

# European Guidelines for Quality Assurance in Cervical Cancer Screening. Second Edition—Summary Document

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European Guidelines for Quality Assurance in Cervical Cancer Screening have been initiated in the Europe Against Cancer Programme. The first edition established the principles of organised population-based screening and stimulated numerous pilot projects. The second multidisciplinary edition was published in 2008 and comprises ~250 pages divided into seven chapters prepared by 48 authors and contributors. Considerable attention has been devoted to organised, population-based programme policies which minimise adverse effects and maximise benefits of screening. It is hoped that this expanded guidelines edition will have a greater impact on countries in which screening programmes are still lacking and in which opportunistic screening has been preferred in the past. Other methodological aspects such as future prospects of human papillomavirus testing and vaccination in cervical cancer control have also been examined in the second edition; recommendations for integration of the latter technologies into European guidelines are currently under development in a related project supported by the European Union Health Programme. An overview of the fundamental points and principles that should support any quality-assured screening programme and key performance indicators are presented here in a summary document of the second guidelines edition in order to make these principles and standards known to a wider scientific community.

**Key words:** cervical cancer, cervical intraepithelial neoplasia, Europe, guidelines, quality assurance, screening

## summary document

Cancer is common in older people but cancer of the uterine cervix primarily affects younger women, with the majority of cases appearing between the ages of 35 and 50, when many women are actively involved in their careers or caring for their families. In the European Union (EU) 34 000 new cases and >16 000 deaths due to cervical cancer are reported annually [1, 2].

The burden of cervical cancer is particularly high in the new member states. The highest annual world-standardised mortality rates are currently reported in Romania and Lithuania (13.7/100 000 and 10.0/100 000, respectively) and the lowest rates in Finland (1.1/100 000). Governmental authorities, parliamentary representatives and advocates should be aware that the substantially higher dimension of this public health problem in the east of the EU requires special attention.

Among all malignant tumours, cervical cancer is the one that can be most effectively controlled by screening. Detection of cytological abnormalities by microscopic examination of Pap smears and subsequent treatment of women with high-grade cytological abnormalities avoids development of cancer [3].

Cytological screening at the population level every 3–5 years can reduce cervical cancer incidence up to 80% [4]. Such benefits can only be achieved if quality is optimal at every step in the screening process, from information and invitation of the eligible target population to performance of the screening test and follow-up, and, if necessary, treatment of women with screen-detected abnormalities.

Quality assurance of the screening process requires a robust system of programme management and coordination, assuring that all aspects of the service are performing adequately. Attention must be paid not only to communication and technical aspects but also to qualification of personnel, performance monitoring and audit, as well as evaluation of the impact of screening on the burden of the disease.

Population-based screening policy and organisation conforming to evidence-based standards and procedures

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**Table 1.** Key characteristics of cervical cancer screening programme

1. Programme structure
1.1 Catchment area
1.2 Start date of the programme (month, year)
1.3 Youngest age targeted for screening
1.4 Oldest age targeted for screening
1.5 Recommended interval between negative tests (in years)
1.6 Groups (if any) not eligible to participate in screening (e.g. hysterectomised) <sup>a</sup>
1.7 Screening test
2. Does the programme invite
2.1 All women in the eligible target population, regardless of Pap test history?
2.2 All women in the eligible target population, except those who had a recent Pap test (within the past 6 months or 1 year)?
2.3 Only the women in the eligible target population who did not receive a Pap test within the recommended screening interval (3 or 5 years)?
2.4 Other, specify:
2.5 No invitations are issued?
3. Does the invitation include?
3.1 A pre-fixed, modifiable appointment
3.2 An invitation to get in touch to arrange an appointment
3.3 Other, specify:
4. Are noncompliers reminded?
4.1 All women
4.2 Some women <sup>b</sup>
4.3 None
5. Diagnostic protocols
5.1 Cytology results for which repeat cytology is recommended
5.2 Cytology results for which referral for colposcopy is recommended

<sup>a</sup>Women with a recent Pap smear who fulfil eligibility criteria are included in the group of women eligible to participate in screening.

<sup>b</sup>Specify, e.g. referral for colposcopy after repeated test? After HPV triage?

HPV, human papillomavirus.

provide the overall programmatic framework essential to implementation of quality assurance and are therefore crucial to the success of any cervical cancer screening programme.

Establishment of screening registries and linkage of individual screening data with cancer registry data, taking into account appropriate data protection standards and methods, are essential tools of monitoring and evaluation.

The first edition of the European Guidelines for Quality Assurance in Cervical Cancer Screening [5] established the principles of organised population-based screening and was pivotal in initiating pilot projects in Europe. A number of countries have in the meantime developed organised population-based screening approaches, which are illustrated in Section 2.4.2 of the second edition [6]. It is hoped that this new guideline edition will have a greater impact on those countries in which opportunistic, rather than organised, population-based screening has been the preferred model in the past.

Transformation of these programmes to the population-based approach with quality assurance at all appropriate levels has the potential to substantially improve the accessibility, the effectiveness and the cost-effectiveness of the respective services. At the same time, substantial numbers of unnecessary screening examinations could be avoided by adhering to the interval for cervical cancer screening recommended in the European guidelines (3–5 years) [7, 8]. Towards this end, considerable attention has been given to the essential aspects of developing an organised population-based programme policy that minimises the adverse effects and maximises the benefits of screening.

The current recommendations are also particularly relevant to planning new cervical cancer screening programmes in Europe. Different solutions fulfilling the recommended methodological standards need to be implemented in different countries and regions with diverse levels of resources and general health care infrastructure.

More than a decade has passed since the publication of the first guideline edition. The current expanded edition therefore also includes extensive updates on technical details and documentation, as well as assessment of new technologies, e.g. liquid-based cytology (LBC), automated interpretation of Pap smears and testing for human papillomaviruses (HPVs). The scope of the current guideline has also been extended to include comprehensive instructions prepared by a multidisciplinary team of experts for general practitioners, gynaecologists and cytopathologists. Much more extensive recommendations on follow-up, diagnosis and management of women with positive cervical cytology have been added. This necessitated the incorporation in the second edition of a separate chapter on techniques and quality assurance in histopathology and, for the first time, detailed guidance for clinicians in dealing with abnormal cytology, including management according to the severity of cytological abnormalities and management of histologically confirmed cervical epithelial neoplasia.

A major further addition has been the inclusion of uniform indicators for monitoring programme performance and for identifying and reacting to potential problems at an early time. The indicators deal with screening intensity, test performance and diagnostic assessment and treatment and address aspects of the screening process that influence the impact as well as the human and financial costs of screening. Standard tables have been provided for documenting screening policies and for tabulating the person-based data used to generate the uniform performance indicators. The availability of these standardised tools will substantially improve data comparability and the exchange of experience and results between screening programmes in Europe. Such exchange, in turn, is essential to effective Pan-European collaboration in implementing and continuously improving the quality and effectiveness of cervical cancer screening programmes.

Cervical cytology still is the cornerstone of cervical cancer prevention programmes in Europe, although new perspectives for other screening technologies are developing rapidly. The principles of quality assurance, performance monitoring and evaluation and many of the procedures and methodological standards laid down in the current guideline edition are of equal relevance to cervical cancer screening on the basis of

other conceivable methods. It is therefore expected that the publication of the updated and revised second edition will also promote rigorous standards in the evaluation and application of new screening technologies, thereby improving the effectiveness of cervical cancer prevention in Europe.

Over the short and medium term, screening for cervical cancer precursors and management of screen-detected lesions will remain the most effective tool for cervical cancer prevention in Europe. However, the field of cervical cancer prevention is rapidly developing due to better understanding of the natural history of the disease. Persistent infection with one of 13–16 oncogenic HPV types is now known to be a key prerequisite for development of cervical cancer [9, 10]. The overwhelming evidence linking HPV infection to cervical cancer has prompted the development of test systems to detect its nucleic acids as well as prophylactic and therapeutic vaccines.

Primary prevention by prophylactic vaccination against the HPV types that are causally linked with most cervical cancers in Europe is likely to become a feasible option for cervical cancer control, provided the current cost of inoculation regimens is substantially reduced.

While prophylactic vaccination, primarily in young girls, may provide important future health gains, cervical screening will need to be continued [11]. Neglecting cervical cancer screening due to the current availability of a vaccine could paradoxically lead to an increase in cancer cases and deaths.

Development of comprehensive European guidelines on prevention of cervical cancer that appropriately integrate screening and vaccination strategies is a key aim of the next phase of guideline development activities supported by the EU Health Programme.

## guideline development process

The current updated and expanded second guideline edition has been prepared by a multidisciplinary team of experts appointed by the European Commission from the former European Cervical Cancer Screening Network (ECCSN) established under the Europe Against Cancer Programme. In addition to the cytopathologists, epidemiologists, general practitioners, gynaecologists, histopathologists, virologists and specialists in social science serving as editors and authors, experts from outside ECCSN were also invited to write, review and contribute to the development of the second edition. Besides the input of the 48 experts from 17 member states directly involved in the production of the guidelines, numerous comments and suggestions were provided by experts attending meetings held in Denmark, Finland, Greece, Hungary and Luxembourg from 2003 to 2006 by ECCSN and the European Cancer Network (ECN) in which the former cancer screening networks have been consolidated.

A draft-revised guideline was made available for public consultation on the internet in December 2003. The results of this consultation were incorporated into a new draft, which was reviewed by experts invited by the International Agency for Research on Cancer (IARC) to Lyon, France, in June 2005. Two or three reviewers were invited for each chapter, in order to comment on the contents and to ensure that all relevant references available had been considered. The further revised guideline content was

subsequently discussed with screening experts from 23 member states and 1 applicant country of the EU at the ECN meeting in February 2006. Since then, IARC has provided technical and scientific support to the editorial board and the authors for the final preparation of the guideline document.

The final recommendations and standards of best practice in the revised and updated second guideline edition are on the basis of the expert consensus in the editorial board after the above-mentioned consultations and discussions. They take into account the available evidence of screening and diagnostic procedures and programmes. For assessing evidence of effectiveness, two criteria were used: study type and study outcomes. Study types were ranked from high- to low-level evidence as follows: (i) randomised clinical trials, (ii) observational studies: case-control studies and cohort studies and (iii) correlational studies (time trends, geographical comparisons). Outcomes of studies were ordered as follows: (i) reduction of mortality from cervical cancer, (ii) reduction of incidence of invasive cervical cancer, (iii) reduction of incidence of cervical intraepithelial neoplasia (CIN) 3 or cancer (CIN3+), (iv) increased detection of high-grade histologically confirmed CIN (CIN3+ or CIN2+), (v) increased test positivity rate without or with small loss in positive predictive value for CIN2+. Throughout this guideline, scientific evidence on which the recommendations are based is indicated by references in the text. Where no observed data were available, outcomes simulated by mathematical models and expert opinion were accepted as lowest level of evidence.

The authors conducted systematic literature searches and used available systematic reviews and published meta-analyses. Publication of the handbook for cervical cancer prevention by the IARC Working Group on the Evaluation of Cancer Preventive Strategies in 2005, which included several ECN experts, was also helpful. Several pioneering population-based randomized trials have been conducted in recent years, or are currently being conducted, in various member states: LBC (Italy, The Netherlands), automated cytological screening (Finland); HPV-based versus cytology and combined (cytology + HPV) screening (Finland, Italy, The Netherlands, Sweden, UK). The results available from these trials were taken into account during the preparation of the second guideline edition up to July 2007. In addition, several meta-analyses were carried out to assess the level of evidence of new screening or management methods: LBC versus conventional cytology; HPV testing in triage of minor cytological lesions to identify women needing further follow-up, in follow-up after treatment of CIN to predict success or possible failure of treatment and in primary screening. In the meta-analyses carried out for the current guideline edition, it was only possible to assess cross-sectional outcomes (outcome types 4–5); an insufficient number of trials had reached longitudinal outcomes before final closure of chapter revisions in mid-2007. One additional meta-analysis concerned obstetrical adverse effects of treatment of precancerous lesions.

Due to the rapid accumulation of evidence on new technologies and prevention strategies, review and updating of the current guidelines has already been initiated under the current EU Health Programme [European Cooperation on

Development and Implementation of Cancer Screening and Prevention Guidelines (ECCG-ECN)].

## fundamental points and principles

### screening policy

- The Council of the EU has recommended implementation of population-based cervical cancer screening programmes to the EU member states, with quality assurance at all levels and in accordance with European guidelines [12].
- Screening recommended by the European Council and the European Guidelines is set up as a population-based public health programme, with identification and personal invitation of each woman in the eligible target population. In addition to invitation, the other steps in the screening process and the professional and organisational management of the screening service, including quality assurance, monitoring and evaluation, are well defined by programme policy, rules and regulations at the regional and national level.
- Designing a cervical cancer screening programme includes defining the screening policy, i.e. choosing the screening test systems, determining the target age group and the screening interval between normal test results (3 or 5 years) and establishing follow-up and treatment strategies for screen-positive women, taking into account the variation in background risk in target populations and the natural history of the disease, which is characterised by a rather long detectable preclinical period and substantial regression rates of the precancerous lesions.
- Cervical cytology is the currently recommended standard test for cervix screening, which should start in the age range 20–30 [12, 13], but preferentially not before age 25 or 30 years, depending on the burden of the disease in the population and the available resources [13, 14]. It is recommended to continue screening at 3- to 5-year intervals until the age of 60 [13, 15] or 65 [4, 5]. Stopping screening in older women is probably appropriate among women who have had three or more consecutive previous (recent) normal cytology results.
- Special attention should be paid to the problem of older women who have never attended screening as they exhibit increased risk for cervical cancer.
- Opportunistic screening, which takes place in clinical settings and depends on the initiative of the individual woman or her doctor, should be discouraged. Such activities are often characterised by high coverage in selected parts of the population which are screened too frequently, coexisting with a low coverage in other population groups with less socioeconomic status, and heterogeneous quality, resulting in limited effectiveness and poor cost-effectiveness.

### screening organisation, monitoring and evaluation

- The programme design must permit evaluation. An experimental design that is suitable for evaluation of new screening policies in organised settings is recommended.

- The success of a screening programme requires adequate communication with women, health professionals and persons responsible for the health care system.
- Moreover, a well-organised screening programme must reach high population acceptance and coverage and must ensure and demonstrate good quality at all levels.
- The communication strategy for cervical cancer screening must be underpinned by robust ethical principles and ensure that the information developed is evidence based, 'women centred' and delivered effectively, taking into account the needs of disadvantaged groups and enabling women to make an informed choice about participation at each step in the screening process [16].
- Population-based information must be established for continuous monitoring of screening process indicators. An appropriate legal framework is required for registration of individual data and linkage between population databases, screening files and cancer and mortality registers. Indicators of screening programme extension and quality need to be published regularly.
- The information system is an essential tool for managing the screening programme; computing the indicators of attendance, compliance, quality and impact; and providing feedback to involve health professionals, stakeholders and health authorities.

### new screening technologies

- An observation that a new screening method detects more precursor lesions than the standard Pap smear does not sufficiently demonstrate improved effectiveness. Due to frequent regression of precursor lesions, high specificity is also required to avoid anxiety, unnecessary treatment and side-effects. Evidence of effectiveness should preferentially be on the basis of reduction of cancer morbidity and mortality. Nevertheless, reduction in incidence of grade 3 cervical intraepithelial neoplasia (CIN3) is a surrogate indicator of effectiveness.
- Before routine implementation of a new screening strategy, the feasibility, cost-effectiveness and quality assurance should be verified and the necessary training and monitoring should be organised. A randomised screening policy, which permits quality-controlled piloting of a new test or procedure in the context of an organised screening programme, is a particularly powerful tool for timely evaluation under real-life conditions.

#### *cytological methods.*

- The occurrence of false-negative and unsatisfactory Pap smears has prompted the development of LBC and automated screening devices. The quality of the evaluation of the performance of these technologies often was poor and rarely on the basis of histologically defined outcomes using randomised study designs. In general, the proportion of unsatisfactory samples is lower in LBC compared with conventional cytology, and the interpretation of LBC requires

less time. The cost of an individual LBC test is considerably higher, but ancillary molecular testing, such as high-risk HPV testing in the case of atypical squamous cells of undetermined significance (ASC-US), can be carried out on the same sample. The economic advantage of LBC due to the reduction of recalls for a new sample depends on the existing rates of inadequate Pap smears, which are highly variable throughout Europe.

- An Italian population-based randomised study recently confirmed that the sensitivities of LBC and conventional cytology are similar [17].
- Computer-assisted screening using LBC is currently being evaluated, but insufficient evidence is available for guidelines.

#### *HPV detection.*

- Several applications for HPV DNA detection have been proposed: (i) primary screening for oncogenic HPV types alone or in combination with cytology; (ii) triage of women with equivocal cytological results; (iii) follow-up of women treated for CIN to predict success or failure of treatment.
- HPV infections are very common and usually clear spontaneously, especially in younger women. Detection of HPV DNA thus carries a risk of unnecessary colposcopies, psychological distress and possibly of overdiagnosis. The need to carry out cervical cancer screening in an organised programme, rather than in an opportunistic setting, therefore applies particularly to screening on the basis of HPV testing.
- Evidence from randomised studies and meta-analyses shows that triage of women with equivocal cytological lesions by HPV testing with the Hybrid-Capture 2 assay is more sensitive and equally specific in finding high-grade CIN compared with repeat cytology. There is also evidence indicating that HPV DNA detection predicts treatment failure more quickly than cytological follow-up.
- The high sensitivity of current HPV DNA detection methods yields very high negative predictive values even for adenocarcinoma precursors that often escape cytological detection. Recent cohort studies indicate a prolonged duration (up to 10 years) of the negative predictive value of HPV testing. Nevertheless, further longitudinal research is necessary, preferably in an organised setting guaranteeing optimal follow-up, using randomised designs and targeting relevant outcomes.
- Current randomised controlled trials may demonstrate lower cumulative incidence of CIN3 and invasive cervical cancer as joint or separate outcomes in HPV-negative compared with cytology-negative women. The results of these trials are needed before screening policies for general primary HPV screening can be recommended in Europe. Such policies would also have to ensure that possible increases in the detection and management of less severe lesions are kept to an appropriate minimum. Introduction of primary HPV screening will require appropriate triage and counselling of HPV-positive women.
- As for any screening policy, future recommendations on primary HPV screening should not be made without specifying the age group to be targeted, the screening interval and the essential elements of quality assurance required for programme implementation.

- Piloting with validated HPV DNA testing can be recommended if carried out in an organised screening programme with careful monitoring of the quality and systematic evaluation of the aimed outcomes, adverse effects and costs. Women <30 years of age should not be screened for HPV, due to the high rate of viral clearance. Rollout towards national implementation can be considered only after the pilot project has demonstrated successful results with respect to effectiveness (relative sensitivity, positive predictive value of the screening test, triage and diagnostic assessment) and cost-effectiveness and after key organisational problems have been adequately resolved.
- HPV screening in an opportunistic setting is not recommended because adherence to appropriate intervals and requisite quality control cannot be adequately assured under such conditions.

#### **guidelines for cytology laboratories**

- Professional and technical guidelines must be followed to assure the collection and preparation of an adequate cervical cell sample [18].
- The quality of a cervical cytology laboratory depends on adequate handling and staining of the samples, screening and interpretation of the slides and reporting of the results. An appropriate balance must be achieved between the best patient care possible, laboratory quality assurance and cost-effectiveness [19].
- Uniform grading of cellular abnormalities is an essential condition for registration and comparisons over time and between different settings. Laboratories should apply only a nationally agreed terminology for cytology that is translatable into the Bethesda Reporting System [20]. The CIN terminology should be reserved for describing histology.

#### **guidelines for histopathology**

- Histopathology provides the final diagnosis on the basis of which treatment is planned and serves as the gold standard for quality control of cytology and colposcopy. It is also the source of the diagnostic data stored at the cancer registry and used for evaluation of screening programmes. It is therefore important that histopathology standards are monitored and are on the basis of CIN or other internationally agreed-upon terminology.
- Histopathologists should be aware of, and familiar with, the nature of cytological changes that may be relevant to their reports.
- The accuracy of the histopathological diagnosis of tissue specimens depends on adequate samples, obtained by colposcopically directed punch biopsies (with endocervical curettage if necessary) or excision of the transformation zone or conisation. An accurate histological diagnosis further depends on appropriate macroscopic description, technical processing, microscopic interpretation and quality management correlating cytological and histological diagnosis.

### guidelines for management of screen-positive women

- A woman with a high-grade cytological lesion, a repeated low-grade lesion or an equivocal cytology result and a positive HPV test should be referred for colposcopy. The role of colposcopy is to identify the location of the abnormal cells, to target taking of biopsies and to decide whether any treatment is required. Colposcopy should only be carried out by adequately trained health professionals [21, 22].
- Guidelines are provided for the management of ASC-US and high-grade squamous intraepithelial lesions. Guidelines for low-grade squamous intraepithelial lesions (LSIL) are difficult to delineate because current evidence does not indicate that any method of management is optimal. Repeat cytology or colposcopy are acceptable options, but HPV testing as an initial management option is not sufficiently selective for all women with LSIL. However, HPV testing in older women with LSIL can be considered [21].
- Quality assurance and collection of data on patient management are important elements of the management and follow-up of women referred with an abnormal cervical smear [23].
- Colposcopy is sometimes proposed as an alternative screening method, but its specificity (and probably also its sensitivity) in primary screening is too low for this purpose.

### complementary strategies of cervical cancer prevention

- Efforts to establish or improve cervical cancer screening should be planned and implemented in the framework of a comprehensive cancer control programme taking into account overall health care needs and priorities as well as feasible and cost-effective complementary preventive strategies, such as evidence-based primary prevention interventions [14, 24–26].
- As a matter of editorial policy, the second edition of the European Guidelines for Quality Assurance in Cervical Cancer Screening provides recommendations on prevention of cervical cancer through early detection programmes for cervical lesions. An appendix on prophylactic HPV vaccination has been added to the second guideline edition in order to summarise the evidence available up to July 2007 but not to formulate European recommendations in this area [27]. There are two prophylactic HPV vaccines containing HPV16 and HPV18 licensed in the EU. These HPV types are causally linked with ~70% of cervical cancers in Europe [28, 29]. Phase 2 and 3 trials have demonstrated strong immunogenicity and good safety profiles over the duration of the studies. Moreover, among girls and young women, aged 15–26 years not infected with those types at the time the vaccine was administered, excellent results were observed regarding protection against cervical cancer precursors and other diseases associated with the vaccine types, over the time span that data are available [27].
- European guidelines on HPV testing and vaccination are currently being developed in the framework of the ECCG-

ECN project. In the meanwhile, it is important to note the uncertainty about the long-term efficacy of currently available vaccines as well as uncertainty about the future impact of oncogenic HPV types which are not targeted by currently available vaccines. Given current knowledge, population-based screening will continue to be necessary in coming decades in the cohorts of women already exposed to oncogenic HPV types. Screening fulfilling the quality assurance principles recommended in the current European cervical screening guidelines may also be necessary to adequately control cervical cancer in women vaccinated before exposure to HPV, although screening protocols and procedures will presumably require modification.

- As with any public health intervention, quality assurance of complementary strategies of cervical cancer prevention should also take into account organisational aspects essential to programme effectiveness and particularly cost-effectiveness. The potential importance of a population-based approach and programme monitoring and coordination to achieving and maintaining high coverage should not be overlooked. Resource limitations and the need to balance competing health priorities require adequate consideration of the marginal cost and benefit of combining cervical cancer screening and vaccination strategies. Consideration should also be given to the high costs of current HPV vaccines, which constitute a major barrier for several member states of the EU. The book containing the full guidelines and other EU documents on cancer screening can be downloaded free from the internet: [http://ec.europa.eu/health/ph\\_determinants/genetics/keydo\\_genetics\\_en.htm](http://ec.europa.eu/health/ph_determinants/genetics/keydo_genetics_en.htm)

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## appendix 1

### key performance indicators

A list of key performance indicators is provided for monitoring the screening process and for identifying and reacting to potential problems at an early time [30]. The indicators address aspects of the screening process which influence the impact as well as the human and financial costs of screening. The present parameters assume that cytology is used as the primary screening test, which is currently recommended. However, most of the present parameters may also be applied, with only small changes, if a different screening method (e.g. HPV DNA testing) is used. Depending on the respective screening test and the screening policy, the values of some parameters (e.g. detection rates of CIN, positive predictive values or specificity) will change. Before calculation of the recommended performance parameters, it is essential to verify key programme conditions which may influence the applicability and the further interpretation of respective parameters. As a minimum, the conditions indicated in Table 1 should be reported. For more information, see Annex 1 of Chapter 2 of the full guideline document [31].

Three groups of indicators can be distinguished:

- Screening intensity: the proportion of the target population actually screened within the recommended interval is the main determinant of the success of a screening programme. However, too frequent testing increases financial and human costs with only marginal gain in reduction of incidence and mortality. The duration of the recommended screening interval must therefore be taken into account in monitoring and evaluating screening intensity. Indicators include

**Appendix Table 1.** Screening intensity

<p>1. Programme extension</p> <ul style="list-style-type: none"> <li>• Programme extension should be calculated regionally and nationally.</li> <li>• If an entire region or country is actively served by a screening programme or programmes, then the programme extension in that region or country is 100%.</li> </ul>	$\frac{\text{N women in target population of catchment area actively served by programme}}{\text{N women in target population of entire respective region or country}}$
<p>2. Coverage of the target population by invitation</p> <ul style="list-style-type: none"> <li>• Length of period corresponds to interval between two negative smear tests recommended by screening programme policy.</li> <li>• Stratification by 5-year age groups is recommended.</li> <li>• Obtain data from Table B1 in annex to Chapter 2 in the full guideline [31]. Also calculate separately using eligible women as denominator.</li> <li>• For short-term monitoring, also calculate separately for women invited in the most recent calendar year in which screening was performed.</li> <li>• For interpretation, take into account whether all women are invited or only a subset (see Table A2 in annex to Chapter 2 in the guideline [31]).</li> </ul>	$\frac{\text{N women invited in defined period (3 or 5 years)}}{\text{N resident women in target population}}$
<p>3. Coverage of the target population by smear tests</p> <ul style="list-style-type: none"> <li>• Calculate separately for subgroups of women defined by: <ul style="list-style-type: none"> <li>1) invitational status: <ul style="list-style-type: none"> <li>a. personally invited</li> <li>b. not personally invited</li> <li>c. unknown</li> </ul> </li> <li>2) programme status, i.e., smear performed: <ul style="list-style-type: none"> <li>a. within organised programme</li> <li>b. outside organised programme</li> <li>c. unknown</li> </ul> </li> </ul> </li> <li>• Stratification by 5-year age groups is also recommended.</li> <li>• Obtain data from Table B2 in annex of Chapter 2 [31] (denominator and numerator).</li> <li>• Also calculate separately with eligible women as denominator</li> </ul>	$\frac{\text{N women screened at least once in defined interval (3 or 5 years)}}{\text{N resident women in target population}}$
<p>4. Compliance to invitation</p> <ul style="list-style-type: none"> <li>• Consider women invited in a given period and those among them screened.</li> <li>• A cut-off date of six months after the end of the respective period is recommended for determining whether a woman was screened in response to the invitation. If a different cut-off procedure is used, this should be specified.</li> <li>• Obtain data from Table B2 in annex of Chapter 2 in [31] (denominator and numerator).</li> </ul>	$\frac{\text{N invited women in a given period who were screened}}{\text{N invited women in that period}}$
<p>5. Smear consumption</p> <ul style="list-style-type: none"> <li>• Include only screening smears (no repeat tests, e.g., after unsatisfactory smears or for follow-up) and count one test per 'screening episode'; see glossary.</li> <li>• For denominator of a) see Table B2, in annex to Chapter 2 [31]</li> </ul>	<p>a) <math display="block">\frac{\text{N screening tests in 3 (5) years in the target population}}{\text{N women in the target population screened in the same period}}</math></p> <p>b) Distribution of screened women by number of screening smears in the same period</p>
<p>6. Incidence of invasive cancer in unscreened and underscreened women in a given interval (3.5 or 5.5 years)</p> <ul style="list-style-type: none"> <li>• Include only fully invasive cancer cases and person-years of the women not attending screening at the regular interval, i.e. women not screened in the previous 3.5 (5.5) years.</li> <li>• Link screening registry and cancer registry data and calculate incidence age-adjusted, and by age group, based on the entire female population in the age groups eligible to attend screening.</li> <li>• Analyse by cancer morphology (squamous vs. non-squamous).</li> <li>• Calculate separately (with appropriate denominators): <ul style="list-style-type: none"> <li>a. women never screened</li> <li>b. women previously screened, but interval to last screening test &gt;3.5 (5.5) years</li> <li>c. women never invited</li> <li>d. invited vs. not invited in respective round</li> </ul> </li> </ul>	$\frac{\text{N fully invasive cancers detected in women not screened in a given interval (3.5 or 5.5 years)}}{\text{N person-years of women not screened in the same interval (3.5 or 5.5 years)}}$



**Appendix Table 2.** Screening test performance

<p>7. Distribution of screened women by the results of cytology</p> <ul style="list-style-type: none"> <li>• Obtain data from Table B3 (numerator) and Table B2 (denominator) in annex to Chapter 2 [31].</li> <li>• Use classification in Table B2 in annex to Chapter 2 [31].</li> <li>• Calculate overall and separately for subgroups of women:               <ol style="list-style-type: none"> <li>a. for the regular screening interval and shorter time periods</li> <li>b. attending initial or subsequent screening</li> </ol> </li> </ul>	$\frac{\text{N screened women with cytological diagnosis}}{\text{N screened women}}$
<p>8. Referral rate for repeat cytology</p> <ul style="list-style-type: none"> <li>• Obtain data from Table B4 (numerator) and Table B2 (denominator) in annex to Chapter 2 [31].</li> <li>• Calculate separately:               <ol style="list-style-type: none"> <li>a. by cytology that resulted in recommendation to repeat</li> <li>b. for initial and subsequent screening</li> </ol> </li> </ul>	$\frac{\text{N screened women advised to repeat test at shorter than regular interval}}{\text{N screened women}}$
<p>9. Compliance with referral for repeat cytology</p> <ul style="list-style-type: none"> <li>• See footnote in Table B4 (numerator) and Table B4 (denominator) in annex to Chapter 2 [31].</li> <li>• Calculate separately:               <ol style="list-style-type: none"> <li>a. by cytology that resulted in recommendation to repeat</li> <li>b. for initial and subsequent screening</li> </ol> </li> </ul>	$\frac{\text{N women screened following recommendation for repeat cytology}}{\text{N women recommended for repeat cytology}}$
<p>10. Referral rate for colposcopy</p> <ul style="list-style-type: none"> <li>• Obtain data from Table B5 (numerator) and from Table B2 (denominator) in annex to Chapter 2 [31].</li> <li>• Calculate separately by:               <ol style="list-style-type: none"> <li>a. cytology that resulted in referral to colposcopy</li> <li>b. for initial and subsequent screening</li> </ol> </li> </ul>	$\frac{\text{N screened women referred for colposcopy}}{\text{N screened women}}$
<p>11. Positive predictive value of referral for colposcopy</p> <ul style="list-style-type: none"> <li>• Obtain data from Table B7 in annex to Chapter 2 [31].</li> <li>• If the number of women, for whom colposcopy was performed is not known, estimate using number of women referred for colposcopy.</li> <li>• Calculate overall and separately by:               <ol style="list-style-type: none"> <li>a. cytology (ASC-US+, LSIL+, HSIL+)</li> <li>b. histology (CIN1+, CIN2+, CIN3+, Invasive Ca)</li> <li>c. initial and subsequent screening</li> </ol> </li> </ul>	$\frac{\text{N screened women who had colposcopy with histologically confirmed CIN+}}{\text{N screened women who had colposcopy}}$
<p>12. Test specificity</p> <ul style="list-style-type: none"> <li>• Calculate overall, and separately by:               <ol style="list-style-type: none"> <li>a. cytology (&lt;ASC-US, &lt;LSIL, &lt;HSIL)</li> <li>b. histology (CIN1+, CIN2+, CIN3+, Invasive Ca)</li> <li>c. initial and subsequent screening</li> </ol> </li> <li>• Test specificity cannot be computed from routine screening and follow-up data, because the true denominator is unknown. Nevertheless, the formulas on the right should be used to approximate specificity.</li> <li>• Normal test results refer to 'negative for intraepithelial lesions' (i.e., results not leading to referral for follow-up or confirmation).</li> </ul>	$\frac{\text{N screened women not referred for colposcopy}}{\text{N screened women who had no histologically confirmed CIN+}}$
<p>13. Detection rate by histological diagnosis</p> <ul style="list-style-type: none"> <li>• Obtain data from Table B7 (numerator) and Table B2 (denominator) in annex to Chapter 2 [31].</li> <li>• Calculate separately:               <ol style="list-style-type: none"> <li>a. by histology (CIN1+, CIN2+, CIN3+, Invasive Ca)</li> <li>b. for the regular screening interval and shorter time periods</li> <li>c. for initial and subsequent screening</li> </ol> </li> </ul>	$\frac{\text{N screened women with histologically confirmed CIN+}}{\text{N screened women}}$

Appendix Table 2. (Continued)

<p>14. Cancer incidence after normal cytology</p> <ul style="list-style-type: none"> <li>• Normal cytology refers to cases recommended for rescreening at the regular interval.</li> <li>• Count only fully invasive cancers among the women who had a normal screening cytology in the previous 3.5 (5.5) years.</li> <li>• Analyse by:             <ol style="list-style-type: none"> <li>a. interval from index cytology</li> <li>b. cancer morphology (squamous vs. non-squamous)</li> </ol> </li> <li>• Cytology should be reviewed mixed with that of other women not developing cancer.</li> </ul>	<table border="1"> <tr> <td style="text-align: center;">N screened women with fully invasive cervical cancer detected within 3.5 (5.5) years of normal cytology</td> </tr> <tr> <td style="text-align: center;">N person-years of screened women for same period after normal cytology</td> </tr> </table>	N screened women with fully invasive cervical cancer detected within 3.5 (5.5) years of normal cytology	N person-years of screened women for same period after normal cytology
N screened women with fully invasive cervical cancer detected within 3.5 (5.5) years of normal cytology			
N person-years of screened women for same period after normal cytology			

programme extension, compliance with invitation, coverage and smear consumption (Appendix Table 1).

- Screening test performance: essential indicators include the referral rates for repeat cytology and for colposcopy, as well as the positive predictive value of referral for colposcopy, the specificity of the screening test and the rate of detection of histologically confirmed CIN (Appendix Table 2).
- Diagnostic assessment and treatment: indicators include compliance to referral for repeat cytology and for colposcopy; treatment of high-grade lesions is also an essential performance indicator. The proportion of women hysterectomised for CIN serves as an indicator of extreme over-treatment (Appendix Table 3).

Widespread application of the following uniform parameters to report programme performance should facilitate collaborative studies and comparison between countries and regions and should thereby help to develop an evidence base for setting future Pan-European quality standards.

#### definition of performance parameters in cervical cancer screening

The rationale and approach for calculation of the following parameters are provided in Sections 7.2–7.4 of Chapter 7 of the full guideline document [30]. Specific instructions are indicated in Section 7.5 of Chapter 7 and are reproduced below. Most of the key performance indicators can be directly computed from the tables presented in the annex of Chapter 2 in the full guideline document (Full pdf guideline version [6]: <http://bookshop.europa.eu/eubookshop/publicationDetails.action?pubuid=547021>) [31]. However,

a number of indicators are on the basis of the incidence of invasive cervical cancers in women with different screening history. These indicators provide a more direct evaluation of the impact of screening, but they need to be computed over longer periods of time and linkage of screening registry data with cancer registry data is required for some indicators; see also Section 5 in Chapter 2 in the full guideline document. For short-term monitoring purposes, the calculations in the annex to Chapter 2 in ref. 31 are on the basis of annually aggregated data. Additional aggregation over different periods of time is recommended, particularly over the full screening interval of a given screening programme (3 or 5 years), and is required for some of the performance parameters. Wherever possible, longer and shorter evaluation periods should also be considered.

For calculations for a given period of time, such as the recommended screening interval (3 or 5 years), the dates on which the period starts and ends and the procedure for determining the target population should be recorded. For calculations on the basis of the size of the target population, use the average over the given time period.

Note that parameters 6 (Incidence of invasive cancer in unscreened women), 14 (Cancer incidence after normal cytology) and 19 (Incidence of invasive cancer after abnormal cytology) require linkage with cancer registry data. The follow-up periods recommended for calculation of cervical cancer incidence are 6 months longer than the recommended screening interval of the respective programme (3.5 or 5.5 years). The purpose of adding one-half year to the screening interval is to include screen-detected cancer at the next screening episode. Calculations on the basis of longer follow-up periods are also recommended.

**Appendix Table 3.** Diagnostic assessment and treatment

<p>15. Compliance to referral for colposcopy</p> <ul style="list-style-type: none"> <li>● Obtain data from Table B6 (denominator) and Table B8 (numerator) in annex to Chapter 2 [31].</li> <li>● Calculate separately by:             <ol style="list-style-type: none"> <li>a. different intervals after referral (3 months/6 months)</li> <li>b. cytology that resulted in referral</li> </ol> </li> </ul>	$\frac{\text{N screened women actually undergoing colposcopy}}{\text{N screened women referred for colposcopy}}$
<p>16. Treatment of high-grade intraepithelial lesions</p> <ul style="list-style-type: none"> <li>● Obtain data from Table B9 in annex to Chapter 2 [31].</li> </ul>	$\frac{\text{N women with screen-detected CIN2 or CIN3 treated}}{\text{N women with screen-detected CIN2 or CIN3}}$
<p>17. Proportion (%) of women hysterectomised on screen-detected intraepithelial lesions</p> <ul style="list-style-type: none"> <li>● Obtain data from Table B9 in annex to Chapter 2 [31].</li> <li>● Calculate separately by histology (CIN1, CIN2, CIN3).</li> <li>● Appropriateness of individual cases should be evaluated by peer review.</li> </ul>	$\frac{\text{N screened women with histological CIN hysterectomised}}{\text{N screened women with histological CIN}}$
<p>18. Proportion (%) of women treated for CIN1</p> <ul style="list-style-type: none"> <li>● Obtain data from Table B9 in annex to Chapter 2 [31].</li> <li>● Appropriateness of individual cases should be evaluated by peer review.</li> </ul>	$\frac{\text{N women with screen-detected CIN1 treated}}{\text{N women with screen-detected CIN1}}$
<p>19. Incidence of invasive cancer after abnormal cytology</p> <ul style="list-style-type: none"> <li>● Include screened women:             <ol style="list-style-type: none"> <li>a. without colposcopy carried out, despite existing indication</li> <li>b. with colposcopy carried out, but no CIN detected</li> <li>c. with CIN detected, but not treated</li> <li>d. treated</li> <li>e. in diagnostic or post-treatment follow-up</li> </ol> </li> <li>● Calculate overall and separately for each of above subgroups.</li> <li>● Include only fully invasive cancers.</li> <li>● Exclude cases detected as a result of screening.</li> </ul>	$\frac{\text{N cases of invasive cancer in screened women after abnormal cytology}}{\text{N person-years of screened women after normal cytology}}$
<p>20. Proportion of women with cytology negative for SIL, 6 months after treatment</p> <ul style="list-style-type: none"> <li>● Obtain data from Table B10 in annex to Chapter 2 [31].</li> <li>● Include women treated for CIN2, CIN3, CGIN or AdenoCa in situ followed at least 6 months after treatment (denominator).</li> <li>● Include women negative for hr-HPV (numerator), if this test is used for follow-up.</li> </ul>	$\frac{\text{N screened and treated women with negative cytology after 6 months}}{\text{N screened and treated women followed-up for 6 months}}$