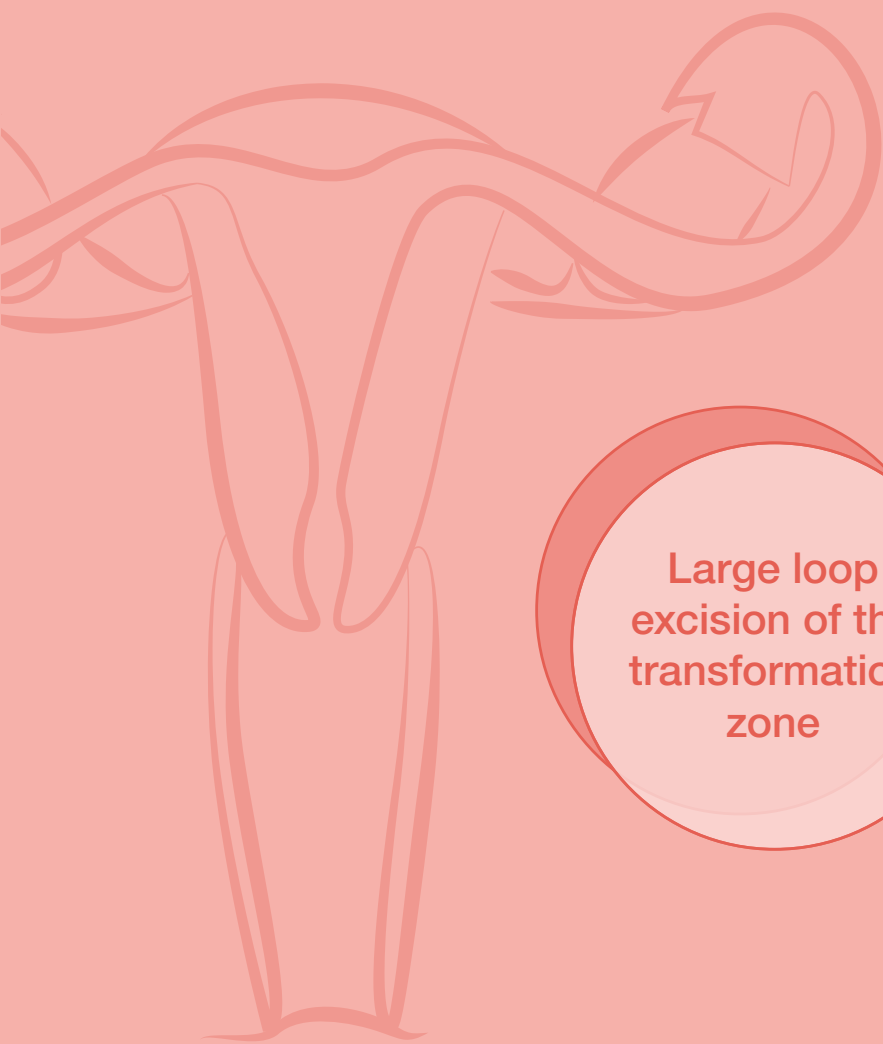


WHO guidelines

# WHO guidelines for treatment of cervical intraepithelial neoplasia 2–3 and adenocarcinoma in situ



Cryotherapy

Large loop  
excision of the  
transformation  
zone

Cold knife  
conization



World Health  
Organization



WHO guidelines

**WHO guidelines for treatment  
of cervical intraepithelial  
neoplasia 2–3 and  
adenocarcinoma in situ:**

cryotherapy, large loop excision of the  
transformation zone, and cold knife conization

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## **Supplemental material: GRADE evidence-to-recommendation tables and evidence profiles for each recommendation\***

\* Available online: [www.who.int/reproductivehealth/publications/cancers/treatment\\_CIN\\_2-3/en/index.html](http://www.who.int/reproductivehealth/publications/cancers/treatment_CIN_2-3/en/index.html)



## Lists of participants

### WHO Steering Group

**Nathalie Broutet (Lead)**

Reproductive Health and Research  
WHO Headquarters

**Jean-Marie Dangou**

Disease Prevention and Control  
WHO Regional Office for Africa

**Ibtihal Fadhil**

Noncommunicable Diseases  
WHO Regional Office for the Eastern  
Mediterranean

**Gunta Lazdane**

Sexual and Reproductive Health  
WHO Regional Office for Europe

**Silvana Luciani**

Cancer Prevention and Control  
WHO Regional Office for the Americas /  
Pan American Health Organization (PAHO)

**Arvind Mathur**

Making Pregnancy Safer and Reproductive  
Health  
WHO Regional Office for South-East Asia

**Amolo Okero**

Counselling and Testing, HIV/AIDS  
WHO Headquarters

**Somchai Peerapakorn**

Reproductive Health  
WHO Country Office – Thailand

**Andreas Ullrich**

Chronic Diseases Prevention and Management  
WHO Headquarters

**Cherian Varghese**

Noncommunicable Diseases and Health  
Promotion  
WHO Regional Office for the Western Pacific

**Adriana Velazquez**

Essential Medicines and Pharmaceutical  
Policies  
WHO Headquarters

**Marco Vitoria**

HIV Treatment and Care  
WHO Headquarters

**Lawrence Von Karsa**

Quality Assurance and Screening  
International Agency for Research on Cancer

### Guideline Development Group

**Marc Arbyn**

Unit of Cancer Epidemiology  
Scientific Institute of Public Health – Louis  
Pasteur  
Brussels, Belgium

**Paul D. Blumenthal**

Population Services International (PSI)  
Stanford University School of Medicine  
Department of Obstetrics and Gynecology  
Stanford, USA

**Joanna Cain (Chair)**

International Federation of Gynecology and  
Obstetrics (FIGO)  
London, United Kingdom

**Michael Chirenje**

Department Obstetrics and Gynaecology  
University of Zimbabwe Medical School  
Harare, Zimbabwe

**Lynette Denny**

Department Obstetrics and Gynaecology  
Groote Schuur Hospital  
Cape Town, South Africa

**Hugo De Vuyst**

Infections and Cancer Epidemiology  
International Agency for Research on Cancer  
Lyon, France

**Linda O'Neal Eckert**

Department of Global Health  
Gynecology Director  
Harborview Center for Sexual Assault and  
Traumatic Stress  
Seattle, USA

**Sara Forhan**

HIV Care and Treatment Branch  
Global AIDS Program  
Centers for Disease Control and Prevention (CDC)  
Atlanta, USA

**Eduardo Franco**

Division of Cancer Epidemiology  
McGill University  
Montreal QC, Canada

**Julia C. Gage**

Division of Cancer Epidemiology and Genetics  
National Cancer Institute  
Rockville, USA

**Francisco Garcia**

American Cancer Society  
Tucson, USA

**Rolando Herrero**

Prevention and Implementation Group  
International Agency for Research on Cancer  
Lyon, France

**José Jeronimo**

PATH  
Seattle, USA

**Enrique R. Lu**

Jhpiego  
Baltimore, USA

**Silvana Luciani**

Cancer Prevention and Control  
PAHO  
Washington DC, USA

**Swee Chong Quek**

Women's and Children's Hospital  
Singapore

**Rengaswamy Sankaranarayanan**

Prevention and Implementation Group  
International Agency for Research on Cancer  
Lyon, France

**Vivien Tsu**

PATH  
Seattle, USA

**Methods Group**

Based at MacGRADE Collaborating Centre,  
McMaster University, Hamilton, Canada:  
systematic review team and GRADE  
methodologists

**Holger Schünemann (Lead Investigator)**

Department of Clinical Epidemiology and  
Biostatistics

**Reem A. Mustafa (Coordinator)**

Department of Clinical Epidemiology and  
Biostatistics

**Nancy Santesso (Coordinator)**

Department of Clinical Epidemiology and  
Biostatistics

**External Review Group****Irene Agurto**

Santiago, Chile

**Ahti Anttila**

Mass Screening Registry  
Finnish Cancer Registry  
Helsinki, Finland

**Partha Sarathi Basu**

Department of Gynecologic Oncology  
Chittaranjan National Cancer Institute  
Kolkata, India

**John-Paul Bogers**

Laboratorium voor Cel – en Weefselleer  
Faculteit Geneeskunde  
Campus Groenenborger  
Antwerp, Belgium



**August Burns**

Grounds for Health  
Waterbury, USA

**Rolando Camacho-Rodriguez**

Cancer Control Coordinator  
Programme of Action for Cancer Therapy  
International Atomic Energy Agency  
Vienna, Austria

**Silvia de Sanjosé**

Institut Català d'Oncologia  
L'Hospitalet de Llobregat  
Barcelona, Spain

**Anne Garnier**

Department of Cancer Screening  
Institut National du Cancer (INCa)  
Boulogne-Billancourt, France

**Martha Jacob**

Kochi  
Kerala State, India

**Namory Keita**

Department of Gynecology and Obstetrics  
Donka Teaching Hospital  
Conakry, Republic of Guinea

**Nancy Kidula**

ACCESS Uzima, Jhpiego  
Nairobi, Kenya

**Rajshree Jha Kumar**

Mumbai, India

**Anne Levin**

Bethesda, USA

**Khunying Kobchitt Limpaphayom**

Department of Obstetrics and Gynecology  
Faculty of Medicine  
Chulalongkorn University  
Bangkok, Thailand

**Ian Magrath**

International Network for Cancer Treatment and  
Research  
Brussels, Belgium

**Raul Murillo**

Subdirección Investigaciones y Salud Pública  
Instituto Nacional de Cancerología de Colombia  
Bogotá, Colombia

**Daniel Murokora**

Uganda Women's Health Initiative  
Kampala, Uganda

**Oneko Olola**

Kilimanjaro Christian Medical Centre  
Moshi, Tanzania

**Groesbeck Parham**

Centre for Infectious Disease Research in  
Zambia  
Lusaka, Zambia

**Patrick Petignat**

Surgical Gynecologic Oncology Unit  
Hôpital Cantonal  
Geneva, Switzerland

**Ilka Rondinelli**

International Planned Parenthood Federation  
London, United Kingdom

**Carlos Santos**

Instituto Nacional de Enfermedades  
Neoplásicas  
Lima, Peru

**Mona Saraiya**

Division of Cancer Prevention and Control  
National Center for Chronic Disease Prevention  
and Health  
CDC  
Atlanta, USA

**Achim Schneider**

Klinik für Gynäkologie und Gynäkologische  
Onkologie  
CharitéCentrum  
Berlin, Germany

**Nereo Segnan**

Department of Cancer Screening  
and Unit of Cancer Epidemiology  
Piemonte and San Giovanni University  
Hospital  
Turin, Italy

**Tshewang Tamang**

Vaccine Preventable Disease Program  
Ministry of Health  
Thimphu, Bhutan

**Nguyen-Toan Tran**

Geneva, Switzerland

**Jérôme Viguié**

Santé Publique  
INCa  
Boulogne-Billancourt, France

**Steven Weyers**

Department of Obstetrics and Gynecology  
Ghent University Hospital  
Gent, Belgium

**Katherine Worsley**

Marie Stopes International  
London, United Kingdom

**Eduardo Zubizarreta**

International Atomic Energy Agency  
Vienna, Austria

# Process for managing declarations and conflicts of interest

## Roles of the technical and working groups

In September 2010, the External Review Group (ERG) met to decide on the update of *Comprehensive cervical cancer control: a guide to essential practice* (C4-GEP), which was originally published in 2006. One of the major conclusions was that the chapter on screening and treatment of precancerous lesions for cervical cancer prevention needed to be updated. This group also made recommendations to the World Health Organization (WHO) on the composition of the Guideline Development Group (GDG).

In 2011, the GDG and the Methods Group (MG) met several times in joint sessions to develop the PICO questions (population, intervention, comparison, outcome), to select and rate the importance of the outcomes for treatment of precancerous cervical lesions and adenocarcinoma in situ, and to discuss and agree on the methodology.

In April 2012, the GDG, the MG and the ERG met in a joint session to discuss the results of the literature review, the GRADE evidence profiles, and to prepare the draft recommendations.

In 2012 and 2013, the GDG and the MG met several times in joint sessions, either by conference call or in person, to further discuss and finalize the draft recommendations. These draft recommendations were then sent to the ERG for endorsement.

## Management of conflicts of interest

Conflicts of interest were managed as follows:

1. All experts who participated in the process were required to complete the WHO Declaration of Interest (DOI) form before they commenced their work for WHO, and to promptly notify WHO if any change in the disclosed information occurred during the course of this work. The completed DOI forms were reviewed by the WHO Secretariat with a view to managing disclosed interests in the field of cervical cancer screening and treatment.
2. At the meeting of the ERG in September 2010 and at the first joint meeting of the GDG, MG and the ERG in 2013, each expert disclosed his/her declared interests to the other experts as part of the round of introductions at the beginning of the meeting so that the group was aware of any existing interests among the members.
3. All declared interests have been reviewed by WHO's Office of the Legal Counsel. The decision was that all experts could participate in the process but interests should be disclosed in the guideline.
4. All relevant declared interests (15 out of 54 experts) are disclosed and summarized in this report (see Annex 1).

It should be noted that these guidelines focus on treatment of precancerous lesions and of adenocarcinoma in situ. These guidelines do not address primary prevention of cervical cancer through vaccination against human papillomavirus (HPV).

## Acknowledgements

Development Group and the Methodology Group for their constant availability and hard work. WHO is also very grateful to the External Review Group for making possible the development of these essential recommendations for treatment of cervical intraepithelial neoplasia 2–3 and adenocarcinoma in situ. The names of the participants in each group are listed on pages v–viii.

In addition, we would also like to thank the following staff, fellows, and students from McMaster University, Hamilton, Canada, who contributed to the work of the systematic review but were not included in the discussion on recommendations: Yaolong Chen, Adrienne Cheung, Charmaine Fraser, Shreyas Gandhi, Jessica Hopkins, Rohan Kehar, Rasha Khatib, Nancy Lloyd, Bin Ma, Ahmad Mustafa, Marco Perez, Wojtek Wiercioch, and Darong Wu.

WHO also wishes to express sincere gratitude to the Flanders International Cooperation Agency (FICA), the Institut National du Cancer (INCa), France, and the Global Alliance for Vaccines and Immunisation (GAVI) for providing the main funding for this document.

## Acronyms and abbreviations

AIS	adenocarcinoma in situ
ASCUS	atypical squamous cells of undetermined significance
CDC	Centers for Disease Control and Prevention (USA)
CIN	cervical intraepithelial neoplasia
CKC	cold knife conization
ERG	External Review Group
FICA	Flanders International Cooperation Agency
GAVI Alliance	Global Alliance for Vaccines and Immunisation
GDG	Guideline Development Group
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HPV	human papillomavirus
IARC	International Agency for Research on Cancer
INCa	Institut National du Cancer (France)
LEEP	loop electrosurgical excision procedure (also LLETZ)
LLETZ	large loop excision of the transformation zone (also LEEP)
MG	Methods Group
NCI	National Cancer Institute (USA)
NIH	National Institutes of Health (USA)
PAHO	Pan American Health Organization
PICO	population, intervention, comparison, outcome
PID	pelvic inflammatory disease
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
WHO	World Health Organization

## Executive summary

Cervical intraepithelial neoplasia (CIN) is a premalignant lesion that is diagnosed by histology as CIN1, CIN2, or CIN3. If left untreated, CIN2 or CIN3 (collectively referred to as CIN2+) can progress to cervical cancer. There are three principal treatments for CIN available in low- and middle-income countries: cryotherapy, large loop excision of the transformation zone (LLETZ, or LEEP), and cold knife conization (CKC). This guideline builds upon the *WHO guidelines: use of cryotherapy for cervical intraepithelial neoplasia* published in 2011, and provides recommendations for the use of cryotherapy versus LEEP versus CKC for the treatment of histologically confirmed CIN2+, and additional recommendations for the treatment of histologically confirmed adenocarcinoma in situ (AIS).

In 2009, the World Health Organization (WHO) committed to updating the 2006 edition of *Comprehensive cervical cancer control: a guide to essential practice* (C4-GEP). For this update process, three new guideline documents have been compiled: (1) *WHO guidelines: use of cryotherapy for cervical intraepithelial neoplasia* (published in 2011); (2) *WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention* (being published concomitantly with these present guidelines); and (3) *WHO guidelines for treatment of cervical intraepithelial neoplasia 2–3 and adenocarcinoma in situ* (i.e. this guideline). This guideline is intended primarily for policy-makers, managers, programme officers, and other professionals in the health sector who have responsibility for choosing strategies for cervical cancer prevention, at country, regional, and district levels, in low-, middle-, and high-income countries.

The methods used to develop these guidelines follow the *WHO handbook for guideline development*, and are described in Chapter 2 of this document. A Guideline Development Group was established that included experts, clinicians, researchers in cervical cancer prevention and treatment, health programme directors and methodologists. Conflicts of interests were managed according to WHO rules. An independent group of scientists at a WHO collaborating centre conducted systematic reviews (see Annexes 2, 3 and 4) and produced evidence summaries following the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach. GRADE evidence profiles were created for nine treatment questions (see Supplemental material: GRADE evidence-to-recommendation tables and evidence profiles for each recommendation, available online).

Although the best evidence to assess treatment strategies is from randomized controlled trials, the systematic reviews identified few such trials and few non-randomized studies with comparison groups. Therefore, most of recommendations for treatment are based on pooled results across non-randomized studies in which single groups of women received treatment, without independent comparison groups. This highlights the need for further research; if randomized controlled trials are not ethically possible or feasible, there is still the potential to conduct rigorous non-randomized studies comparing two groups receiving different treatments.

This guideline provides seven recommendations. While a brief summary of the recommendations is included on the next page, the complete recommendations with remarks and a summary of the evidence for each can be found in Chapter 3 of this document.

## Summary treatment recommendations

For women with histologically confirmed CIN2+ disease, regardless of HIV status	
Strong recommendation	<p><b>The expert panel<sup>1</sup> recommends:</b></p> <p>1. Use cryotherapy over no treatment. ⊕⊕⊕⊕ evidence</p> <p>2. Use loop electrosurgical excision procedure (LEEP) over no treatment. ⊕⊕⊕⊕ evidence</p> <p>3. Use cold knife conization (CKC) over no treatment. ⊕⊕⊕⊕ evidence</p>
	<p><b>The expert panel suggests:</b></p> <p>4. Use either cryotherapy or LEEP in women for whom either cryotherapy or LEEP is appropriate to use and available. ⊕⊕⊕⊕ evidence</p>
	<p><b>The expert panel recommends:</b></p> <p>5. Use cryotherapy over CKC in women for whom either cryotherapy or CKC is appropriate to use. ⊕⊕⊕⊕ evidence</p> <p>6. Use LEEP over CKC in women in whom either LEEP or CKC is appropriate to use. ⊕⊕⊕⊕ evidence</p>
For women with histologically confirmed AIS disease, regardless of HIV status	
Conditional recommendation	<p><b>The expert panel suggests:</b></p> <p>7. Use CKC over LEEP. ⊕⊕⊕⊕ evidence</p>

Note: The quality of the evidence or confidence in the effect estimates for each recommendation is presented as high ⊕⊕⊕⊕, moderate ⊕⊕⊕⊕, low ⊕⊕⊕⊕, or very low ⊕⊕⊕⊕, according to the GRADE criteria.

<sup>1</sup> The expert panel includes all members of the WHO Steering Group, the Guideline Development Group (GDG), and the External Review Group (ERG).





# 1. Introduction

Cervical intraepithelial neoplasia (CIN) is a premalignant lesion that is diagnosed by histology as CIN1, CIN2, or CIN3.<sup>2</sup> If left untreated, CIN2 or CIN3 (collectively referred to as CIN2+) can progress to cervical cancer. It is estimated that approximately 1–2% of women have CIN2+ each year, with higher rates reported for women of HIV-positive status, at 10% (2–6). A diagnosis of CIN2+ is an histological diagnosis obtained from biopsies of the suspect lesions, either with or without colposcopy, for which treatment is recommended. Adenocarcinoma in situ (AIS) is a precursor lesion for cervical cancer that is diagnosed by cytology and can be treated. The majority of AIS are found in the transformation zone. AIS may be associated with CIN. There are three principal treatments available in low- and middle-income countries to treat CIN: cryotherapy, large loop excision of the transformation zone (LLETZ, or LEEP), and cold knife conization (CKC).

In 2006, the World Health Organization (WHO) published a guide to assist clinicians and programme managers to diagnose and treat CIN in order to prevent and control cervical cancer: *Comprehensive cervical cancer control: a guide to essential practice* (C4-GEP) (7). The C4-GEP provides background information about CIN, diagnosis, and treatments. However, in 2009, WHO committed to updating this guide to reflect new evidence available on HPV vaccination, cervical cancer screening methods, and treatments for cervical pre-cancer, and

to make treatment recommendations. In 2011, WHO recommendations for the use of cryotherapy to treat CIN were developed and published (8, 9). Those recommendations covered the use of different techniques of cryotherapy, such as single- and double-freeze methods, and its use in specific populations, including pregnant women, and women of HIV-positive status. This guideline covers treatments for histologically confirmed CIN2+, including cryotherapy, LEEP, and CKC. Another guideline has been developed concurrently on strategies to screen and treat precancerous cervical lesions when there is no histological confirmation of CIN2+ (10).

## Target audience

This document is intended primarily for policy-makers, managers, programme officers, and other professionals in the health sector who have responsibility of choosing strategies for cervical cancer prevention, at country, regional, and district levels. Individuals working in reproductive health care programmes, particularly programmes for prevention of sexually transmitted infections (STIs) including HIV/AIDS and for family planning, at the district and primary health care levels, should also consult this document to understand how recommendations are developed and why it is vitally important to select and implement evidence-based strategies to prevent cervical cancer.

## Purpose

This guideline builds upon the *WHO guidelines: use of cryotherapy for cervical intraepithelial neoplasia* published in 2011 (9), and provides recommendations for the use of cryotherapy versus LEEP versus CKC for the treatment of histologically confirmed CIN2+, and additional recommendations for the treatment of histologically confirmed AIS. This document also describes the WHO methodology that was used for the development of these guidelines based on the GRADE (Grading of

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<sup>2</sup> Diagnosis of CIN is established by histopathological examination of a cervical punch biopsy or excision specimen. A judgement of whether or not a cervical tissue specimen reveals CIN, and to what degree, is dependent on the histological features concerned with differentiation, maturation, and stratification of cells and nuclear abnormalities. The proportion of the thickness of the epithelium showing mature and differentiated cells is used for grading CIN. More severe degrees of CIN are likely to have a greater proportion of the thickness of epithelium composed of undifferentiated cells, with only a narrow layer of mature differentiated cells on the surface (1).

Recommendations, Assessment, Development and Evaluation) approach, and provides GRADE evidence profiles<sup>3</sup> and evidence-to-recommendation tables<sup>4</sup> for each

recommendation (see: Supplemental material: GRADE evidence-to-recommendation tables and evidence profiles for each recommendation).

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<sup>3</sup> The GRADE evidence profiles summarize the evidence from the systematic reviews and the model, as well as the quality of the evidence.

<sup>4</sup> The evidence-to-recommendation tables describe the process of going from the evidence to developing the recommendations, and explain the judgements and rationale for factors that are not part of the GRADE evidence profiles.

## 2. Methods

The methods to develop these guidelines followed the *WHO handbook for guideline development* (11, 12).

### Guideline groups

WHO formed a Guideline Development Group (GDG), chaired by Joanna Cain. The 17 selected members provided expert clinical guidance and support throughout the guideline development process. WHO also selected an External Review Group (ERG) comprising 33 professionals, including health-care providers with experience in screening and treating CIN, pathologists, researchers in cervical cancer prevention and treatment, programme directors, health educators, epidemiologists, public health officers, nurses and methodologists. A Methods Group (MG) from the MacGRADE Centre at McMaster University, a WHO collaborating centre, provided expertise in evidence synthesis and guideline development processes.

### Formulating questions and determining outcomes

In February 2011, the GDG met to discuss the questions and outcomes to address in the chapter on the treatment of CIN and AIS to appear in the updated C4-GEP, in order to incorporate new evidence. The GDG identified nine potential questions to guide the evidence review on the treatment of CIN and AIS. The treatment questions followed the format of PICO (population, intervention, comparison, and outcomes). The population (i.e. women who have histologically confirmed CIN2+ or AIS), intervention (i.e. cryotherapy, LEEP, or CKC), and comparison group (i.e. other or no treatment) are indicated in the questions below (Box 1), while the priority outcomes are described separately (see Box 2).

During this same meeting, the GDG developed a list of outcomes that should be considered when making decisions and recommendations for the treatment strategies. These outcomes

#### Box 1: Prioritized questions for treatment of CIN and AIS

- Should cryotherapy or no treatment be recommended for women who have histologically confirmed CIN2+ disease?
- Should LEEP or no treatment be recommended for women who have histologically confirmed CIN2+ disease?
- Should CKC or no treatment be recommended for women who have histologically confirmed CIN2+ disease?
- Should cryotherapy or CKC be recommended for women who have histologically confirmed CIN2+ disease?
- Should CKC or LEEP be recommended for women who have histologically confirmed CIN2+ disease?
- Should CKC or no treatment be recommended for women who have histologically confirmed AIS disease?
- Should cryotherapy or no treatment be recommended for women who have histologically confirmed AIS disease?
- Should LEEP or no treatment be recommended for women who have histologically confirmed AIS disease?
- Should cryotherapy, LEEP or CKC be recommended for women who have histologically confirmed AIS disease?

were informed by the work previously conducted for the preparation of the 2011 *WHO guidelines: use of cryotherapy for cervical intraepithelial neoplasia*. Following the

meeting, the MG surveyed all GDG and ERG members online using Survey Monkey<sup>5</sup> and asked them to identify and rank the critical outcomes for making recommendations. Participants ranked outcomes on a scale from 1 (not at all important) to 7 (critical) in terms of importance for decision-making. Thirty of the 50 members surveyed provided responses and an average ranking was calculated for each outcome. Outcomes with an average ranking of 4 (important) or higher were included for the evidence review and considered when making the recommendations (see Box 2).

### Synthesis of the evidence and preparation of evidence profiles

The recommendations were based on questions comparing cryotherapy, LEEP, and CKC to each other and to no treatment for CIN2+ and AIS. The MG therefore searched for, synthesized, analysed, and presented the evidence for benefits and harms, and for patient values and preferences for these different treatment options. However, data for harms were also collected from studies in which treatment was provided for any stage of CIN, as the GDG indicated during a guideline development meeting in April 2012 that harms of treatments are unlikely to depend on the stage of CIN. Issues relating to resource use and feasibility were identified and summarized by the WHO Steering Group, the GDG, and the ERG.

The MG searched the MEDLINE and EMBASE online databases up to February 2012 for benefits and up to July 2012 for harms of treatment options for CIN and up to February 2012 for AIS. The search was not restricted by language or study design in order not to exclude primary studies or previously published systematic reviews in this area (Annex 2). Reference lists of relevant studies were reviewed and the GDG was contacted for additional references.

#### Box 2: Outcomes for treatment strategies identified as important for making recommendations (in order of importance)

1. Residual/recurrent CIN2+ (after 6, 12, and 24 months)
2. Damage to other organs/other surgery required – such as injury to bladder or urethra
3. Major bleeding (requiring hospitalization/blood transfusion)
4. Maternal death
5. HPV-negative status (after 6, 12, and 24 months)
6. Major infections (requiring hospital admission and antibiotics)
7. Premature delivery
8. Fetal/neonatal spontaneous abortions
9. Pelvic inflammatory disease (PID)
10. Infertility
11. Minor bleeding (requires packing or suturing)

At least two members of the MG independently screened titles and abstracts and the full text of relevant articles, and a third investigator resolved disagreements. Randomized or quasi-randomized controlled trials, non-randomized studies comparing at least two groups of women receiving different interventions, and non-randomized studies with one group of at least 100 women were included. Studies had to include non-pregnant women aged 18 years or older who had not been previously treated for CIN or AIS. Studies could include women of known or unknown HIV status. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was used to develop the flow diagram for inclusion and exclusion of studies (Annex 3). A list of all studies included in the reviews is provided in Annex 4.

Two members of the MG independently abstracted data about patient characteristics, diagnosis, the surgical interventions, setting, follow-up and outcomes, using a pre-tested

<sup>5</sup> Survey Monkey: [www.surveymonkey.com](http://www.surveymonkey.com)

data abstraction form. Data to assess the quality of the studies was also collected using the Cochrane risk of bias tool for randomized controlled trials and the Newcastle-Ottawa Scale for non-randomized studies (13, 14). The MG analysed the data using RevMan 5.1 (review manager software). Relative risks (e.g. Risk Ratios and Odds Ratios) were calculated when possible and the effects were normalized over a period of one year. When data were available, subgroup analyses were performed to determine the effects of treatments by HIV status and age. The results of the systematic reviews and of the meta analysis are being prepared for publication and will be available through the WHO website.<sup>6</sup>

Two members of the MG evaluated the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluations (GRADE) approach (15, 16) and presented the evidence with its quality in GRADE evidence profiles (see Supplemental material). The evidence was presented in absolute effects by applying the Risk Ratios to an agreed-upon baseline risk (typically derived from non-randomized studies). Absolute effects over one year and 95% confidence intervals (CI) around that effect were presented as “X/1000 fewer outcomes (95% CI from X to X)”. The quality of the evidence or confidence in the effect estimates was assessed as high ⊕⊕⊕⊕, moderate ⊕⊕⊕⊖, low ⊕⊕⊖⊖, or very low ⊕⊖⊖⊖, according to the GRADE criteria. Tables to facilitate decision-making for recommendations (evidence-to-recommendations tables) were produced for each recommendation. These tables included a summary of the evidence (benefits and harms), an assessment of the quality of the evidence, relevant patient values and preferences, and any implications for use of resources and feasibility. A summary of the judgements of the GDG for each recommendation is also provided (see Supplemental material).

## Development of the recommendations

In early 2012 (26–28 April), the GDG, the ERG and the MG met to discuss the recommendations. One member each from the GDG and the MG chaired the meeting, which was attended by experts from around the world, representing various public health and medical disciplines. Members of the MG presented evidence profiles and evidence-to-recommendation tables, which included the evidence about the benefits and harms, values and preferences, resources and feasibility.

After the April 2012 meeting, more work was done to finalize the remarks and to confirm the data on harms. An update of the search was performed and the recommendations did not change after considering the additional evidence.

WHO has recently developed the WHO cervical cancer prevention and control costing tool (17). This tool includes two modules: one on the cost of HPV vaccination and the other on the cost of a screen-and-treat programme. The purpose of the tool is to help programme managers develop a budget for the programme. In order to develop the tool, the cost of each intervention was collected, including detailed costing of surgery, for a range of countries and the calculation tables developed. This, in addition to the experience of the members of the ERG, was essential to the discussion of the resources needed for each of the treatments.

Recommendations were made by the GDG and ERG by balancing the overall desirable and undesirable consequences of each treatment, which included consideration of important outcomes, values and preferences, resources and feasibility, along with the level of certainty of that information. Members of the panel discussed the consequences and reached consensus for the final recommendations. In rare cases of disagreement, members voted and discussed until there was 100% agreement. The results

<sup>6</sup> Available at: [www.who.int/reproductivehealth/publications/cancers/treatment\\_CIN\\_2-3/en/index.html](http://www.who.int/reproductivehealth/publications/cancers/treatment_CIN_2-3/en/index.html)

of those discussions are documented in the evidence-to-recommendation tables for each recommendation, available online in the Supplemental material. The GDG and ERG also identified key research gaps.

The recommendations were assessed as ‘strong’ or ‘conditional’ in accordance with the *WHO handbook for guidelines development* (11, 12). Strong recommendations have been worded as ‘we recommend’ and conditional recommendations as ‘we suggest’. A strong recommendation means that it was clear to the panel that the net desirable consequences of the specified strategy outweighed those of the alternative strategy. But a conditional recommendation was made when it was less clear whether the net desirable consequences of the specified strategy outweighed those of the other strategy. In this guideline, many recommendations are conditional. Table 1 provides a guide to the interpretation of the strength of the recommendations.

### Guideline review and approval process

This guideline underwent the following peer review process before and during development:

The questions formulated for the development of the guidelines were circulated among the WHO Steering Group, who also discussed them with the GDG. When the GDG and the WHO Steering Group had reached agreement on the questions, these were sent to the ERG.

The protocol for systematic reviews was circulated among the GDG. This protocol was also discussed during the ERG meeting, which was also attended by the European Guidelines Development Group in addition to the WHO Steering Group, the GDG and the MG. During that meeting the evidence that had been identified and the draft evidence profiles were discussed.

Discussions and conference calls were regularly held with the GDG to discuss the data from the literature review, the GRADE evidence profiles, and the recommendations.

The final draft guideline with the recommendations was circulated among the members of the GDG for review before WHO clearance. No disagreements were noted.

**Table 1. Interpretation of strong and conditional recommendations**

Implications	Strong recommendation “We recommend...”	Conditional recommendation “We suggest...”
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Clinicians should recognize that different choices will be appropriate for each individual and that clinicians must help each individual arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful to help individuals make decisions consistent with their values and preferences.
For policy-makers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.



### 3. Recommendations

These guidelines provide recommendations for the treatment of histologically confirmed CIN2+ or adenocarcinoma in situ (AIS) with cryotherapy, loop electrosurgical excision procedure (LEEP)/large loop excision of the transformation zone (LLETZ), or cold knife conization (CKC). The appropriate use of these treatments should first be determined by eligibility criteria. Eligibility for cryotherapy follows the guidance provided in the update of the C4-GEP (7), which will be published in 2014: a woman is eligible for cryotherapy if the entire lesion is visible, the squamocolumnar junction is visible, and the lesion does not cover more than 75% of the ectocervix. If the lesion extends beyond the cryoprobe being used, or into the endocervical canal, the woman is not eligible for cryotherapy.

These recommendations apply to all women regardless of HIV status. Although few studies measured the outcomes of interest according to HIV status the evidence suggests that there is no modification of the effects of treatments by HIV status.

**Recommendation 1. The expert panel recommends cryotherapy over no treatment for women who have histologically confirmed CIN2+ disease (strong recommendation, ⊕⊕⊕⊕ evidence)**

**Remarks:** This recommendation is strong, although the available evidence was very low quality. The expected benefit of cervical cancer prevention is very high and outweighs harms and any use of resources, but there is uncertainty related to preterm delivery in future pregnancies. However, the panel felt that women would prefer to be treated despite the uncertainty of these risks. This recommendation applies to women regardless of HIV status.

**Summary of the evidence:** Very-low-quality evidence for most outcomes was from non-randomized studies with one group of women, leading to a high risk of bias. This evidence suggests that recurrence of CIN2+

over 12 months may be 4% with cryotherapy, with 647/1000 fewer recurrences when compared to the natural history of persistence of CIN2+. Major and minor adverse events may occur rarely with cryotherapy. It was unclear whether there is a difference in spontaneous abortion and infertility, but there may be 55/1000 more preterm deliveries (from 38 fewer to 1000 more) with cryotherapy. Maternal mortality and HPV clearance was not measured. Limited qualitative evidence suggests that women are satisfied with cryotherapy. See Supplemental material for details.

**Recommendation 2. The expert panel recommends LEEP over no treatment for women who have histologically confirmed CIN2+ disease (strong recommendation, ⊕⊕⊕⊕ evidence)**

**Remarks:** This recommendation is strong despite low-quality evidence. The benefits outweigh any uncertainty about harms and the use of resources. This recommendation places a high value on women's preference for treatment. This recommendation applies to women regardless of HIV status.

**Summary of the evidence:** Low-quality to very-low-quality evidence came from non-randomized studies with one group of women, leading to a high risk of bias. Other reasons for downgrading the quality of evidence include inconsistency. Based on 19 non-randomized studies, there may be 647/1000 fewer recurrences of CIN2+ (from 631 to 663 fewer) at 12 months with LEEP. However, premature delivery may be increased with LEEP compared to no treatment based on 8 non-randomized studies with a Risk Ratio of 1.85 (95% CI: 1.59–52.15), which means there may be 37/1000 more preterm deliveries (from 26 to 51 more). The effect of LEEP on spontaneous abortion and infertility is unclear, as is the effect on HPV clearance at 6 or 12 months. There may be little to no difference in major infections, major bleeding, or damage to organs requiring surgery. However,

minor bleeding may be increased (200 more women with minor bleeding per 1000). See Supplemental material for details.

**Recommendation 3. The expert panel recommends cold knife conization (CKC) over no treatment for women who have histologically confirmed CIN2+ disease (strong recommendation, ⊕⊕⊕⊕ evidence)**

**Remarks:** This recommendation considers that no other treatments may be available. In such situations, CKC is recommended over no treatment as the benefits outweigh the harms, and patient preference for treatment was likely to be greater than the preference for no treatment. More data are needed to determine the risk of preterm births, the safety of CKC in settings with differing availability of resources, and whether CKC should be recommended for both CIN2 and CIN3. This recommendation applies to women regardless of HIV status.

**Summary of the evidence:** The quality of the available evidence ranged from low to very low; the available data were from non-randomized studies with one group of women, leading to a high risk of bias. There was also some inconsistency across studies. Data from 11 non-randomized studies were pooled and showed that there are probably 677/1000 fewer recurrences of CIN2+ when treated with CKC (from 690 to 670 fewer) compared to no treatment. However, there may be more harm: major bleeding (9/1000 more, 25 studies), major infections (9/1000 more, 9 studies), minor bleeding (24/1000 more, 8 studies), and damage to organs (3/1000 more, 27 studies). According to three non-randomized studies, CKC may carry a higher risk of premature delivery (Risk Ratio 3.41; 95% CI: 2.38–34.88) and a higher risk of spontaneous abortion compared to no treatment. No study reported on maternal mortality or infertility outcomes. See Supplemental material for details.

**Recommendation 4. The expert panel suggests cryotherapy or LEEP for women who have histologically confirmed CIN2+ disease (conditional recommendation, ⊕⊕⊕⊕ evidence)**

**Remarks:** This recommendation is distinct from recommendations made for women who have screened positive without histology or for women with histologically confirmed CIN1. For women who have histologically confirmed CIN2+, the overall benefits may be greater with LEEP, and adverse events are similar with LEEP or cryotherapy. The availability and implementation of LEEP or cryotherapy will depend on resources. This recommendation applies to women regardless of HIV status.

**Summary of the evidence:** Evidence of moderate quality from one randomized controlled trial indicated greater recurrence rates of CIN2+ at 12 months with cryotherapy (Risk Ratio 3.00; 95% CI: 0.99–8.38), but this was inconsistent with the very-low-quality evidence from non-randomized studies (Risk Ratio 0.78; 95% CI: 0.1–3.55). There may be little or no difference in major bleeding or major infections; however, there may be fewer women who have minor bleeding with cryotherapy (108/1000 fewer). It is unclear what the effects are on premature delivery (very-low-quality evidence indicated that there may be 18/1000 more premature deliveries with cryotherapy (from 74 fewer to 672 more). It is also unclear whether there was a difference in spontaneous abortions or infertility. The differences in HPV clearance could not be determined. Evidence from one randomized controlled trial showed no difference in patient satisfaction, and limited qualitative evidence suggested that women are satisfied with cryotherapy. See Supplemental material for details.

**Recommendation 5. The expert panel recommends cryotherapy over CKC for women who have histologically confirmed CIN2+ disease and for whom cryotherapy**



**or CKC could be appropriate (strong recommendation, ⊕⊕⊕⊕ evidence)**

**Remarks:** There is low-quality to very-low-quality evidence for the benefits and harms of cryotherapy and CKC. Although there may be fewer recurrences of CIN2+ with CKC than with cryotherapy, the harms may be greater. The resources required are also greater for CKC, including the need for operating rooms, anaesthesia, and highly trained providers or specialists. The limited data on values and preferences of women for either treatment were considered similar. This recommendation applies to women regardless of HIV status.

**Summary of the evidence:** Evidence came from non-randomized studies with one group of women, leading to a high risk of bias most likely due to selective reporting of outcomes, and inconsistency among studies. Six non-randomized studies found that recurrence rates of CIN2+ are probably greater with cryotherapy (Risk Ratio 3.29; 95% CI: 2.67–4.02) than with CKC. However, indirect evidence from a systematic review of premature delivery showed that there may be less risk of premature delivery (<37 weeks) with cryotherapy: 45/1000 fewer preterm deliveries over 12 months. Up to 44 studies contributed data on harms and showed that there may be fewer women who have major bleeding requiring hospital admission or blood transfusion with cryotherapy (8/1000 fewer) as well as fewer major infections (7/1000 fewer), fewer women with damage to other organs requiring surgery (3/1000 fewer), and fewer women who have minor bleeding (23/1000 fewer). Due to very low quality evidence, often due to very few or no studies, it is unclear whether there is a difference in maternal mortality, HPV clearance, infertility outcomes, or spontaneous abortions. See Supplemental material for details.

**Recommendation 6. The expert panel recommends LEEP over CKC for women who have histologically confirmed CIN2+ disease and for whom LEEP or CKC could**

**be appropriate (strong recommendation, ⊕⊕⊕⊕ evidence)**

**Remarks:** The quality of evidence was low for some outcomes and very low for critical outcomes, often with inconsistent results. Therefore, the overall benefits and harms of LEEP over CKC were unclear. Typically, CKC is provided over LEEP for clinical reasons and in specific situations. However, in situations in which there is a choice, the panel agreed that most women would prefer LEEP, as CKC is considered major surgery compared to LEEP. The resources required are also greater with CKC, including anaesthesia, operating rooms, and skilled providers. This recommendation applies to women regardless of HIV status.

**Summary of the evidence:** The available evidence was generally very low quality and came from non-randomized studies with one group of women and some randomized controlled trials, with the results often inconsistent between the studies. Recurrence rates of CIN2+ may be lower at 12 months with CKC compared to LEEP, with a Risk Ratio of 0.52 (95% CI: 0.13–1.41) based on two randomized controlled trials and Risk Ratio of 0.64 (95% CI: 0.34–1.2) based on data from seven non-randomized studies. There was inconsistent evidence for major bleeding, although there may be greater risk of major infection with CKC, as well as more preterm deliveries. There is uncertainty about the differences in spontaneous abortion, infertility, and HPV clearance. See Supplemental material for details.

**Recommendation 7. The expert panel suggests CKC over LEEP for women who have histologically confirmed AIS disease (conditional recommendation, ⊕⊕⊕⊕ evidence)**

**Remarks:** This recommendation is based on very low quality evidence, which resulted in imprecise data for the differences in benefits and harms between CKC and LEEP. CKC

may result in fewer recurrences and the panel felt these benefits outweighed the additional resources required for CKC. The preferences of women were also felt to be variable as women in higher income countries may not have as much aversion to CKC (e.g. anaesthesia), while women in lower income countries may prefer LEEP due to the additional risks associated with invasive surgery. This recommendation applies to women regardless of HIV status.

**Summary of the evidence:** Very-low-quality evidence came mostly from non-randomized studies with one group of women, but no evidence was available from randomized controlled trials. Results were imprecise due to very few events and participants in the studies. Critical outcomes, such as recurrence of AIS,

damage to other organs, major bleeding, maternal mortality, HPV status, major infections, PID, infertility, and minor bleeding were not measured. Based on seven non-randomized studies, there may be greater recurrence of AIS with LEEP compared to CKC: 31/1000 more recurrences (from 20 fewer to 137 more). There may also be 49/1000 more invasive adenocarcinomas (from 17 fewer to 282 more) with LEEP compared to CKC based on three non-randomized studies. However, not all studies reported whether invasive cancer had occurred or not. Although very-low-quality evidence indicates fewer preterm deliveries with LEEP, there may be more spontaneous abortions with LEEP compared to CKC. See Supplemental material for details.

## 4. Research gaps and further considerations

The GDG identified and prioritized treatment outcomes that were important to the decision-making process. For many of these outcomes, in particular fertility and reproductive outcomes, there was low-quality to very-low-quality data, or no data. There was also little research about the effects of the treatments in women of HIV-positive status, and few studies had measured the potential for HIV transmission following treatment.

Much of the data came from non-randomized studies based on single groups of women receiving treatment without an independent comparison group. This meant that many comparisons between surgical treatments –

cryotherapy versus LEEP, for example – were made by comparing the results from single-arm non-randomized studies of cryotherapy to single-arm non-randomized studies of LEEP. When comparing these studies, it is often unclear whether the populations, settings, interventions, and outcomes are adequately similar. The results were therefore assessed as inconsistent and/or indirect, leading to low- to very-low-quality evidence. Although randomized controlled trials may not be ethically possible or feasible in some situations, there is still the potential to conduct rigorous non-randomized studies comparing two treatments, which could provide higher quality evidence.

## 5. Use of the guidelines

### Guideline dissemination

These guidelines will be available online at the WHO Library database and there will be a link on WHO's Sexual and Reproductive Health web page and in the WHO Reproductive Health Library (RHL), an electronic review journal.<sup>7</sup> The publication will also be announced in the UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP) WHO Reproductive Health Update,<sup>8</sup> which reaches more than 2000 subscribers and numerous organizations with whom we are working. Many of these organizations will also copy the announcement in their newsletters.

The guidelines will be distributed in print to subscribers to WHO publications, to the WHO mailing list for mandatory free distribution (national chief health executives, ministers of health or directors-general of health, depository libraries for WHO publications, WHO representatives/liaison officers, WHO headquarters library, WHO regional offices, and off-site office libraries), additional non-mandatory free recipients (competent national authorities for sexual and reproductive health, cancer control programmes, national research centres in reproductive health, and WHO collaborating centres), WHO staff at headquarters, regional and country offices and elsewhere, concerned NGOs, medical societies concerned with cancer control and/or sexual and reproductive health, scientific journals (including general medical journals and journals specialized on sexual and reproductive health or cancer),

international organizations, and donors, potential donors, potential publishers of translated versions, as well as all those who contributed to the documents.

Conference invitations to discuss and present the guidelines will be accepted.

Regional conferences have already been held in the Americas and Africa in 2013, to present the new recommendations to a number of stakeholders involved in national programme planning. The other regions will be covered in 2014.

If requested by regional offices, countries will be supported to adapt the guideline to their country-specific needs and to integrate the material with existing national guidelines. Adaptation will be done by organizing regional, sub-regional and country-level workshops for discussion of each recommendation, in order to adapt them to the national epidemiologic, cultural, and socioeconomic context.

Initially, the guidelines will be available in English only and translations will be developed subject to the availability of funding. Translation into non-UN languages and publication in these languages by third parties will be encouraged.

### Guideline evaluation

The number of downloads from the WHO web sites (headquarters and regional) will be used as an indicator of interest to these guidelines.

We are working with the WHO regional offices to monitor requests from countries for technical assistance to use these guidelines. For this purpose, national stakeholder meetings will be organized in-country, and feedback on the clarity, feasibility, and usefulness of the recommendations will be recorded.

We will also monitor, with the regional offices, how many countries change their

<sup>7</sup> The WHO Library database is available at <http://www.who.int/library/databases/en/>; WHO's Sexual and Reproductive Health web page is available at <http://www.who.int/reproductivehealth/topics/cancers/en/index.html>; WHO's RHL is available at <http://apps.who.int/rhl/en/>.

<sup>8</sup> A subscription to HRP's *WHO Reproductive Health Update* can be requested at <http://www.who.int/reproductivehealth/RHUpdate/en/index.html>.

recommendations based on the publication of these new treatment recommendations.

### Guideline update

The GDG will continue to work with WHO in an ad hoc manner, so that the research gaps identified during the process can be addressed. Since the search for evidence was conducted early in 2012, we will monitor

the literature for additional evidence and for evidence on new treatment methods, so that updates to these recommendations can be promptly considered. We anticipate that approximately three years after the publication of these recommendations sufficient new evidence will be available to update the present recommendations and potentially add new ones.

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## Annex 1. Declarations of interest

Out of the 54 experts who participated in this work, 15 declared an interest related to cervical cancer. Although not all of these interests are specifically related to cervical cancer screening and treatment, they are nonetheless all disclosed and summarized below.

**Marc Arbyn** was invited by the European Research Organisation on Genital Infection and Neoplasia (EUROGIN) to speak at its 2011 conference in Lisbon. EUROGIN covered his travel and lodging expenses. EUROGIN is an organization that promotes and develops, at the level of the European region, research, training, screening, prevention and information concerning genital infections, pre-cancers and cancers in women. EUROGIN conferences are financially supported by a range of pharmaceutical companies with an interest in cervical cancer.

**Paul Blumenthal** was the principal investigator of an operations research study conducted by the Department of Obstetrics and Gynecology at Stanford University School of Medicine to evaluate the feasibility and acceptability of introducing a new rapid HPV test (careHPV) manufactured by Qiagen for low- and middle-income settings. Qiagen lent the equipment and provided the tests for this research.

**John-Paul Bogers** is employed by the University of Antwerp and acts as a consultant for SonicHealthcare Benelux to perform clinical pathology work and validate new technologies in the field of treatment of cervical intraepithelial neoplasia (CIN). SonicHealthcare Benelux is a commercial laboratory that inter alia performs cervical cancer (cytology and HPV) screening. Bogers has also performed work for three other companies with an interest in cervical cancer screening: (1) an analytical validation of an HPV test for Innogenetics (contract value: €60 000); (2) an analytical validation of a Becton-Dickinson (BD) pathway machine (contract value: €10 000); and (3) a literature review in the field of treatment of CIN for Hologic (contract value: €5000).

**August Burns** is the Executive Director of Grounds for Health, a non-profit organization that aims to create sustainable and effective cervical cancer prevention and treatment programmes in coffee-growing communities, with the goal of decreasing the rate of cervical cancer. To support its projects, Grounds for Health received US\$ 15 000 from the Union Internationale Contre le Cancer (UICC), a nongovernmental, non-profit organization that inter alia receives funding from companies with an interest in cancer.

**Lynette Denny** has spoken on HPV vaccination at various speakers' forums organized by the companies GlaxoSmithKline (GSK) and Merck. The honoraria for these activities amounted to approximately US\$ 4000 per company per year and were paid to her employer, the University of Cape Town. The Department of Obstetrics and Gynaecology of the University of Cape Town, of which Denny is the head, has furthermore conducted two HPV vaccine trials for GSK and Merck. For these trials the University of Cape Town received US\$ 1.6 million from GSK, but no funding from Merck as that funding was paid to the Department of Health, KwaZulu Natal. All work done on the project by Denny was done pro bono. Denny gave a talk on cost-effectiveness of HPV testing in Hong Kong, in 2012, and Qiagen paid for her registration, travel and accommodation. Denny is currently running a trial for Roche on the ability of the cobas® 4800 System to detect cancer – the cost is US\$ 25 000. All the funds received by Denny either as a principal investigator or as a speaker are paid entirely to the University of Cape Town research accounts.

**Silvia de Sanjosé** has received occasional travel support from Sanofi, Merck and Qiagen to attend and present results of studies coordinated by her institution at national and international conferences. The amounts ranged from approximately US\$ 1000 to US\$ 3000 per trip, depending on



the location of the conference. None of the funders had any role in the presentation of results. Some research studies in which de Sanjosé participates have been partially supported by GSK, Sanofi Pasteur MSD, Qiagen, Roche and Merck & Co., Inc., representing over US\$ 100 000 a year for the last four years. None of the funders have had any role in the data collection, analysis or interpretation of the results.

**Eduardo Franco** has participated in advisory board meetings and forums relating to cervical cancer prevention strategies organized by Merck, Roche and Gen-Probe (either on HPV vaccines or HPV tests). He has received an average honorarium of US\$ 4000 per company for these activities over the last four years.

**Julia Gage** has, as part of her work for the United States National Cancer Institute (NCI) of the National Institutes of Health (NIH), conducted an operations research project in Nigeria to evaluate the effectiveness of the careHPV screening test manufactured by Qiagen. Qiagen donated and shipped the reagents, equipment and supplies. NCI paid for all other aspects of the study.

**Francisco Garcia** was the principal investigator for drug trials of novel agents for the treatment of cervical cancer while he was employed at the University of Arizona. These trials were conducted by the University of Arizona under research contracts with Roche (US\$ 150 000), Inovio (US\$ 70 000), Photocure (US\$ 120 000) and Roche/Ventana (US\$ 100 000). Garcia did not receive any personal income for these trials.

**José Jeronimo** is an employee of PATH, an international non-profit organization involved in the development and delivery of high-impact, low-cost tools for global health. PATH has concluded collaborative research and development agreements for the development of a rapid HPV test with Qiagen (careHPV) and a rapid test for cervical cancer screening with Arbor Vita (identification of the E6 and E7 oncoproteins). PATH has received samples and equipment from both companies to conduct studies in different countries for the validation of these tests. In the PATH–Qiagen agreement, the commercialization of the test in China and India is considered a priority, with other countries to be included according to the conditions in each geographical area. These tests will be made available at low cost to the public sector in low-resource countries.

**Enriquito Lu** was the principal investigator of an HPV vaccination study conducted by his employer, the international, non-profit organization Jhpiego, under agreement with Merck. The purpose of the study was to evaluate the feasibility and acceptability of a strategy to deliver comprehensive cervical cancer prevention services in Thailand and the Philippines by integrating HPV vaccination for girls aged 9–13 into screening and treatment programmes for mothers. For this purpose, Jhpiego received from Merck US\$ 850 000 and HPV vaccines for up to 4000 girls in each country project site. Lu did not receive any personal income for his work on this study.

**Raul Murillo** was a consultant for GSK to analyse the cost-effectiveness of the HPV vaccine. He received a total honorarium of US\$ 5000 for this consultancy (which ended in 2010).

**Swee Chong Queck** has, over the past four years, participated in advisory board meetings and speakers' forums organized by GSK and Qiagen. These meetings and forums related to cervical cancer prevention strategies, HPV vaccine efficacy studies and clinical relevance of HPV vaccination for the prevention of cervical cancer and other HPV-related diseases. The total combined income received by Queck for these activities over the last four years was S\$ 9000 (Singapore dollars).

**Achim Schneider** serves as an advisor to the company Karl Storz in the development of laparoscopic techniques and instruments for the treatment of cervical cancer and other benign or malignant diseases, for which he receives an annual honorarium of €40 000. Schneider has also participated in advisory board meetings and lectures relating to HPV vaccination, organized by GSK and Sanofi, respectively. For these latter activities he has received a total combined income of US\$ 20 000 over the last four years.

**Vivien Tsu** is an employee of PATH, an international non-profit organization involved in the development and delivery of high-impact, low-cost tools for global health. As such, Tsu was involved in: (1) large-scale demonstration projects on the prevention, screening and treatment of cervical cancer in developing countries for which PATH received donated vaccine from GSK and Merck and careHPV tests from Qiagen; and (2) an alternative-dose-schedule study in Viet Nam, for which PATH received donated vaccine from Merck.

## Annex 2. Search strategy for evidence reviews

Cryotherapy, large loop excision of the transformation zone (LLETZ or LEEP), and cold knife conization (CKC)

**Search in OVID MEDLINE** (up to February 2012 for benefits of treatment of cervical intraepithelial neoplasia [CIN], up to July 2012 for harms of treatment of CIN, and up to February 2012 for benefits and harms of treatment of adenocarcinoma in situ [AIS])

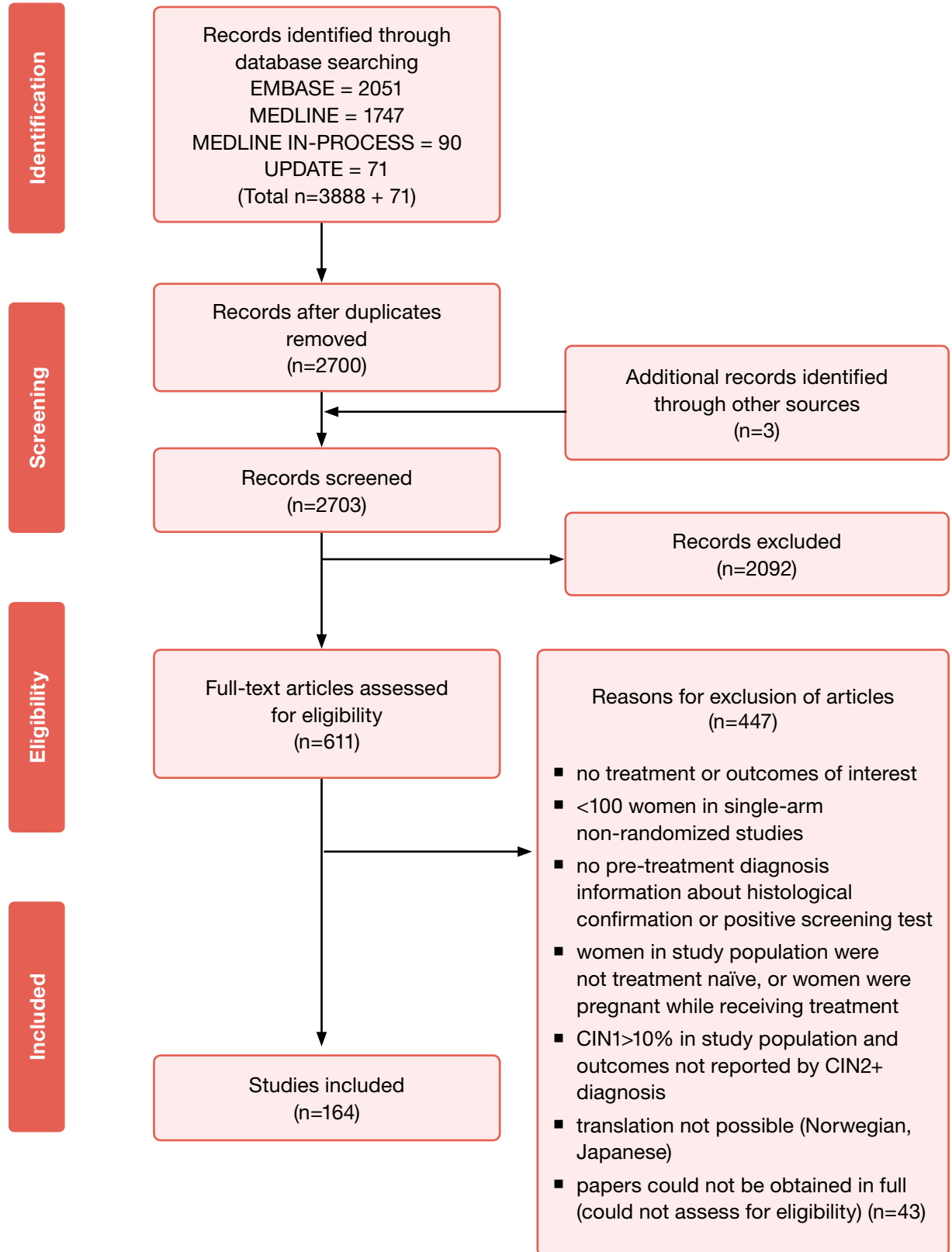
- 1 cervical intraepithelial neoplasia/
- 2 uterine cervical dysplasia/
- 3 uterine cervical neoplasms/
- 4 ((precancer\* or pre-cancer\* or neoplas\* or dysplasia or lesion\* or premalignan\* or malignan\* or cancer\* or carcinoma\*) adj3 cervi\*).tw.
- 5 (cin or cin2\* or cin3\* or cin1).tw.
- 6 1 or 2 or 3 or 4 or 5
- 7 (co or ae or su or th).fs.
- 8 6 and 7
- 9 (cone or coni?ation).tw.
- 10 (biopsy or knife or cold).tw.
- 11 9 and 10
- 12 cold knife.tw.
- 13 conization/
- 14 11 or 12 or 13
- 15 14 and 8
- 16 (leep or lletz).tw.
- 17 electrosurgery.sh.
- 18 loop.tw.
- 19 or/16-18
- 20 19 and 8
- 21 cryotherapy.tw.
- 22 cryosurgery/
- 23 21 or 22
- 24 23 and 8
- 25 15 or 20 or 24

### Searches in EMBASE, the Cochrane Library, and LILACS

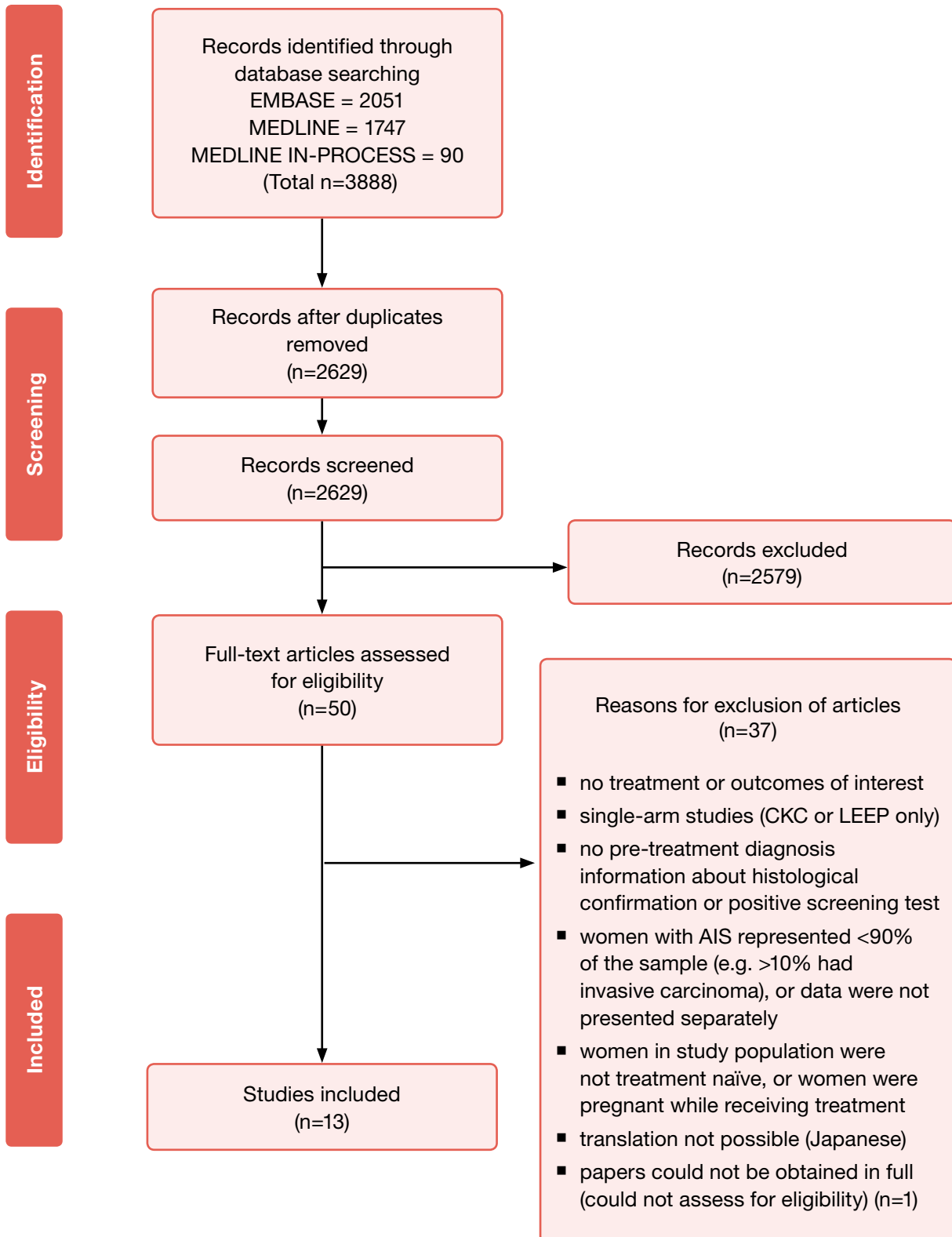
The OVID MEDLINE search was adapted to the subject headings appropriate for each database.

## Annex 3. PRISMA flow diagram for inclusion and exclusion of studies for evidence reviews

Treatments for CIN: cryotherapy, large loop excision of the transformation zone (LLETZ or LEEP), and cold knife conization (CKC)



## Treatments for adenocarcinoma in situ (AIS)



## Annex 4. List of references for studies included in evidence reviews

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For more information, please contact:  
Department of Reproductive Health and Research  
World Health Organization  
Avenue Appia 20, CH-1211 Geneva 27  
Switzerland  
Fax: +41 22 791 4171  
E-mail: [reproductivehealth@who.int](mailto:reproductivehealth@who.int)  
[www.who.int/reproductivehealth](http://www.who.int/reproductivehealth)



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