used with medical device labels, labelling and information to be supplied -- Part 1: General requirements.
ENVIRONMENTAL REQUIREMENTS		
34	Context-dependent requirements	3-5% acetic acid is used under ambient conditions. Environmental conditions vary globally and can be extreme. It is the responsibility of the procurement body to ensure that the manufacturer's recommended operation and storage conditions are respected. If the product requires that the operating and/or storage environment be climate-controlled, appropriate temperature and humidity control systems, including monitoring, should be applied to avoid premature degradation of product.

TRAINING, INSTALLATION AND UTILISATION		
35	Pre-installation requirements (if relevant)	N/A
36	Requirements for commissioning (if relevant)	N/A
37	Training of user/s (if relevant)	Clinical staff training in vaginal examinations and targeted training for dilution preparation (if relevant)
38	User care (if relevant)	N/A
WARRANTY AND MAINTENANCE		
39	Warranty	N/A - Explicit expiry date on packaging of original solution, 3 years after date of manufacture
40	Maintenance tasks	N/A
41	Type of service contract	N/A
42	Spare parts availability post-warranty	N/A
43	Software / Hardware upgrade availability	N/A
DOCUMENTATION		
44	Estimated Life Span	• If using glacial acid, product must have a Drug Identification Number (DIN) from national or regional health authority. • User language prioritized for labelling, otherwise English is mandatory. • Contact details of manufacturer, supplier and local agent. • Supplier to describe any materials that are classified as hazardous under local regulations.
DECOMMISSIONING		
45	Estimated Life Span	N/A

SAFETY AND STANDARDS		
46	Risk Classification	Hazard pictograms (GHS): GHS02 GHS05 Signal word (GHS): Danger Hazard statements (GHS): H226 - Flammable liquid and vapour. H314 - Causes severe skin burns and eye damage. H402 - Harmful to aquatic life. Precautionary statements (GHS): P210 - Keep away from heat, sparks, open flames, hot surfaces. No smoking. P233 - Keep container tightly closed. P240 - Ground/bond container and receiving equipment. P241 - Use explosion-proof electrical, ventilating, lighting equipment. P242 - Use only non-sparking tools. P243 - Take precautionary measures against static discharge. P260 - Do not breathe mist, vapours, spray. P264 - Wash exposed skin thoroughly after handling. P273 - Avoid release to the environment. P280 - Wear protective clothing, protective gloves, eye protection, face protection. P301 + P330 + P331: IF SWALLOWED, rinse mouth. Do NOT induce vomiting. P303 + P361 + P353: IF ON SKIN (or hair), remove/take off all contaminated clothing immediately. Rinse skin with water/shower. P304 + P340: IF INHALED, remove victim to fresh air and keep at rest in a position comfortable for breathing. P305 + P351 + P338: IF IN EYES, rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. P310 - Immediately call a poison centre or doctor/physician. P363 - Wash contaminated clothing before reuse. P370 + P378: In case of fire, use carbon dioxide (CO_2), powder, alcohol-resistant foam to extinguish. P403 + P235: Store in a well-ventilated place. Keep cool. P405 - Store locked up. P501 - Dispose of contents/container to comply with local, state and federal regulations.

47	Regulatory Approval / Certification	N/A
48	International standards	Listed on the United States TSCA (Toxic Substances Control Act) inventory Listed on the Canadian DSL (Domestic Substances List) Listed on the Canadian IDL (Ingredient Disclosure List)
49	Reginal / Local Standards	Country-specific and regional standards may apply
50	Regulations	N/A

Annex 4
Technical Specifications for Colposcopes

MEDICAL DEVICE SPECIFICATION **(including information on the following where relevant/appropriate, but not limited to)**		
i	**Version No.**	**1**
ii	**Date of initial version**	**December 2019**
iii	**Date of last modification**	
iv	**Date of publication**	**February 2020**
v	**Completed / submitted by**	**WHO**
NAME, CATEGORY AND CODING		
1	WHO Category / Code	Colposcopes, XD2AZ1
2	Generic name	Colposcope
10	Alternative name/s (optional)	Colpomicroscopes, vaginoscopes
11	Alternative code/s (optional)	N/A
12	Keywords (optional)	surgical, gynaecology, magnification

PURPOSE OF USE		
14	Clinical or other purpose	A colposcope is a low magnification, light-illuminated visualization device for examining the cervix, across an area measuring approximately 20 to 30 mm in diameter, with enough distance between the colposcope lens and the cervix to accommodate the surgical instruments needed for the examination and/or treatment. It allows the examiner to view the epithelial tissues of the cervix and other anogenital areas.
15	Level of use (if relevant)	Clinic, health centre, (district) hospital, specialized clinic
16	Clinical department/ward (if relevant)	Family medicine; gynaecology; outpatient clinic; outreach; oncology; obstetrics; surgery; nursing services
17	Overview of functional requirements	Colposcope functional requirements: 1) the colposcope head housing the optics capable of magnification and focus 2) the light source and green light filters for improved visualization of vasculature 3) the body or stand to facilitate and optimises biopsy and excisional treatment.

TECHNICAL CHARACTERISTICS		
18	Detailed requirements	• Magnification: A range of optical magnification between 3x to 15x (either stepped or continuously variable) • Illumination: o Light sources shall be either halogen or LED to guarantee full-spectrum visible light (white light) - Halogen light: 15 V/150 W - LED: 20,000-35,000 LUX (at 300 mm working distance) o An illumination adjustment knob to change the intensity of light o A fan to cool the bulbs (if halogen bulbs are used) • Green light filters; however, blue filters are also acceptable but not the preferred option • Ingress protection rating: IPX2 (minimum)
19	Displayed parameters	N/A
20	User adjustable settings	- Coarse and fine optical magnification - Illumination
PHYSICAL / CHEMICAL CHARACTERISTICS		
21	Components (if relevant)	N/A
22	Mobility, portability (if relevant)	N/A
23	Raw Materials (if relevant)	N/A
UTILITY REQUIREMENTS		
24	Electrical, water and/or gas supply (if relevant)	• The unit is suggested to be connected to a reliable power source. • Electrical source requirements (based on country/setting of use): o Amperage: _____ o Voltage: _____ o Plug type: _____ .

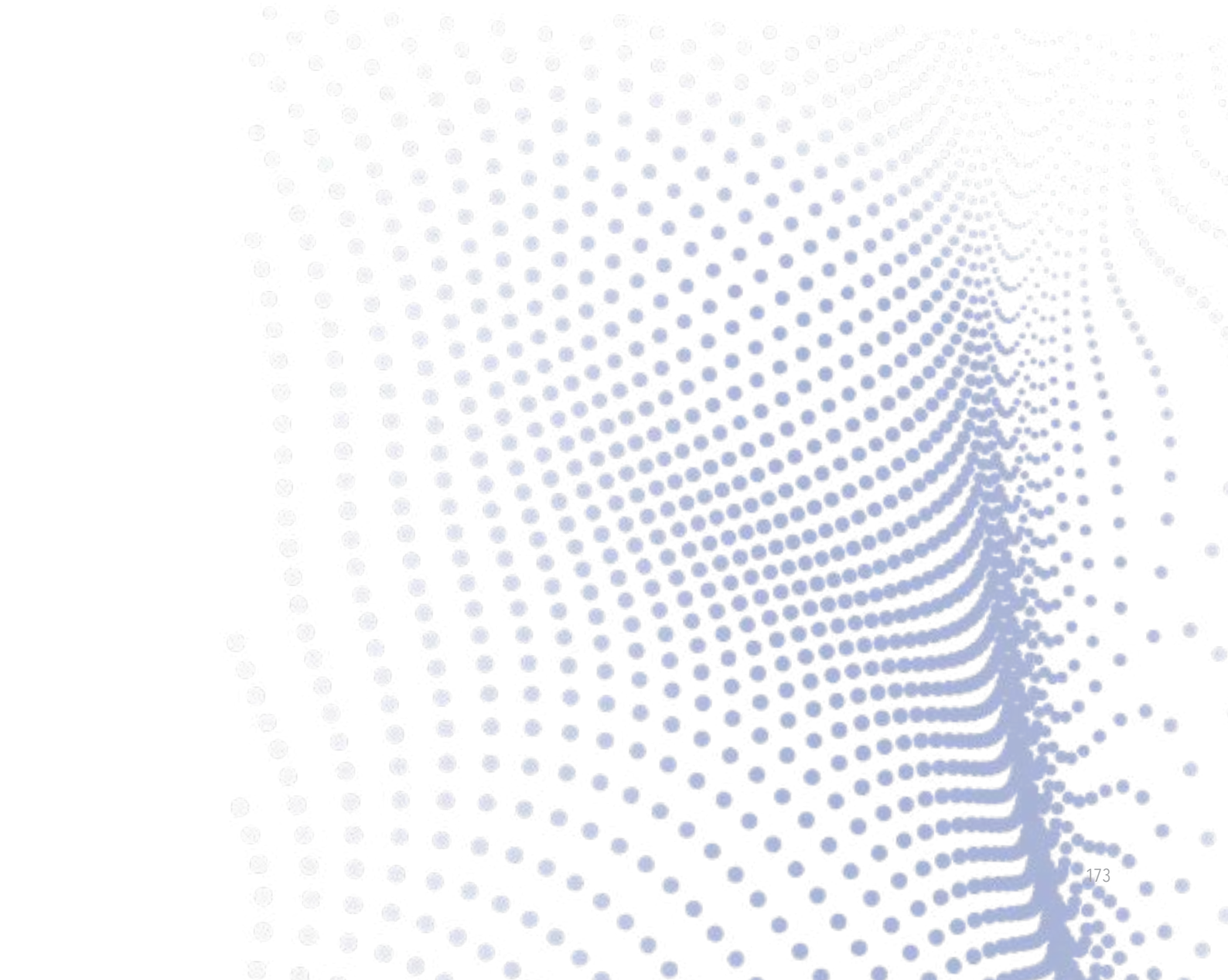
ACCESSORIES, CONSUMABLES, SPARE PARTS AND OTHER COMPONENTS		
25	Accessories (if relevant)	• Stand or mount to allow for hands-free operation • LED TV or medical grade monitor if not integrated (optional) • Single-use sheath (if using invasive portable model)
26	Sterilization process for accessories (if relevant)	N/A
27	Consumables / reagents (if relevant)	N/A
28	Spare parts (if relevant)	Lamp bulbs and fuses.
29	Other components (if relevant)	N/A
PACKAGING		
30	Sterility status on delivery (if relevant)	N/A
31	Shelf life (if relevant)	N/A
32	Transportation and storage (if relevant)	Storage area should be clean and dust-free, dry, cool, well-lit, ventilated and vermin-proof. Store device in original packaging on a shelf or on in a storage cabinet. Devices should be able to withstand storage temperatures ranging from 15°C to 30°C, relative humidity ≤ 85% (non-condensing), and be protected from dripping water (IPX2).
33	Labelling (if relevant)	Labelling on the primary packaging should include the name and/or trademark of the manufacturer and should adhere to the most current version of ISO 15223 – 1: Medical devices -- Symbols to be used with medical device labels, labelling and information to be supplied -- Part 1: General requirements.

ENVIRONMENTAL REQUIREMENTS		
34	Context-dependent requirements	Environmental conditions vary globally and can be extreme; however, the following are tenable: - Operating temperature: 15°C to 35°C - Operating relative humidity: ≤ 85%, non-condensing It is the responsibility of the procurement body to ensure that the manufacturer's recommended operation and storage conditions are respected. If the device requires that the operating and/or storage environment be climate-controlled, appropriate temperature and humidity control systems, including monitoring, should be applied to avoid premature material disintegration and/or device failure.
TRAINING, INSTALLATION AND UTILISATION		
35	Pre-installation requirements (if relevant)	N/A
36	Requirements for commissioning (if relevant)	N/A
37	Training of user/s (if relevant)	Training of users in operation and basic maintenance shall be provided. Clinical staff training in cervical precancer lesion treatment guidelines and device use to be provided.
38	User care (if relevant)	N/A
WARRANTY AND MAINTENANCE		
39	Warranty	Minimum one year. Specific inclusions and exclusions to be listed. Contact details of manufacturer, supplier and local service agent to be provided.
40	Maintenance tasks	Limited maintenance requirements. Standard colposcopes may require replacement of worn parts including lamps, eyepiece rings, light guides and fuses. Follow device-specific service manual, as instructions are specific to each colposcope model.
41	Type of service contract	N/A

42	Spare parts availability post-warranty	8 years minimum, starting from installation/commissioning
43	Software / Hardware upgrade availability	N/A
DOCUMENTATION		
44	Documentation requirements	• Instructions for use and service manuals to be provided (including procedures for decontamination) • User language preference prioritized, English is mandatory. • Contact details of manufacturer, supplier and local service agent. • Certificate of calibration and inspection to be provided (if applicable). • List to be provided of equipment and procedures required for local calibration and routine maintenance. • List to be provided of common spares and accessories, with part numbers.
DECOMMISSIONING		
45	Estimated Life Span	10 years
SAFETY AND STANDARDS		
46	Risk classification	US FDA: Device Class 2 EU: Class IIa
47	Regulatory Approval / Certification	Compliance to (where applicable, but not limited to): - National Regulatory Agency/Authority (NRA) requirements compliance - Approval by regulatory body of country of manufacturer (if applicable) And at least one of: - FDA 510k clearance (US FDA) - CE mark (EU), with indication of Notifying Body (when applicable) - Other regulatory body in an IMDRF founding member country such as Australia, Canada, or Japan.

48	International standards	Compliant with active version of the following standards (or equivalent): **General manufacturing:** • ISO 13485: Medical Devices - Quality Management Systems - Requirements for Regulatory Purposes • ISO 14971: Medical Devices - Application of Risk Management to Medical Devices • ISO 15223-1: Medical devices -- Symbols to be used with medical device labels, labelling and information to be supplied -- Part 1: General requirements **Safety & product standards:** • IEC 60601-1 - Medical electrical equipment - Part 1: General requirements for basic safety and essential performance • IEC 60601-1-2: Medical electrical equipment - Part 1-2 General requirements for basic safety and essential performance - Collateral Standard: Electromagnetic disturbances - Requirements and tests **For vaginally-inserted colposcopes:** • Biocompatibility: o ISO 10993-1: Biological evaluation of medical devices Part 1: Evaluation and testing within a risk management process o ISO 10993-5: Biological evaluation of medical devices Part 5: Tests for in vitro cytotoxicity o ISO 10993-10: Biological evaluation of medical devices Part 10: Tests for irritation and skin sensitization • Endoscopy (pertaining to inserted scope): o ISO 8600-1: Endoscopes – Medical endoscopes and endotherapy devices – Part 1: General requirements o ISO 8600-3: Optics and optical instruments – Medical endoscopes and endoscopic accessories – Part 3: Determination of field of view and direction of view of endoscopes with optics o ISO 8600-4: Endoscopes – Medical endoscopes and endotherapy devices – Part 4: Determination of maximum width of insertion portion o ISO 8600-5: Optics and photonics – Medical endoscopes and endotherapy devices – Part 5: Determination of optical resolution of rigid endoscopes with optics o ISO 8600-6: Optics and photonics – Medical endoscopes and endotherapy devices – Part 6: vocabulary
49	Regional / local standards	Country-specific and regional standards may apply

50	Regulations	US regulations: 21 CFR part 820 Quality System Regulation 21 CFR part 884.1630 - Colposcope EU regulations: European Commission Regulation (EU) No. 2017/745 (replacing 93/42/EEC)



Annex 5
Technical Specifications for Thermal Ablation Units

MEDICAL DEVICE SPECIFICATION		
i	**Version No.**	**1**
ii	**Date of initial version**	**December 2019**
iii	**Date of last modification**	
iv	**Date of publication**	**February 2020**
v	**Completed / submitted by**	**WHO**
NAME, CATEGORY AND CODING		
1	WHO Category / Code	
2	Generic name	Thermal ablation device
3	Specific type or variation (optional)	Portable, handheld thermal ablation device Benchtop thermal ablation device
10	Alternative name/s (optional)	Thermal coagulator; thermocoagulator; cold coagulator; Semm coagulator; thermoablation device
12	Keywords (optional)	Thermal ablation device; cervical precancer; destruction of abnormal human cervical tissue.

PURPOSE OF USE		
14	Clinical or other purpose	A thermal ablation device is a self-contained, electrically powered medical instrument with a probe tip heated to 100°C designed to destroy tissue of the uterine cervix.
15	Level of use (if relevant)	Handheld device: health posts, clinics or outreach, hospitals Benchtop device: hospitals or clinics with mains electricity
16	Clinical department/ward(if relevant)	Family medicine; gynaecology; outpatient clinic; outreach; oncology; obstetrics; surgery; nursing services
17	Overview of functional requirements	• Probe tip temperature controlled to reach 100°C • Visual and/or audible cues to ensure working temperature reached • Simple and easy to use, appropriate for all levels of care. • Handheld device has added feature of portability with rechargeable batteries.
TECHNICAL CHARACTERISTICS		
18	Detailed requirements	Portable, handheld thermal ablation device OR Benchtop thermal ablation device: • Probe tip temperature controlled to reach 100°C • Visual and/or audible cues to ensure working temperature reached • Simple and easy to use, appropriate for all levels of care. • Handheld device has added feature of portability with rechargeable batteries. • Rated IPX1 (console) and IPX7 (therapy probe and or instrument cable on benchtop)

19	Displayed parameters	User interface should provide audible and/or visual feedback: • Handheld: light/beep when temperature reached • Benchtop: display to indicate temperature.
20	User adjustable settings	Benchtop: user can adjust temperature between 60°-120°C
PHYSICAL / CHEMICAL CHARACTERISTICS		
21	Components(if relevant)	• Minimum of 2 probe tips required: o One probe must be flat. o The second probe can be either flat or can have a gentle nipple extrusion not exceeding 5mm (so as to anchor in centre of cervix but not to ablate endocervix). o Probes should not have any sharp edges. o Varying diameters, ranging from 8 mm to 25 mm o Biocompatible, material that will not adhere to cervix o Reusable and thus able to be decontaminated Approximate dimensions of the thermal ablation devices: - Handheld: 5 cm (W), 20 cm (H), 5 cm (D) and weighs <400g - Benchtop: 35 cm (W), 15 cm (H), 10 cm (D) and weighs 3.5 kg Both devices come with power adaptors Recommended extra battery for handheld unit
22	Mobility, portability (if relevant)	Handheld device Can be easily carried in a case or backpack, with all accessories, all totalling <2kg Benchtop device: Not intended for portability
23	Raw Materials (if relevant)	N/A
UTILITY REQUIREMENTS		
24	Electrical, water and/or gas supply (if relevant)	• The unit (either benchtop or handheld when charging) is suggested to be connected to a reliable power source • Handheld, battery operated device to have a minimum cumulative run-time of 1 hour on a single charge. • Electrical source requirements (based on country/setting of use): o Amperage: _____; o Voltage: _____; o Plug type: _____ .

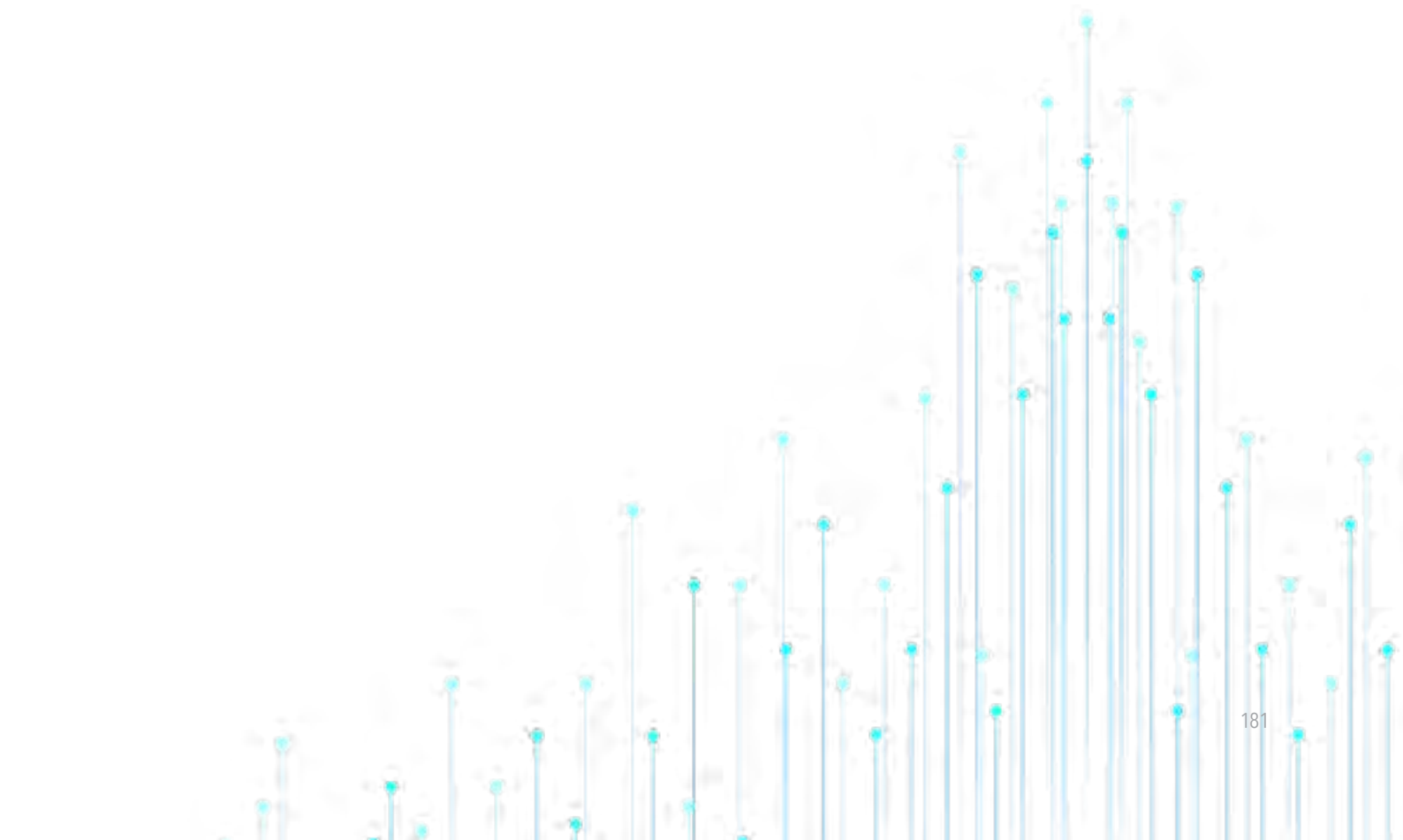
ACCESSORIES, CONSUMABLES, SPARE PARTS, OTHER COMPONENTS		
25	Accessories (if relevant)	• Speculum • Light source • Timer
26	Sterilization process for accessories (if relevant)	- Probes should withstand repeated cycles of decontamination, done so according to manufacturers' instructions. - Device handle, charging base, benchtop unit, power supply should be cleaned and decontaminated after each use according to manufacturer's instructions.
27	Consumables / reagents (if relevant)	N/A
28	Spare parts (if relevant)	• Consider extra probes to account for decontamination cycles and patient scheduling. • A backup battery pack is recommended for handheld devices. Note: probes and spares are not interchangeable between devices of different brands and models and can vary in their design and lifetime.
29	Other components (if relevant)	N/A
PACKAGING		
30	Sterility status on delivery (if relevant)	N/A
31	Shelf life (if relevant)	N/A
32	Transportation and storage (if relevant)	Storage area should be clean and dust-free, dry, cool, well-lit, ventilated and vermin-proof. Store device in original packaging on a shelf or on in a storage cabinet. Devices should be able to withstand storage temperatures ranging from 15°C to 30°C, relative humidity ≤ 60% (non-condensing), and be protected from dripping water.
33	Labelling (if relevant)	Labelling on the primary packaging should include the name and/or trademark of the manufacturer and should adhere to the most current version of ISO 15223 – 1: Medical devices -- Symbols to be used with medical device labels, labelling and information to be supplied -- Part 1: General requirements.

ENVIRONMENTAL REQUIREMENTS		
34	Context-dependent requirements	Environmental conditions vary globally and can be extreme; however, the following are tenable: - Operating temperature: 15°C to 35°C - Operating relative humidity: ≤ 85%, non-condensing It is the responsibility of the procurement body to ensure that the manufacturer's recommended operation and storage conditions are respected. If the device requires that the operating and/or storage environment be climate-controlled, appropriate temperature and humidity control systems, including monitoring, should be applied to avoid premature material disintegration and/or device failure.
TRAINING, INSTALLATION AND UTILISATION		
35	Pre-installation requirements (if relevant)	Handheld: no pre-installation requirements. Benchtop: if necessary, clear instructions/diagrams for assembly/reassembly must be included.
36	Requirements for commissioning (if relevant)	N/A
37	Training of user/s (if relevant)	Training of users in operation and basic maintenance shall be provided. Clinical staff training in cervical precancer lesion treatment guidelines and device use to be provided.
38	User care (if relevant)	Prior to use: • Inspect for visible damage to device (handle, probes, any connections). • Make sure that no parts are missing or loose. • Make sure that connecting elements between instruments function properly.
WARRANTY AND MAINTENANCE		
39	Warranty	Minimum one year. Specific inclusions and exclusions to be listed. Contact details of manufacturer, supplier and local service agent to be provided.
40	Maintenance tasks	Handheld device: no user-serviceable parts. Benchtop device: see manual or contact manufacturer for information

41	Type of service contract	Costs and types of post-warranty service contract available shall be described (if applicable).
42	Spare parts availability post-warranty	8 years minimum, starting from installation/commissioning
43	Type of service contract	Costs and types of post-warranty service contract available shall be described (if applicable).
DOCUMENTATION		
44	Documentation requirements	• Instructions for use and service manuals to be provided (including procedures for decontamination) • User language preference prioritized, English is mandatory. • Contact details of manufacturer, supplier and local service agent. • Certificate of calibration and inspection to be provided (if applicable). • List to be provided of equipment and procedures required for local calibration and routine maintenance. • List to be provided of common spares and accessories, with part numbers.
DECOMMISSIONING		
45	Estimated Life Span	Handheld device: 7 years (can vary) Benchtop main unit: approximately 10 years if maintenance and service requirements are met.
SAFETY AND STANDARDS		
46	Risk Classification	US FDA: Device Class 2 EU: Class IIa

47	Regulatory Approval / Certification	Compliance to (where applicable, but not limited to): - National Regulatory Agency/Authority (NRA) requirements compliance - Approval by regulatory body of country of manufacturer (if applicable) And at least one of: - FDA 510k clearance (US FDA) - CE mark (EU), with indication of Notifying Body (when applicable) - Other regulatory body in an IMDRF founding member country such as Australia, Canada, or Japan.
48	International standards	Compliant with active version of the following standards (or equivalent): **General manufacturing:** • ISO 13485: Medical Devices - Quality Management Systems - Requirements for Regulatory Purposes • ISO 14971: Medical Devices - Application of Risk Management to Medical Devices • ISO 15223-1: Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements **Safety & product standards** • IEC 60601-1 - Medical electrical equipment - Part 1: General requirements for basic safety and essential performance • IEC 60601-1-2: Medical electrical equipment - Part 1-2 General requirements for basic safety and essential performance - Collateral Standard: Electromagnetic disturbances - Requirements and tests **Probe-specific requirements:** • ISO 10993-1: Biological evaluation of medical devices Part 1: Evaluation and testing within a risk management process • ISO 10993-5: Biological evaluation of medical devices Part 5: Tests for in vitro cytotoxicity • ISO 10993-10: Biological evaluation of medical devices Part 10: Tests for irritation and skin sensitization **Battery-operated only:** • IEC 62133 - Secondary cells and batteries containing alkaline or other non-acid electrolytes – Safety requirements for portable sealed secondary cells o Part 1: Nickel o Part 2: Lithium
49	Regional / Local Standards	Country-specific and regional standards may apply

50	Regulations	US regulations: 21 CFR part 820 Quality System Regulation EU regulations: European Commission Regulation (EU) No. 2017/745 (replacing 93/42/EEC)



Annex 6
Technical Specifications for Cryotherapy Units

MEDICAL DEVICE SPECIFICATION (Including information on the following where relevant/appropriate, but not limited to)		
i	**Version No.**	**1**
ii	**Date of initial version**	**December 2019**
iii	**Date of last modification**	
iv	**Date of publication**	**February 2020**
v	**Completed / submitted by**	**WHO**
NAME, CATEGORY AND CODING		
1	WHO Category / Code	Cryosurgery units, XD9LJ9
2	Generic name	Cryosurgical Unit, Gynaecological
10	Alternative name/s (optional)	Cryoprobes; Cryostats; Cryo Units; CSU; Probes,
12	Keywords (optional)	surgical, gynaecology, dermatology, cryotherapy, cryocautery, cryosurgery, "cryo"

PURPOSE OF USE		
14	Clinical or other purpose	Cryosurgical unit with a gas (carbon dioxide,CO2, or nitrous oxide, N_2O) cooled or electrically-cooled cryoprobe intended to destroy tissue of the uterine cervix with the application of extreme cold.
15	Level of use (if relevant)	Health posts, health centres, specialty clinics, hospitals
16	Clinical department/ward (if relevant)	Family medicine; gynaecology; outpatient clinic; outreach; oncology; obstetrics; surgery; nursing services
17	Overview of functional requirements	The metal probe head (cryotip) makes contact with epithelium to destroy tissue.
TECHNICAL CHARACTERISTICS		
18	Detailed requirements	• Cryosystems include the hand-held unit with use-specific cryotips: • Temperature at probe edge shall be no greater than -20 °C (can be colder, NOT warmer) • If gas-cooled: - either carbon dioxide (CO2) or nitrous oxide (N2O) is used - must be a closed system, whereby the cryogen circulates through probe head, and then back through shaft. • If electrically-cooled, an ethanol-based solution and electricity are necessary.
19	Displayed parameters	N/A
20	User adjustable settings	Pressure gauge (for gas-cooled units), cryogun trigger

PHYSICAL / CHEMICAL CHARACTERISTICS		
21	Components (if relevant)	• Minimum of 2 cryotips are required: - One cryotip must be flat. - The second cryotip can be either flat or can have a gentle nipple extrusion not exceeding 5mm (so as to anchor in centre of cervix but not to ablate endocervix). - Cryotip diameters ranging from 17 mm to 23 mm - Biocompatible, material that will not adhere to cervix - Reusable and thus able to be decontaminated • The overall length of the cryoshaft and cryotip assembly should be between 170 and 200 mm. Gas tank, pressure gauge, handheld unit with probe, scavenging/ suction system if using N2O
22	Mobility, portability (if relevant)	Can be portable or handheld.
23	Raw Materials (if relevant)	N/A
UTILITY REQUIREMENTS		
24	Electrical, water and/or gas supply (if relevant)	For gas-based: N2O or CO2 The N2O units should only be used with scavenging ability. For electrically cooled: • The unit is suggested to be connected to a continuous, reliable power source • Electrical source requirements (based on country/setting of use): o Amperage: _____ o Voltage: _____ o Plug type: _____ .

ACCESSORIES, CONSUMABLES, SPARE PARTS AND OTHER COMPONENTS		
25	Accessories (if relevant)	• Speculum • Light source • Timer
26	Sterilization process for accessories (if relevant)	- Probes should withstand repeated cycles of decontamination, done so according to manufacturers' instructions. - Device handle, charging base or gas tank and accessories (whichever applicable) to cleaned and decontaminated after each use according to manufacturer's instructions.
27	Consumables / reagents (if relevant)	Gas-based: N2O or CO2 gas Electrically cooled: ethanol-based solution
28	Spare parts (if relevant)	Consider extra probes to account for decontamination cycles and patient scheduling. Note: probes and spares are not interchangeable between devices of different brands and models and can vary in their design and lifetime.
29	Other components (if relevant)	N/A
PACKAGING		
30	Sterility status on delivery (if relevant)	N/A
31	Shelf life (if relevant)	N/A
32	Transportation and storage (if relevant)	Storage area should be clean and dust-free, dry, cool, well-lit, ventilated and vermin-proof. Store device in original packaging on a shelf or on in a storage cabinet. Devices should be able to withstand storage temperatures ranging from 15°C to 30°C, relative humidity ≤ 85% for gas-based systems or ≤ 60% for electrically cooled systems (both non-condensing), and be protected from dripping water. For compressed gases in cylinders (for gas-based system), both storage and transport can pose as a risk. Transport and storage shall adhere to local regulations; however, gases should never be stored at temperatures in excess of 30°C.

33	Labelling (if relevant)	Labelling on the primary packaging should include the name and/or trademark of the manufacturer and should adhere to the most current version of ISO 15223 – 1: Medical devices -- Symbols to be used with medical device labels, labelling and information to be supplied -- Part 1: General requirements.
ENVIRONMENTAL REQUIREMENTS		
34	Context-dependent requirements	Environmental conditions vary globally and can be extreme; however, the following are tenable: - Operating temperature: 15°C to 35°C - Operating relative humidity: ≤ 85%, non-condensing It is the responsibility of the procurement body to ensure that the manufacturer's recommended operation and storage conditions are respected. If the device requires that the operating and/or storage environment be climate-controlled, appropriate temperature and humidity control systems, including monitoring, should be applied to avoid premature material disintegration and/or device failure.
TRAINING, INSTALLATION AND UTILISATION		
35	Pre-installation requirements (if relevant)	N/A
36	Requirements for commissioning (if relevant)	Supply of either a gas (N2O or CO2) or ethanol-based solution a requisite for operations
37	Training of user/s (if relevant)	Training of users in operation and basic maintenance shall be provided. Clinical staff training in cervical precancer lesion treatment guidelines and device use to be provided.
38	User care (if relevant)	• The cryosurgical unit shall be decontaminated between patients. • Probes should be inspected regularly for mechanical integrity.
WARRANTY AND MAINTENANCE		
39	Warranty	Minimum one year. Specific inclusions and exclusions to be listed. Contact details of manufacturer, supplier and local service agent to be provided.

40	Maintenance tasks	- Routine check of probe and device mechanical integrity recommended (refer to user manual). - List shall be provided of equipment and procedures required for routine inspection. - Advanced maintenance tasks required are not recommended to be performed in the hospital due to safety concern.
41	Type of service contract	Costs and types of post-warranty service contract available shall be described (if applicable).
42	Spare parts availability post-warranty	8 years minimum, starting from installation/commissioning
43	Software / Hardware upgrade availability	N/A
DOCUMENTATION		
44	Documentation requirements	• Instructions for use and service manuals to be provided (including procedures for decontamination) • User language preference prioritized, English is mandatory. • Contact details of manufacturer, supplier and local service agent. • Certificate of calibration and inspection to be provided (if applicable). • List to be provided of equipment and procedures required for local calibration and routine maintenance. • List to be provided of common spares and accessories, with part numbers.
DECOMMISSIONING		
45	Estimated Life Span	10 years
SAFETY AND STANDARDS		
46	Risk Classification	US FDA: Device Class 2 EU: Class IIa

47	Regulatory Approval / Certification	**Compliance to (where applicable, but not limited to):** - National Regulatory Agency/Authority (NRA) requirements compliance - Approval by regulatory body of country of manufacturer (if applicable) **And at least one of:** - FDA 510k clearance (US FDA) - CE mark (EU), with indication of Notifying Body (when applicable) - Other regulatory body in an IMDRF founding member country such as Australia, Canada, or Japan.
48	International standards	Compliant with active version of the following standards (or equivalent): **General manufacturing:** • ISO 13485: Medical Devices - Quality Management Systems - Requirements for Regulatory Purposes • ISO 14971: Medical Devices - Application of Risk Management to Medical Devices • ISO 15223-1: Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements **Safety and product standards for electrically-cooled systems:** • IEC 60601-1 - Medical electrical equipment - Part 1: General requirements for basic safety and essential performance • IEC 60601-1-2: Medical electrical equipment - Part 1-2 General requirements for basic safety and essential performance - Collateral Standard: Electromagnetic disturbances - Requirements and tests **Safety and product standards for gas-based systems:** • ISO 21969 High-pressure flexible connections for use with medical gas systems **Probe-specific requirements:** • ISO 10993-1: Biological evaluation of medical devices Part 1: Evaluation and testing within a risk management process • ISO 10993-5: Biological evaluation of medical devices Part 5: Tests for in vitro cytotoxicity • ISO 10993-10: Biological evaluation of medical devices Part 10: Tests for irritation and skin sensitization
49	Reginal / Local Standards	Country-specific and regional standards may apply

50	Regulations	US regulations: 21 CFR part 820 Quality System Regulation EU regulations: European Commission Regulation (EU) No. 2017/745 (replacing 93/42/EEC)

Annex 7
Technical Specifications for ESUs for LLETZ

MEDICAL DEVICE SPECIFICATION (Including information on the following where relevant/appropriate, but not limited to)		
i	**Version No.**	**1**
ii	**Date of initial version**	**December 2019**
iii	**Date of last modification**	
iv	**Date of publication**	**February 2020**
v	**Completed / submitted by**	**WHO**
NAME, CATEGORY AND CODING		
1	WHO Category / Code	Under development
2	Generic name	Electrosurgical Unit
3	Specific type or variation (optional)	LLETZ Electrosurgical generator
10	Alternative name/s (optional)	Bovies; Coagulators, Electrosurgical; Diathermy Units, Surgical; Electrocautery Units; Electrosurgical Generators; ESUs; Hyfrecators; Stimulators, Muscle; Surgical Diathermy Units; Surgical Units; electrosurgical; Surgical diathermy generator
11	Alternative code/s (optional)	N/A
12	Keywords (optional)	electrosurgical, ablation, surgery, cautery

PURPOSE OF USE		
14	Clinical or other purpose	Electrosurgical units (ESUs) are used in a variety of surgical procedures for surgical cutting and for the control of bleeding (coagulation). With respect to cervical cancer prevention, ESUs are used to carry out LLETZ (LEEP) procedures.
15	Level of use (if relevant)	Health Centre / District Hospital / Provincial Hospital / Specialized Hospital
16	Clinical department/ ward (if relevant)	Family medicine; gynaecology; outpatient clinic; oncology; obstetrics; surgery; nursing services
17	Overview of functional requirements	Devices intended for surgical cutting (wire electrodes) and for controlling bleeding (ball electrode) by causing coagulation (haemostasis) at the surgical site with the safe passage of electricity at a high frequency to and through tissue. ESUs require highly-trained clinicians and are meant for use at higher-level health facilities.

TECHNICAL CHARACTERISTICS		
18	Detailed requirements	• Control panel for adjusting and displaying power settings. • Hand or foot switch to activate different electrodes or settings. • Minimum 1 monopolar handpiece port, 1 monopolar return electrode port (with alarm when poor contact quality), 1 bipolar outlet (bipolar not required for LLETZ). • Radiofrequency range from 200,000 Hz to 5,000,000 Hz. **General ESU Modes:** • coagulation mode: up to 80 W / 150 Ω, • cutting mode: up to 110 - 200 W / 300 -400 Ω, • blended current mode optional; **LLETZ-specific setting:** • blended current option mandatory, • coagulation: 30 - 50 W settings available • cutting: 30 - 50 W settings available
19	Displayed parameters	Different modes, current output, bipolar/monopolar indicator, blended option, error status
20	User adjustable settings	Mode selection, current output, bipolar/monopolar selection, blended current.
PHYSICAL / CHEMICAL CHARACTERISTICS		
21	Components (if relevant)	- Electrodes: wired, various sizes and shapes, at a minimum has: electrode (3-5mm ball), square loop electrode (smaller), semicircular loop electrode (larger); and, return electrode (typically a pad). - Electrodes can be reusable or single-use. A contact quality monitor (CQM) as an added feature, with either alarm or current shut-off, is highly recommended for patient safety.
22	Mobility, portability (if relevant)	Models with battery to increase portability are available; however, such devices do not preclude need for electricity (for charging). All other feature requirements apply.
23	Raw Materials (if relevant)	Electrode should be made of stainless steel or tungsten wire.

UTILITY REQUIREMENTS		
24	Electrical, water and/or gas supply (if relevant)	• The unit is suggested to be connected to a continuous, reliable power source (leveraging facility UPS) • Electrical source requirements (based on country/setting of use): o Amperage: _____ o Voltage: _____ o Plug type: _____ .
ACCESSORIES, CONSUMABLES, SPARE PARTS AND OTHER COMPONENTS		
25	Accessories (if relevant)	Speculum Light
26	Sterilization process for accessories (if relevant)	- Electrodes are to be sterilized after each use and must be done so according to manufacturer's instructions (Single-use electrodes are to be disposed of according to medical waste management protocol) - Rest of device to be decontaminated according to the manufacturer's instructions.
27	Consumables / reagents (if relevant)	If single-use electrodes are used, a continuous supply is necessary.
28	Spare parts (if relevant)	Consider extra electrodes to account for decontamination cycles and patient scheduling. Manuals should list spare parts available for device (Note: spare parts are not interchangeable between devices of different brands and models and can vary in their design and lifetime).
29	Other components (if relevant)	N/A
PACKAGING		
30	Sterility status on delivery (if relevant)	N/A
31	Shelf life (if relevant)	N/A

32	Transportation and storage (if relevant)	Storage area should be clean and dust-free, dry, cool, well-lit, ventilated and vermin-proof. Store device in original packaging on a shelf or on in a storage cabinet. Devices should be able to withstand storage temperatures ranging from 15°C to 30°C, relative humidity ≤ 60% (non-condensing), and be protected from dripping water.
33	Labelling (if relevant)	Labelling on the primary packaging should include the name and/or trademark of the manufacturer and should adhere to the most current version of ISO 15223 – 1: Medical devices -- Symbols to be used with medical device labels, labelling and information to be supplied -- Part 1: General requirements.
ENVIRONMENTAL REQUIREMENTS		
34	Context-dependent requirements	Environmental conditions vary globally and can be extreme; however, the following are tenable: - Operating temperature: 15°C to 35°C - Operating relative humidity: ≤ 85%, non-condensing It is the responsibility of the procurement body to ensure that the manufacturer's recommended operation and storage conditions are respected. If the device requires that the operating and/or storage environment be climate-controlled, appropriate temperature and humidity control systems, including monitoring, should be applied to avoid premature material disintegration and/or device failure.
TRAINING, INSTALLATION AND UTILISATION		
35	Pre-installation requirements (if relevant)	N/A
36	Requirements for commissioning (if relevant)	The unit should be tested before commissioning. Electrical protection of the apparatus with an UPS is highly recommended.
37	Training of user/s (if relevant)	The electrosurgical unit should only be operated by a person who has received adequate training, typically surgeons.

38	User care (if relevant)	ESU can produce high current and can injure both patient and operator if not properly used. Follow safety use closely, clean electrode tip frequently, always use lowest possible generator setting that achieves desired surgical effect. • Ground plate must always be used • Do NOT use in the presence of flammable agents or in oxygen-enriched environments. • Patient must remove all jewellery • Patient with metal implants require specialist consultation prior to procedure • LLETZ should be performed with access to resuscitation facilities.
WARRANTY AND MAINTENANCE		
39	Warranty	Minimum one year. Specific inclusions and exclusions to be listed. Contact details of manufacturer, supplier and local service agent to be provided.
40	Maintenance tasks	• Routine check of unit for mechanical integrity recommended (refer to user manual) • List shall be provided of equipment and procedures required for local routine maintenance. • Advanced maintenance tasks required shall be documented. Routine maintenance recommended.
41	Type of service contract	Costs and types of post-warranty service contract available shall be described (if applicable).
42	Spare parts availability post-warranty	8 years at least, starting from installation and commissioning
43	Software / Hardware upgrade availability	Guaranteed time period of support availability post-warranty shall be described.

DOCUMENTATION		
44	Documentation requirements	• Instructions for use and service manuals to be provided (including procedures for decontamination) • User language preference prioritized, English is mandatory. • Contact details of manufacturer, supplier and local service agent. • Certificate of calibration and inspection to be provided (if applicable). • List to be provided of equipment and procedures required for local calibration and routine maintenance. • List to be provided of common spares and accessories, with part numbers.
DECOMMISSIONING		
45	Estimated Life Span	10 years
SAFETY AND STANDARDS		
46	Risk Classification	US FDA: Device Class 2 EU: Class IIb
47	Regulatory Approval / Certification	Compliance to (where applicable, but not limited to): - National Regulatory Agency/Authority (NRA) requirements compliance - Approval by regulatory body of country of manufacturer (if applicable) And at least one of: - FDA 510k clearance (US FDA) - CE mark (EU), with indication of Notifying Body (when applicable) - Other regulatory body in an IMDRF founding member country such as Australia, Canada, or Japan.

48	International standards	Compliant with active version of the following standards (or equivalent): **General manufacturing** o ISO 13485: Medical Devices - Quality Management Systems o ISO 14971: Medical Devices - Application of Risk Management to Medical Devices o ISO 15223-1: Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied **Product-specific standards** o ISO 10993-1: Biological evaluation of medical devices Part 1: Evaluation and testing within a risk management process o ISO 10993-5: Biological evaluation of medical devices Part 5: Tests for in vitro cytotoxicity o ISO 10993-10: Biological evaluation of medical devices Part 10: Tests for irritation and skin sensitization o ISO 13402: Surgical and dental hand instruments -- Determination of resistance against autoclaving, corrosion and thermal exposure **Safety standards:** • IEC 60601-1 - Medical electrical equipment - Part 1: General requirements for basic safety and essential performance • IEC 60601-1-2: Medical electrical equipment - Part 1-2 General requirements for basic safety and essential performance - Collateral Standard: Electromagnetic disturbances - Requirements and tests • IEC 60601-2-2: Medical electrical equipment – Part 2-2: Particular requirements for the basic safety and essential performance of high frequency surgical equipment and high frequency surgical accessories **If battery-powered:** • IEC 62133: Secondary cells and batteries containing alkaline or other non-acid electrolytes – Safety requirements for portable sealed secondary cells o Part 1: Nickel o Part 2: Lithium
49	Reginal / Local Standards	Country-specific and regional standards may apply
50	Regulations	US regulations: 21 CFR part 820 Quality System Regulation 21 CFR part 878.4400 - Electrosurgical cutting and coagulation device and accessories EU regulations: European Commission Regulation (EU) No. 2017/745 (replacing 93/42/EEC)

Annex 8
Glossary of terms

-A-

Acetowhite: A transient, white-appearing epithelium following the application of acetic acid during a VIA screening.

Active defrost: a mechanism within some cryosystems that accelerates the return of the cryotip towards ambient temperature.

-B-

Bar: a metric unit of pressure, not approved as part of the International System of Units, but commonly used. It is defined as exactly equal to 100,000 Pa (100 kPa).

Bodok seal: A particular type of washer/seal, comprising a circular metal casing with an embedded rubber washer that functions with the pin-index system for gas cylinders to ensures a gas-tight seal between the cylinder yoke and regulator set.

-C-

CE: From the French "Conformité Européenne" or "European Conformity". It is a specific mark on the label, instruction for use and on the product itself (CE marking). It indicates that the product complies with the essential or general requirements of the relevant European health, safety and environmental protection legislation (Directives or Regulations).

Cryotip: an interchangeable tip designed to fit a specific anatomical site (cervix) for the purpose of freezing the tissue. A closed cryotip will not vent gas or cryogen in the vicinity of the tissue. An open cryotip directly jets the gas or cryogen onto the tissue and is not appropriate for use in treating cervical lesions.

Compressed gas cylinder: a container that is specifically designed to store a gas or liquid under elevated pressure conditions.

Critical point: the end point of a phase equilibrium curve. The most prominent example is the liquid-vapour critical point, the end point of the pressure-temperature curve that designates conditions under which a liquid and its vapour can coexist.

Critical state: the state of a substance when it is at the critical point, i.e., at critical temperature (the temperature of a gas or vapour in its critical state. Above this temperature, a gas cannot be liquefied by pressure alone) and critical pressure (the pressure of a gas or vapour in its critical state).

Cryoadhesion: cryotip attachment to target tissue.

Cryogen: a substance, such as compressed gas or liquid, used to obtain reduced temperatures. Cryogens are usually classed by their boiling points and their grade. The most common cryogens for precancerous cervical lesions and their respective boiling points are as follows:

	Cryogen Boiling Point at STP (°C)
Carbon Dioxide (CO_2)	-78.6
Nitrous Oxide (N_2O)	-88.5

Cryonecrosis: destruction of tissue cells using cryogen (see clinical references for additional detail).

Cryoshaft: the component onto which the cryotip is attached. The cryoshaft may be detachable or fixed, and should be thermally insulated.

Cryosystem: collectively, all parts of a system necessary to apply cryogen therapeutically, for the treatment of cervical precancer. It excludes the gas and its tank, the compressed gas cylinder valve, and the adaptor.

Cytology: the examination of human cells under a microscope. Specific to the cervix, a Papanicolaou, Pap-smear, or simply "Pap" test is a cytology-based method for cervical cancer screening.

-D-

Desiccation: (or electrodessication) one of the four major modalities of electrosurgery and, along with fulguration, is one of the two monoterminal techniques. In this modality, the electrode touches the tissue directly and the amount of heat is such that superficial and subdermal tissue dries out, forming a coagulum. Electrodessication is not meant to take place during LLETZ (LEEP) and causes partial-thickness wounds. It occurs when cutting is attempted, not enough heat has been generated, and results in the formation of a dry patch of dead tissue.[114]

Diathermy: a surgical technique involving the production of heat in a part of the body by high-frequency electric currents, to stimulate the circulation, relieve pain, destroy unhealthy tissue, or cause bleeding vessels to clot.

-F-

Fasciculation: a brief, spontaneous contraction affecting a small number of muscle fibres, often causing a flicker of movement or "twitch" under the skin.

FDA: see US FDA

Fulguration: one of the four major modalities of electrosurgery and, along with electrodessication, is one of the two monoterminal techniques. In this modality, the electrode is held at a slight distance from the tissue to produce a sparking at the surface and more shallow tissue destruction (then in desiccation) occurs – thus the treatment area is more superficial.[114]

-G-

Gasket: a round, flat plastic or rubber ring (that looks like a washer), which is usually placed between the connector to the cryosystem and the compressed gas cylinder valve.

References

[114] Hainer, Barry L. "Electrosurgery for the skin." American family physician 66.7 (2002): 1259-1266. https://www.aafp.org/afp/2002/1001/p1259.html#sec-1

-H-

Haemostasis: the stopping of flow of blood (can be achieved via coagulation using electrosurgical units).

Hose assembly: polymer tubes that carry the cryogen from the regulator to the handle. In cryosystems, it is common to have an assembly in which there may be tubes inside a main hose.

HLD: High-level disinfectant. It is a type of germicide that acts as a "non selective agent" inactivating all microbes, human pathogens, and non-pathogens in (or on) a container for a short contact time.

-I-

Inner diameter: The length from one interior edge to the other of a circular shape.

In vitro diagnostic (IVD): tests done on human blood or tissue samples. IVDs can detect diseases or other conditions, and can be used to monitor overall health to prevent, diagnose, treat or monitor diseases.

-M-

Mechanical integrity: the ability of all components of a cryosystem to withstand the pressures and temperatures that may be encountered during use as recommended by the manufacturer.

Multiparous: referring to a woman who has given birth, more than once.

-N-

Notified Body: in relation to medical devices or in vitro diagnostic medical devices, an organization designated by a Competent Authority for Designation of a European Member State to determine whether a medical device meets the essential or general requirements of the European legislation (such as the medical device Directive 93/42/EEC and the in vitro diagnostic medical devices Directive 98/79/EC, as well as the new Regulations (EU) 2017/745 on medical devices and (EU) 2017/746 on in vitro diagnostic medical devices).

Nulliparous: referring to a woman who has no biological children (includes stillbirth).

-O-

O-ring: a ring of rubber or silicon usually inserted at a joint to ensure an effective seal to avoid leaking (i.e. of liquids or gases).

-P-

Passive defrost: a function of a cryosystem (without active defrost) to return towards ambient temperature. Passive defrost is typically a slower process of defrosting the cryotip than active defrost.

-R-

Regulator: a device for maintaining a constant gas pressure. Note that most cryosurgical devices are not equipped with a regulator.

-S-

Safety valve: a valve, usually a rupture disc, to release excessive pressure in the system. Can also be called a pressure relief valve.

Silicone: Class of synthetic materials based on chains of alternate silicon and oxygen atoms used to make rubber and plastics.

Single-use disposable: any device, which is designed to be discarded after one use.

Squamous dysplasia: Dysplasia is abnormal epithelial growth defined by a spectrum of cytologic, differentiation and architectural changes. Squamous dysplasia consists in altered epithelium with an increased likelihood of progression to squamous cell carcinoma. According to the entity of cytology modifications, "low" and "high" grades are defined.

-T-

Target tissue: the specific anatomical area of the cervix intended to be treated.

Thermal insulation: a material used to prevent unintended cryonecrosis, inflammatory responses, or cryoadhesion to non-target tissues.

Thermocouple: a junction of two dissimilar metals that produce an output voltage proportional to the temperature of the junction. The output is directly correlated to the temperature to which the sensing junction is exposed.

Tractive force: the level of attraction between the cryotip and the target tissue during cryoadhesion, i.e. when the tip freezes to the tissue.

Trigger mechanism: the mechanism that is activated (or squeezed, pressed, or pushed) to release the cryogen into the cryotip. Cryosystems may also include triggers for active defrosting.

-U-

US FDA: United States Food and Drug Administration, an agency within the U.S. Department of Health and Human Services that protects public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products, medical devices, the food supply, cosmetics, dietary supplements, and products that give off radiation.

Annex 9
Declarations of Interest

Out of the 24 experts who participated in this work, 6 have declared an interest within 5 years from the review period related to cervical cancer. Although not all of these interests are specifically related to cervical cancer screening and treatment, they are nonetheless all disclosed and summarized below.

Name Affiliation	Conflict of Interest
Mohammed Ameel *NHRSC INDIA*	None
Partha Basu *IARC*	None
Paul Blumenthal *Stanford University and Populations Services International*	None
Eunice Lourenço *WHO consultant*	None
Miriam Cremer *Cleveland Clinic and Basic Health International*	None
Noni Gachuhi *Intellectual Ventures*	Employed by Intellectual Ventures/ Global Good Fund, which is funded by Gates Ventures and works on the subject in WHO's work. Intellectual Ventures has partnered with QuantuMDx in the development of a point of care PCR test for HPV (the investment is valued at over $5000 USD).

Babacar Gueye *MOH&SW, Senegal*	None
Karen Hariharan *CHAI*	None
Jose Jeronimo *Peruvian League Against Cancer/ Liga Contra el Cáncer, Peru*	Former employee of PATH, which has concluded collaborative research and development agreements for the development of a rapid HPV test with Qiagen (careHPV). Consulting: • For Qiagen Inc in 2017 and Q1 2018 on work related to the careHPV test; • Currently a member of Merck's Global HPV Vaccine Advisory Board in relation to facilitating global access to the vaccine; • Currently consulting with Global Good on works related to the validation of a new HPV test for LRS. Investment interests (>$5,000): • Until February 2017, owned shares of OncoPrev International, a health company in Peru providing cervical cancer prevention services, including HPV testing services for NGOs and private clinics. The company began commercialization of medical devices after shares sold.
Paolo Lago *Fondazione IRCCS Policlinico San Matteo – WHO Collaborating Centre*	None
Ricky Lu *JHPIEGO*	None
Mauricio Maza *Basic Health International*	None
Mona Mazgani *BC Cancer Clinic*	None
Miriam Mikhail *Rad-Aid International*	Hired as a consultant for DITTA for the 2017 calendar year to assist in their formal collaboration with the WHO as a non-state actor (<$10,000 USD). Currently contracted by the IAEA, another UN agency, in research: a Lancet commission on cancer imaging (<$10,000 USD).
Seloi Mogatle *UNFPA*	None

Raul Murillo *Centro Javeriano de Oncología – Hospital Universitario San Ignacio*	None
Raul Murillo *Centro Javeriano de Oncología – Hospital Universitario San Ignacio*	None
Nicolas Pallikarakis *INBIT Greece*	None
Groesbeck Parham *University of North Carolina, Chapel Hill*	None
Colin Pfaff *Baylor College of Medicine, Malawi*	None
Walter Prendiville *IARC*	• Royalties from Utah Medical <=$1,000 p.a.; • Introduced LLETZ (now also known as LEEP) into clinical practice in the 1980s; • Advised and helped in the design and development of the Liger thermal coagulator without receiving any financial reward for this; • Owns IP (patents, trademarks, and/or copyrights).
Silvia de San José *PATH*	None
Linda Serwaa *UNFPA*	None
Minna Soikkeli *UNFPA*	None
Dario Trapani *WHO Consultant*	None
Vivien Tsu *University of Washington*	Former employee of PATH, an international non-profit organization involved in the development and delivery of high-impact, low-cost tools for global health as a full-time staff. Ceasing employment in December 2018.

Dinsie Williams *WHO Consultant*	None
Laura Alejandra Velez Ruiz Gaitan *WHO Consultant*	None
Safina Yuma *Ministry of Health & Community Development, Gender, Elderly and Children, Tanzania*	None

Annex 10
WHO's 4th Global Forum on Medical Devices.
(December 2018)

During the 4th Global Forum on Medical Devices, which took place in Vishakaptnam, India, 13 to 15 December 2018, the technical specifications for precancerous cervical lesions were presented and discussed, among participants.
The forum had 1200 participants from 102 Member States.

The full report can be seen in: https://apps.who.int/iris/bitstream/handle/10665/312154/WHO-MVP-EMP-2019.04-eng.pdf

Different events to discuss the technologies for cervical cancer are presented below:

1. Workshop: Technologies for cervical cancer can be seen at: https://www.who.int/medical_devices/global_forum/4th_gfmd_Workshops/en/index11.html

2. Plenary session: Medical devices for non-communicable diseases:

   a. Cervical cancer an avoidable NCD with gross inequities can be seen at: https://www.who.int/medical_devices/global_forum/4th_gfmd_plenary_presentations/en/index5.html

These sessions help raise the awareness of the importance to have the appropriate technologies to tackle cervical cancer in all Member States, following the WHO call for action.

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