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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# 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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# Acknowledgements

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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).

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# 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

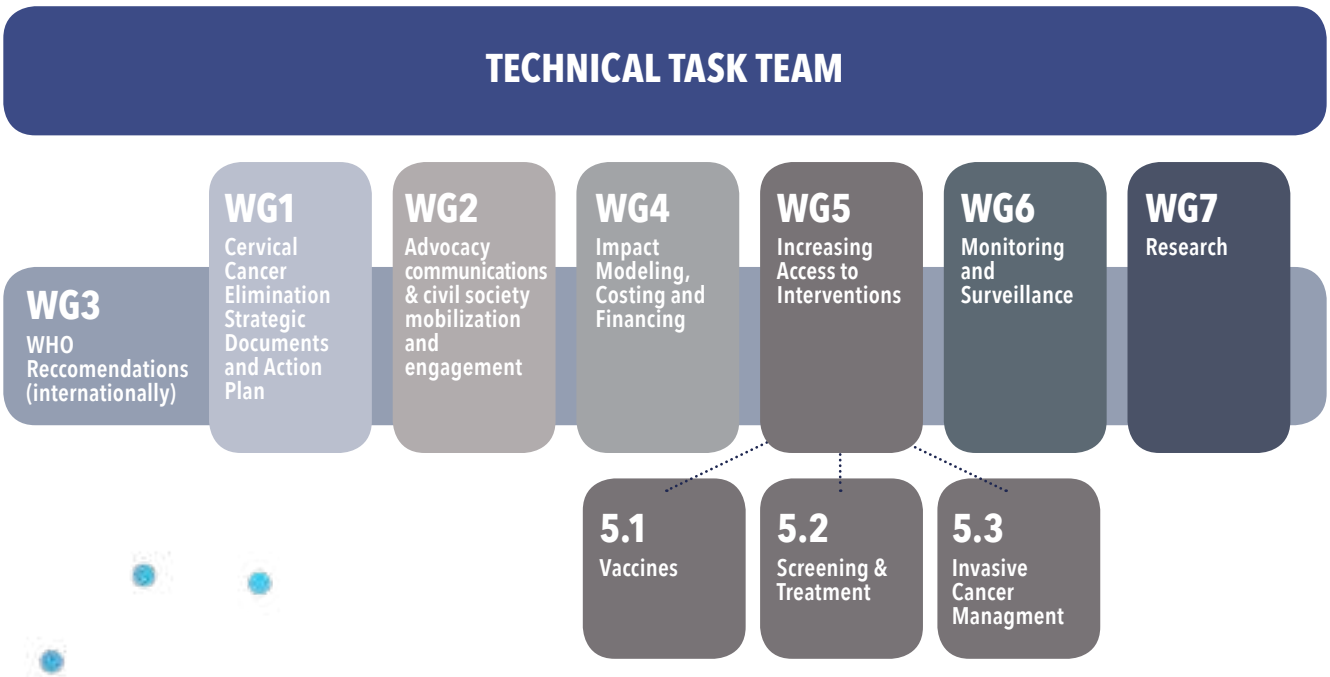
The call to action made by Dr Tedros Adhanom Ghebreyesus, Director General WHO, in May 2018 has resulted in accelerating plans to meet the challenge of improving cancer control under the elimination threshold in terms of cervical cancer incidence. Achieving elimination of cervical cancer requires collective 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.

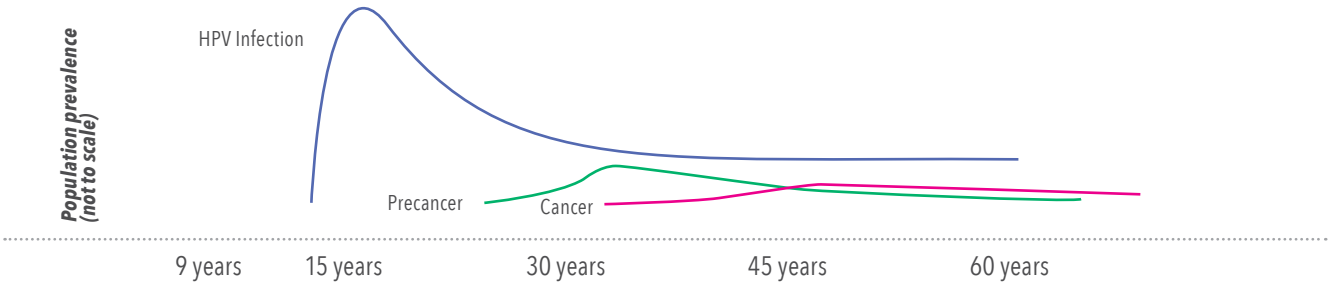
Working group 5.2 refers to all processes related to Screen and Treatment, and it is under this iniciative that this publication is developed, to ensure technologies are available to screen and treat patients that have pre-cancerous lesions, as can be seen in figure 1.

**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.

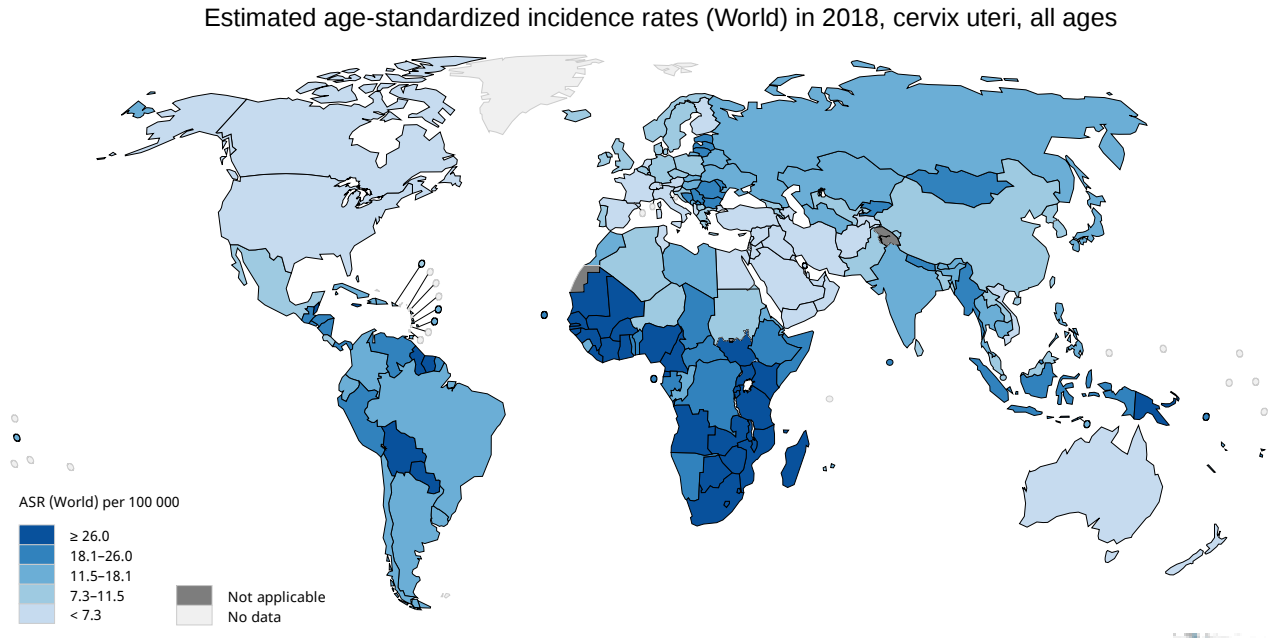
**The goal of cervical cancer screening is to accurately detect high-grade precursor lesions of the cervix to allow timely treatment of cervical intraepithelial neoplasia (CIN)**

### 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.**

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

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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

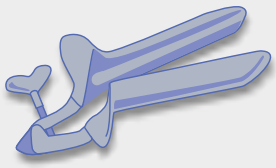
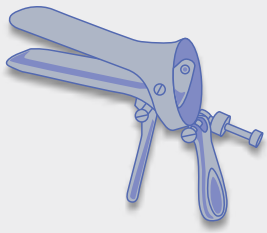
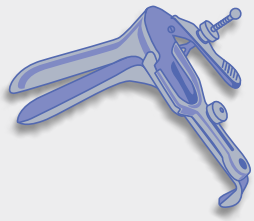
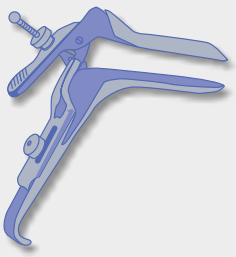
A vaginal speculum is a device intended to hold open the vaginal canal to enable a healthcare provider to visually inspect the cervix and collect vaginal or cervical specimens and/or perform surgical operations in a woman's lower genital tract. They are available in a variety of sizes and models to accommodate 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.<br>• Can be used for minor gynaecological procedures | • Commonly used for inspection, smear sampling and colposcopy.<br>• Can be used for minor gynaecological procedures | • Used for pelvic and cervix examination, smear sampling and gynaecological procedures.<br>• 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<br>• Available in different sizes<br>• Protects vaginal walls during procedures | • Available as normal or wide-mouthed<br>• Provides greater aperture at the introitus than Cusco and Collins | • Can provide greater aperture than the Cusco and Collins<br>• 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%).

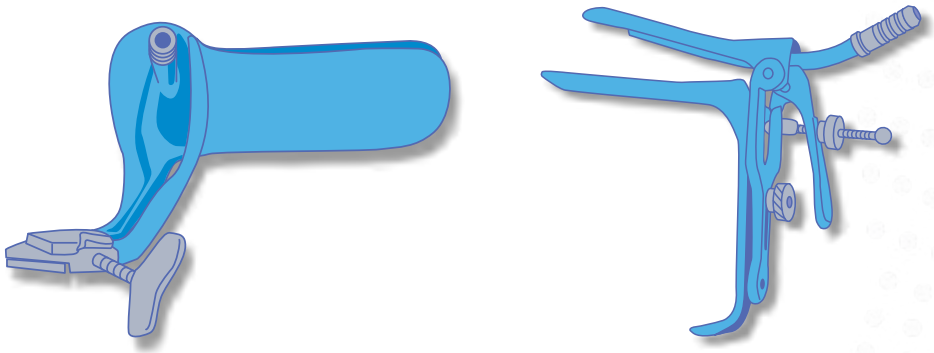
## 1.4. Operational considerations

### 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.

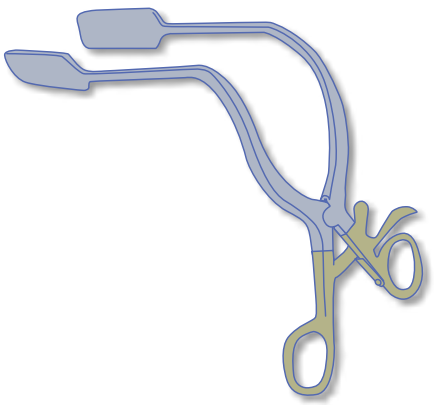
To note, insulated specula are more prone to wear and tear as a result of coating materials being subjected to requisite decontamination after each use. Hospital staff will have to examine coated specula very carefully for cuts, voids, cracks, tears, abrasions, etc. that can appear with frequent use.

**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<br>• Single-use specula made of appropriate biocompatible materials<br>• Bivalve and self-retaining to maintain an open vaginal canal<br>• Available in a variety of sizes. |
| **Operational requirements** | • Temperature: 15 to 35°C<br>• Relative humidity: ≤85%<br>• (Storage temperature: 15 to 30°C, ≤85%, non-condensing). |
| **Documentation requirements** | • Instructions for use and service manuals to be provided<br>• 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):<br>• ISO 13485: Medical Devices - Quality Management Systems - Requirements for Regulatory Purposes;<br>• ISO 14971: Medical Devices - Application of Risk Management to Medical Devices;<br>• ISO 15223-1: Medical devices -- Symbols to be used with medical device labels, labelling and information to be supplied -- Part 1: General requirements.<br><br>Safety and product standards:<br>• ISO 7151: Surgical instruments -- Non-cutting, articulated instruments -- General requirements and test methods;<br>• ISO 7153-1: Surgical instruments – Materials -- Part 1: Stainless steel;<br>• ISO 10993-1: Biological evaluation of medical devices Part 1: Evaluation and testing within a risk management process;<br>• ISO 10993-5: Biological evaluation of medical devices Part 5: Tests for in vitro cytotoxicity;<br>• ISO 10993-10: Biological evaluation of medical devices Part 10: Tests for irritation and skin sensitization;<br>• ISO 13402: Surgical and dental hand instruments -- Determination of resistance against autoclaving, corrosion and thermal exposure.<br><br>For products supplied as sterile:<br>• ISO 17664: Processing of health care products – Information to be provided by the medical manufacturer for the processing of medical devices;<br>• ISO 11135: Sterilization of health-care products - Ethylene oxide;<br>• ISO 11137: Sterilization of health care products – Radiation;<br>• ISO 11607: Packaging for terminally sterilized medical devices. |
| **Regulatory requirements** | Compliance to (where applicable, but not limited to):<br>• National Regulatory Authority requirements compliance<br>• Approval by regulatory body of country of manufacturer (if applicable).<br><br>And at least one of:<br>• United States regulations: US FDA 510(k):<br>» Device Class 1 for metal speculum<br>» Device Class 2 for non-metal speculum.<br>• European regulatory framework:<br>» Regulation (EU) 2017/745 of the European Parliament and the Council;<br>» Manufacturer must affix the CE marking and indicate the Notified Body number (when applicable) in the labelling and in the device, when possible.<br>• 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

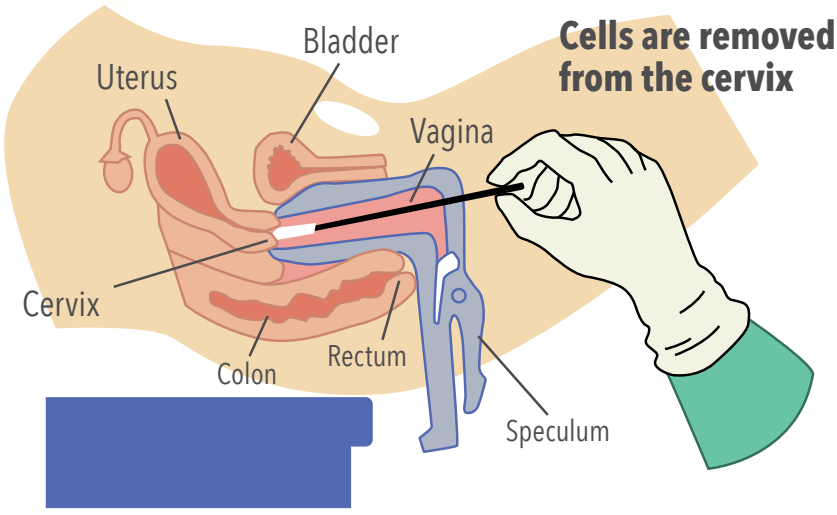
### 2.2.2.1. Healthcare-Provider Collected

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.

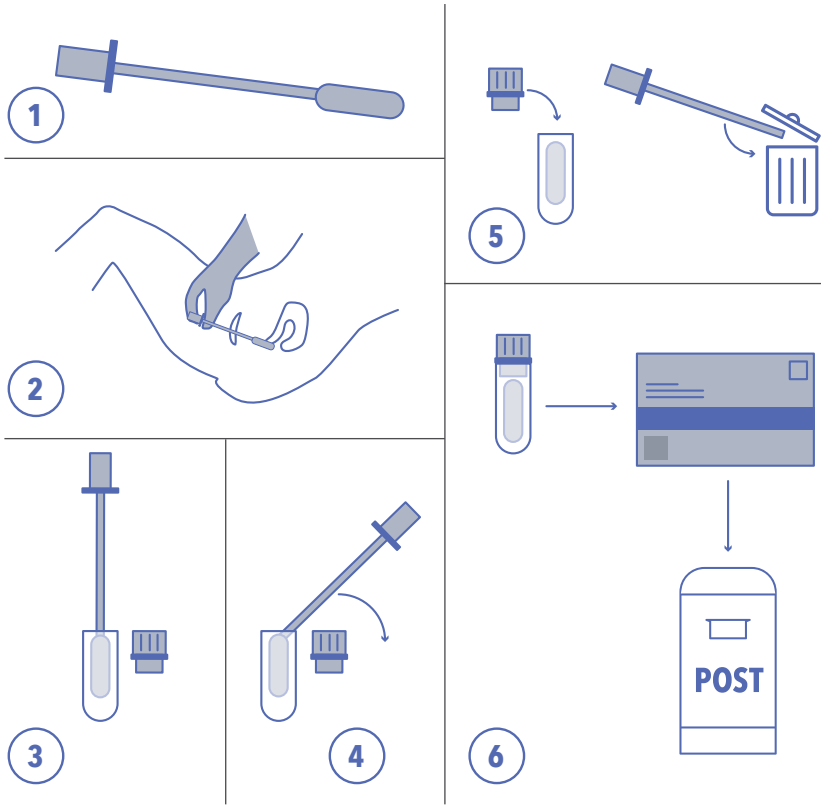
**Figure 7: Health care provider collecting a specimen for HPV NAT by scraping the cervix.**



#### 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]

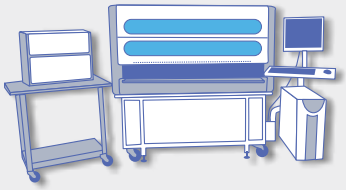
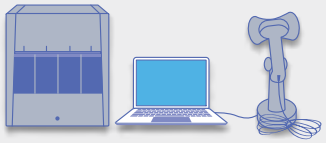
HPV NAT IVDs have been performed on self-collected specimens using a variety of collection devices (swabs, brushes, lavage). Various devices for specimen collection can be used and the manufacturer of the IVD will generally specify the appropriate collection device. The manufacturer's instructions for 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

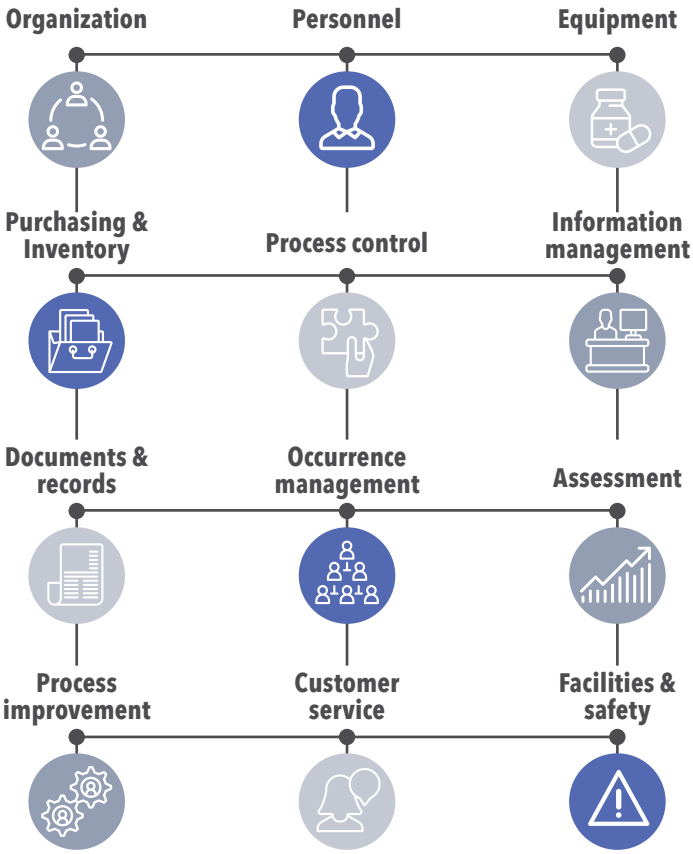
Health workers and laboratory technicians involved in specimen collection, screening and treatment need to be trained on the appropriate equipment requirements per the manufacturer's instructions for use. Instrument cleaning, calibration and proper storage are required.

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<br>or<br>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;<br>• 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;<br>• Results must be presented as specific individual genotypes or as a pooled result<br>• 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;<br>• 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:<br><br>1. Specimen collection device and transportation media<br>2. Reagent kit(s) or cartridge<br>3. Analyser(s) for extraction, amplification and detection, separate or combined. |
| **Operational requirements** | • Test-run timing:<br>» For manual test systems, the hands-on-time, the specimens per run and overall time must be specified;<br>» For automated test systems, the specimens per run, total run time, hands-on-time and walk-away time must be specified;<br>• Specimen volume: The required specimen volume for testing must be specified;<br>• Storage and transport requirements: special indications, such as refrigeration or freeze, for reagents must be listed;<br>• Stability: Requirements for stability prior to and during use;<br>• Laboratory information systems compatibility: Inter-operability with laboratory information systems should be described;<br>• The unit is suggested to be connected to a continuous, reliable power source;<br>• Electrical source requirements (based on country/setting of use):<br>» Amperage: _____.<br>» Voltage: _____..<br>• Plug type: _____. |
| **Documentation requirements** | • Instructions for use and service manuals to be provided<br>• User language preference prioritized, otherwise English is mandatory. |
| **Warranty** | Minimum 24 months. |
| **Standards** | Compliant with active version of the following standards (or equivalent):<br><br>• ISO 13485: Medical devices–Quality management systems;<br>• ISO 14971: Medical devices–Application of risk management to medical devices;<br>• 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.<br>Compliance to (where applicable, but not limited to):<br><br>• NRA requirements compliance<br>• Approval by regulatory body of country of manufacturer (if applicable).<br><br>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:<br><br>• WHO Prequalification;<br>• United States regulations: US FDA 510(k): Device Class III;<br>• European regulatory framework:<br>» Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998<br>» Regulation (EU) 2017/746 of the European Parliament and the Council: Class C under the IVDR;<br>» Manufacturer must indicate affix the CE marking and indicate the Notified Body number on the label.<br>• 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:<br><br>• Glacial acetic acid or other high concentration acetic acid solution<br>• Personal protective equipment: goggles, gloves, and lab coat<br>• Distilled or boiled water<br>• Glass container with lid for 3-5% diluted solution<br>• Graduated cylinder and syringe (or small graduated cylinder). |
| **Operational requirements** | Dilutions are to be made fresh and used daily under ambient conditions.<br><br>Concentrated acetic acid should be stored in original closed container between 15°C to 30°C with relative humidity ≤ 60% (non-condensing).<br><br>Must be stored separately from oxidizing materials and alkaline substances. |
| **Standards** | Compliant with active versions (or equivalent) of:<br><br>• International Pharmacopoeia (WHO); and/or<br>• European Pharmacopoeia; and/or<br>• US Pharmacopeia.<br><br>Globally Harmonized System of Classification and Labelling of Chemicals (GHS). |

***Chapter 3 references***

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[11] 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.

[12] IPC is a scientific approach encompassing epidemiology, social science and health system strengthening to provide a comprehensive approach to infection 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 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.

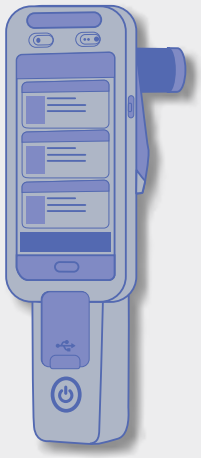
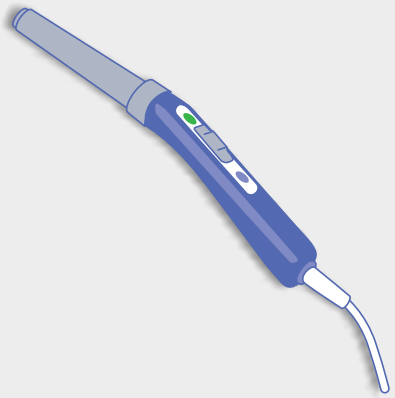
## 4.3. Types of colposcopes

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);<br>• Corrects for any near- or far-sightedness of the examiner. | • Can be handheld or mounted;<br>• Autofocus of image if kept at a distance of 25–30 cm from the object;<br>• 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;<br>• Restricted mobility – not portable;<br>• Photo or video camera may be attached, though must be procured separately. | • Requires external monitor to see and interpret the two-dimensional images;<br>• 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;<br>• Battery operated (uses phone or laptop);<br>• Low power requirements, draws off mobile phone/laptop<br>• Can capture and store images. | |
| Limitations | • Mobile phone/laptop necessary for image viewing and capture must be procured separately;<br>• May not work with all makes/models;<br>• If optical zoom not featured, digital optics may be inferior;<br>• 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.**