

# Cancer screening: policy recommendations on governance, organization and evaluation of cancer screening

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## Main messages

- 1 **National structures for governance of screening** are here identified as important requirements for evidence-based decision-making and for establishing adequate legal, financial and organizational frameworks for effective cancer screening programmes with integrated quality assurance. We recommend transparent, structured and publicly documented decision-making, informed political commitment and broad stakeholder involvement in order to build strong professional support for the aims and means of the screening programme. Governance structures recommended here are currently lacking in many European settings, which may contribute substantially to inequalities in cancer prevention outcomes observed both between and within countries.
- 2 **Organization** for the practical implementation and the continual gradual improvement of population-based cancer screening programmes further requires careful coordination of this multistep process with feedback and corrective modification at each step, plus revolution of the quality circle. Information systems that permit registration and monitoring of process and outcome are crucial for maintaining current levels of quality, and for guiding further improvement.
- 3 **Evaluations** of the benefit-harm balance and cost-effectiveness of screening are required periodically for existing programmes and prospectively for new screening programmes. The population targeted by screening have an ethically mandated right to clear information on benefits and harms for an informed choice about participation. Indicators for equity in participation and health outcomes need to be included in the routine quality assurance capabilities of population-based screening programmes.
- 4 **New screening programmes** require step-wise decision-making which includes the establishment of evidence of effectiveness, benefits that outweigh the harms and cost-effectiveness. Once evidence exists to support these criteria, implementation research in each country is needed to assess the feasibility of fulfilling the national requirements in practice. In light of currently available evidence, some prostate cancer screening policies may be cost-effective but questions remain on the optimal benefit-harm balance. Forthcoming results of European trials are expected to inform policy-making on lung cancer screening in Europe. New trials need to be financed to investigate optimal strategies for gastric cancer screening.

## Introduction

Screening refers to the use of relatively simple tests across an apparently healthy population in order to identify individuals who have risk factors or an unrecognized disease or defect. Box 4.1 outlines the terms used within this chapter when discussing aspects that impinge on screening. A screening test is not intended to be diagnostic, and persons with a positive or suspicious finding must be referred for a confirming diagnosis and necessary treatment (1). It is essential that screening identifies those who are more likely to be helped than harmed by further tests or treatment to reduce the risk of a disease or its complications (2). The WHO criteria for screening (1) date from 1968 and have since been refined to highlight the importance of evidence of an acceptable balance between benefit and harm, integrated monitoring and evaluation, equity, and informed choices based on available evidence (Box 4.2) (3). Based on the criteria by WHO and others (1,3,4), three conditions determine the relevance of a screening programme: there has to be evidence for the effectiveness of screening, that the benefits of screening outweigh the harms and that screening is cost-effective (4). These refined criteria are relevant for decision-making concerning screening programmes in the 21st century and form a backdrop for discussion of the collection of evidence before implementation and in routine monitoring and the decision-making processes concerning screening programmes in this chapter.

### **Box 4.1** Terms used in Chapter 4

#### **Audit**

Audit is the systematic examination of current practice against guidelines or a defined desired standard. Cancer screening audits examine the screening history of cancer patients and controls in order to identify and quantify failures of the screening process and the potential for improvement.

#### **Governance**

Governance in the health sector refers to a wide range of steering and rule-making functions carried out by governments and other decision-makers to achieve and develop the national health policy objectives.

#### **Opportunistic testing**

Opportunistic testing is initiated by individual members of the public or their health advisors. It may or may not be based on national guidelines on intervals, target population and screening tests.

#### **Population-based screening**

Population-based screening is conducted according to nationally implemented guidelines defining who should be invited, how frequently they should be screened and how any abnormalities detected should be followed up and treated. The screening programme identifies each individual to be personally invited from a population register. Adherence to national guidelines is monitored in a screening register. Population-based screening programmes generally require a high degree of organization in order to assure that the invitational activities are performed reliably and effectively and are adequately coordinated with the subsequent steps in the screening process.

**Risk-stratified screening**

In risk-stratified screening, the specific screening policy regarding screening ages, intervals, tests and follow-up algorithms is based on the risk profile of a group of individuals in the population. This may include no screening for those at lowest risk and an unfavourable expected benefit-harm ratio. Risk-stratified screening should not be confused with clinically initiated risk profiling, for example genetic testing of patients with breast cancer and their relatives for follow-up of BRCA positive status. Risk-stratified approaches have a theoretical potential to improve overall cost-effectiveness and benefit-harm ratios of population-based screening programmes.

**Stewardship**

Stewardship in health implies that the ministries in charge of health assume the ultimate responsibility for the management of the national resources to the health benefit of their entire population, by directing the establishment of as good and fair health system as possible and by promoting health aspects in all policies.

**Quality assurance**

Quality assurance encompasses activities intended to assure and improve quality at all levels of the screening process in order to maximize benefits and cost-effectiveness while minimizing harms. The concept includes the assessment or evaluation of quality, identification of problems or shortcomings in the delivery of care, the design of activities to overcome these deficiencies and follow-up monitoring to ensure effectiveness of corrective steps.

**Box 4.2 Synthesis of emerging screening criteria proposed since 1968**

- The screening programme should respond to a recognized need
- The objectives of screening should be defined at the outset
- There should be a defined target population
- There should be scientific evidence of screening programme effectiveness
- The programme should integrate education, testing, clinical services and programme management
- There should be quality assurance, with mechanisms to minimize the potential risks of screening
- The programme should ensure informed choice, confidentiality and respect for autonomy
- The programme should promote equity and access to screening for the entire target population
- Programme evaluation should be planned from the outset
- The overall benefits of screening should outweigh the harm

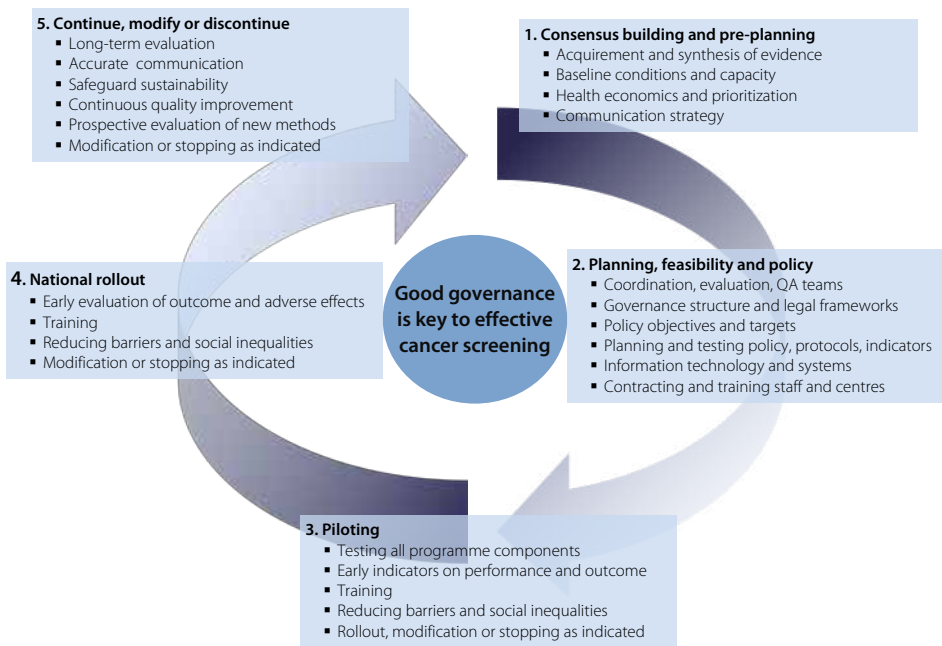
*Source: Andermann et al. 2008 (3).*

In agreement with the WHO criteria, the Council of the European Union has recommended cancer screening with a systematic population-based approach and quality assurance at all appropriate levels (5). Screening programmes are recommended for breast, cervical and colorectal cancers in

agreement with evidence-based guidelines. According to the final report on the implementation of the Council recommendation on cancer screening, most EU countries are planning, piloting or implementing population-based screening programmes for breast, cervical and colorectal cancers (6). However, there are deficiencies in utilization of some programmes (e.g. because of very low attendance rate), indicating ineffectiveness and likely social inequalities, and in the monitoring and evaluation capabilities required for comprehensive quality assurance.

The quality-assured implementation of cancer screening for the above three cancers involves careful planning and piloting, and scaling up from pilot to sustainable full-scale national roll-out based on social and service provider acceptance (7,8). Fig. 4.1 illustrates various steps and phases of the process. Formulation of a screening policy proposal requires evidence on the effects of screening, disease burden, quality-assured testing and treatment and primary prevention possibilities. Adequate performance must be verified from the beginning, allowing the detection and correction of potential undesirable trends. When problems are identified, the activity needs improvement, reorganization or even discontinuation (Fig. 4.1) (2,7,9). Modifications of existing programmes are also needed to reflect developments in screening, diagnostic and treatment methods, or because of developments in complementary primary prevention (e.g. HPV vaccination). Systematic quality assurance needs continuous well-integrated interplay between policy-making, evaluation and implementation.

**Fig. 4.1** Examples of tasks of organization, evaluation and governance in different phases of implementation and quality improvement of a cancer screening programme



The purpose of the chapter is to produce further advice and guidance for the development and implementation of cancer screening in the EU Member States in accordance with the EU Council recommendation and the current European quality assurance guidelines. Given their scale, population-based programmes need solid governance structures. Appropriate legal frameworks are required to run and monitor organized programmes and evaluate their outcomes; in addition, human and financial resources are needed for assuring the appropriate organization and quality control (5). The chapter presents 12 recommendations covering the spectrum of themes relevant for initiating and running population-based cancer screening programmes: governance of cancer screening, organizational requirements, the need for integrated evaluation and the approach and considerations for potential new cancer screening programmes. Solid screening governance is necessary throughout the process illustrated in Fig. 4.1. The organizational requirements deal with key issues, particularly for building capacity and capabilities in phases 2 through 4 outlined in Fig. 4.1. Integrated evaluation is necessary to inform actions at each step of the cycle. Before exploring these themes, the methodology and evidence base are described.

## Methods

Evidence on efficacy and effectiveness of cancer screening was drawn from recent systematic reviews, and European quality assurance guidelines with ratings of evidence were utilized. The information was supplemented and updated also with conventional literature searches using PubMed. The most relevant guidelines and systematic reviews used were: European guidelines for quality assurance on breast (10,11), cervix (8,12) and colorectal (13) cancer screening; WHO position paper on mammography screening (14); IARC Handbook on Breast Cancer Screening (15); Cochrane review on colorectal cancer screening by test methods (16,17), supplemented with a more recent meta-analysis on flexible sigmoidoscopy screening (18); and the European Code against Cancer's scientific justification on recommendations for cancer screening (19). Specific literature searches were used for potential new screening programmes for prostate, lung, gastric and ovarian cancers. Current evidence for prostate and gastric cancer screening was discussed at the respective consensus meetings with international experts.

Status reports on the implementation of cancer screening were available from surveys: IARC 2008 (20), EUNICE (21), EuroScreen (22), EU Joint Research Centre (23,24), IARC ongoing (6) and the CanCon cervical cancer screening working group (supplemental information available at the CanCon web site, <http://www.cancercontrol.eu/>). Earlier documents on the concepts and further recommendations on the implementation of cancer screening as a part of cancer control policies were also reviewed: EPAAC documents on planning for cancer control strategies with a section on cancer screening, the curriculum report ESSM (25) and materials EUROCOURSE (26) and the European Science Advisory Network for Health documents and reports (7,27).

Supplementary data on current implementation status of cancer screening programmes in individual Member States, including further organizational details, resources, governance and decision-making processes, legal frameworks, quality assurance and quality management systems, were obtained through the partners and experts participating in the working group meetings for the Work Package on Cancer Screening, held between May 2015 and February 2016. This data collection process obtained information not published in scientific papers. Information was requested on particular achievements as well as bottlenecks and barriers. In the working group meetings, suggestions of relevant topics regarding policy-making were collected.

Recommendations of the guide chapter were drafted by the authors of the chapter and delivered for comments and review within the working group. In connection with the Cervical Cancer Screening Working Group, a survey on governance and legal frameworks was performed for all 35 EU and European Fair Trade Association countries and devolved nations of the United Kingdom (supplemental information available at the CanCon web site; <http://www.cancercontrol.eu/>). Information on this survey in this document is based on answers from the 33 countries that had responded by September 2016.

In the formulation of the general recommendations on governance structures and functions, the publicly available protocols from the United Kingdom, Norway and Sweden, specifically developed to deal with issues concerning national screening programmes, were consulted (2,28,29).

## Governance of cancer screening

Governance and decision-making processes are at the core of well-functioning cancer screening (Fig. 4.1). Governance is here to be understood in the conceptual framework of stewardship as elaborated by WHO (30–32). This implies that the ministries in charge of health assume the ultimate responsibility for the management of the national resources to the health benefit of their entire population by directing the establishment of as good and fair a health system as possible and by promoting health aspects in all policies (33,34). Governance in the health sector refers, therefore, to a wide range of steering and rule-making functions carried out by governments and decision-makers to achieve and develop national health policy objectives. This involves policy development and implementation, detecting and correcting undesirable trends, influencing or regulating health care funders and providers, and establishing accountability mechanisms (e.g. by monitoring and evaluating health system performance). While the scope for governance is usually greatest at the national or legislative level, it also covers the steering role of regional and local authorities, and involvement of stakeholders at all levels is essential.

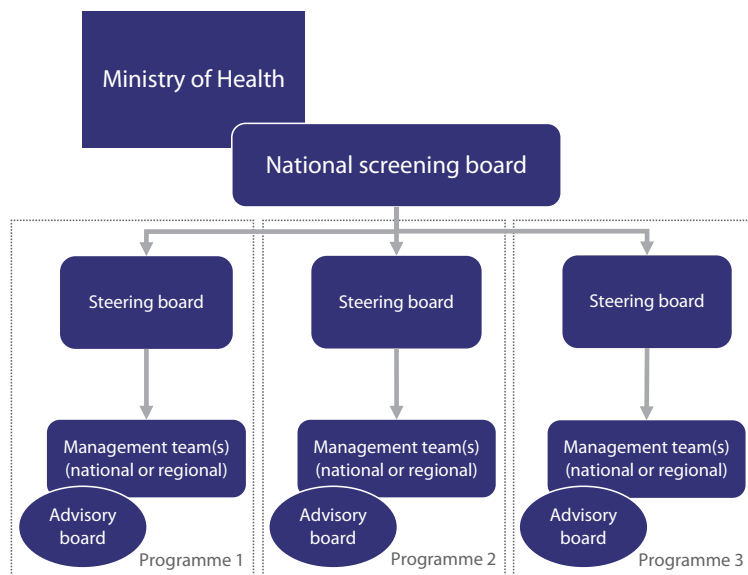
For screening in particular, the national policy-making and governance structure should ensure a thorough and professionally sound procedure for the assessment and introduction of new national screening programmes and for major modifications to, and if necessary the discontinuation of, those programmes. Appropriate legal provisions must be in place and the governance structure should ensure follow-up, quality assurance and evaluation of existing programmes. These requirements are common to all cancer screening programmes and, therefore, governance according to a common general template can be recommended. In what follows, we describe the policy-making and governance structures, legal framework and quality assurance mechanisms that are needed for well-functioning screening programmes.

## Governance structures, policy-making and stakeholder support

Many Member States have found it challenging to implement sustainable screening programmes that fulfil the potential for equitable cancer prevention as recommended by the Council of the European Union in 2003 (20,35–37). The lack of adequate governance and policy-making structures to ensure infrastructure and organizational support appears to be a key barrier (36,37). There are examples where screening programme implementation has failed to produce expected benefits, or has suffered from severe impediments, because necessary organizational, legal, logistic or financial frameworks were not adequately addressed in advance (37,38). In these cases, a more structured approach to governance and decision-making would be beneficial (39).

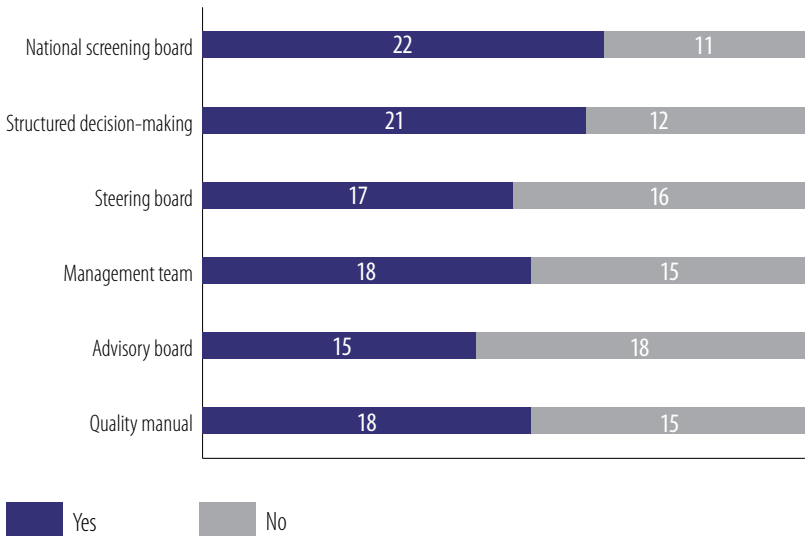
Fig. 4.2 shows what a governance structure can look like covering the key tasks: (i) policy-making, here embodied as a national screening board advising the ministry; (ii) supervision by cancer site-specific steering boards; (iii) management, here performed by one national or several regional management team(s); and (iv) feedback from screening providers and the scientific community through advisory boards or similar organs. All these functions and designated responsibilities should be covered in the governance structure, while allowing considerable adaptation according to the local setting and circumstances. Each of the elements will be looked at in detail below.

**Fig. 4.2** Organizational chart of an example national governance structure



In a small number of countries with successful population-based screening programmes, decision-making and governance structures, tasks and procedures have been formally defined (2,28,29,40). The policy-making and screening governance in the Netherlands provides a good example where the Health Council, which produces scientific advice on health policy, both unsolicited and solicited by the ministry in charge of health, includes a permanent Committee on Population Screening (corresponding to a national screening board in Fig. 4.2, below) (40). The resulting detailed advice includes provisions for the requirements for successful implementation (41). The Centre of Population Screening of the Dutch National Institute for Public Health and the Environment carries out feasibility studies and finances, directs and coordinates implemented programmes. Where an effective monitoring system is in place, the process, costs and effects of new policies, introduced on a small scale under controlled circumstances, can be easily measured and tailored if necessary before general roll-out. Well-developed policy-making and governance structures should also promote the allocation of necessary resources for RCTs and for piloting programmes or modifications as randomized health service studies (42–44). An interim analysis of the results of a survey conducted as part of the activities of CanCon suggests that many European countries lack several components of the governance structure of cervical cancer screening (Fig. 4.3).

**Fig. 4.3 Governance of cervical cancer screening in Europe**



**Note:** The figure summarizes the number of countries reporting the presence of each governance structure component (see the text for definitions of each component addressed).

The EU Council recommendations and the EU guidelines set a common framework for quality-assured screening. Each country has to assess how screening according to these principles can feasibly be organized within their health system and should identify and remedy gaps in the available resources and infrastructure. In countries where domestic experience of effective, well-organized population-based cancer screening is lacking, international collaboration with expert units experienced in coordinating and evaluating screening programmes can be useful or necessary in the planning and piloting phases (25,45). It is not necessary for each Member State to perform all generic health technology assessments independently; collaboration could save significant resources and avoid duplication, for example on choice of test technology. European-level data repositories and the production of standardized quality indicators would also be desirable in that it would promote comparability of programmes, compliance with guidelines and quality of screening across the EU.

### The importance of political commitment

The quality of political decision-making is critical for any public health activity. In the case of cancer screening, this includes a long-term commitment to follow guidelines and to assure quality at all stages of the screening chain (7). Appropriate synthesis of evidence and assessment of baseline conditions such as disease burden and existing and potential treatment capacity are of utmost importance from the outset. Commitment to invest implies expected returns in terms of deaths prevented, quality-adjusted life-years (QALYs) gained and/or downstream treatment costs saved. Political decision-making without commitment to assure quality of the screening process may be detrimental to trust in cancer screening, both in the target population and among professionals, and should be strongly discouraged. A regional or national parliament agreement may be needed in order to assure the long-term commitment.



## **A national screening board to advise decision-makers on national screening programmes**

A designated national screening board, or other such competent entity, should be responsible for advice on policies and decision-making regarding new population-based screening programmes or modifications to existing programmes (Fig. 4.2). The process should be structured and defined in a transparent procedure based on clear, evidence-based criteria to ensure that a proposed new or modified screening programme is able to reach an optimal balance between benefit, harm and costs (by measures capturing the relevant health impacts to a sufficient degree, such as cost per QALY gained). The board should ensure that the necessary organizational, logistic, legal and financial frameworks exist or can be developed. Defining institutional responsibilities, collaboration between the key institutes and consultation with relevant stakeholders allows benefit from existing expertise and broad support and commitment. The decision should be reviewed before each step in the implementation process: feasibility testing, piloting and full-scale roll-out of service screening (Fig. 4.1) (7). A multistep decision-making process is necessary because the performance and outcomes of the proposed screening programme may differ significantly from those demonstrated in controlled trials, as well as from other service settings, and the full impact of these differences may not be evident in advance (43).

## **Programme-specific steering boards: oversight and sustainability**

Once a decision to implement a screening programme has been politically ratified, a programme-specific steering board is required. The steering board oversees both the implementation phases and the sustainability and continuous incremental improvement through the quality assurance processes of the established programme. The steering board should shoulder the executive professional responsibility for the performance, quality assurance and evaluation of the screening programme, including the continuous assessment of the test methods and procedures, and the financial, ethical and legal frameworks. It officially sets and maintains the overall goals of the screening programme. It also ensures that the means and mechanisms are in place to monitor and achieve those goals. It is the forum for resolving political, legal, organizational, technical, cost and management issues that have not been resolved elsewhere. To fulfil its tasks, the steering board must have access to both political and high-level administrative decision-makers, and it must be representative of the key stakeholders, including programme management. The steering board may also decide to submit a proposal for a major modification or cessation of the screening programme under its jurisdiction to the national screening board. The steering board should convene regularly, several times a year.

## **Programme-specific management teams: execution and reporting**

Successful implementation and a sustainable screening programme with integrated quality assurance and the capacity for continuous quality improvement requires a competent management team running the programme on a day-to-day basis at the national or regional level, with a clear mandate from the steering board and the necessary resources to fulfil its responsibilities (see below). These responsibilities include coordination or supervision of all steps in the screening process from identification of the target population to surveillance after treatment of screen-detected cases. It further includes the development and dissemination of information material, collection and validation of monitoring data, regular compilation and linkage with other relevant registers for reporting of performance and outcome of screening, coordination of quality assurance activities, and the further development and continuous quality improvement of

the screening programme according to directions and frameworks given by the steering board. Periodic formal programme evaluation may be tasked to an independent unit in order to avoid self-assessment by the management team. Some responsibilities may feasibly be delegated to the regional and local levels along with the adequate mandates and resources. In federated and larger countries, regions may have their own management teams, but policy should be formulated at the national level. Programme evaluation should also have a national scope.

### **Advisory boards: linking management and providers**

Successful programme management depends on good communication with all screening service providers, and access to their expertise (25). A multidisciplinary advisory board or forum can fulfil these functions by providing representation for the professional groups and institutions that screening delivery depends upon, facilitating the flow of information of issues of current import between management and the screening service providers and advocacy groups, and sharing information with academic and professional societies and institutions. The advisory board to the Norwegian screening programme for cervical cancer, as an example, is a multidisciplinary board including representatives from professional bodies (pathology, clinical cytology, gynaecology, gyno-oncology, general medicine, medical laboratory technology, epidemiology, microbiology) in addition to the Cancer Society and the National Reference laboratory for HPV (46). The appointment of one advisory board member as responsible for equity issues in the screening programme is recommended. Based on the cooperation of the advisory board and the management team, it is advisable to produce a programme-specific quality manual that describes the procedures and protocols that fulfil the quality requirements in that particular programme (47). The local quality manual should be in accordance with the relevant European quality assurance guidelines. Only a handful of countries in Europe have screening programmes with all or most of the governance structure components described in this section. A survey of governance structures for cervical cancer screening in 33 countries showed that countries are often lacking one or more governance component (Fig. 4.3).

#### **Recommendation 4.1**

Successful evidence-based cancer screening needs a competent, multidisciplinary and transparent governance structure with political, financial and stakeholder support.

### **Legal framework for population-based cancer screening**

Population-based screening is a complex undertaking that needs careful coordination and monitoring of performance and outcome. In most cases, a legal framework needs to be developed that is designed to run the health services and to regulate the comprehensive information systems required to manage and to ensure the quality of population-based screening programmes. The legal framework should provide regulation of patient rights, consent requirements, institutional responsibilities, financing and tendering, personal data safety, electronic health records, tissue sampling and biobanking, population and cancer registration, and scientific research and development (12,48).

The legal framework and information systems for population-based screening must secure an adequate balance between fundamental rights of privacy and access to effective, safe, high-quality and cost-efficient health services. Confidentiality of personally identifiable information on health status must be protected while fulfilling the duty to demonstrate and optimize health benefits and minimize negative effects and costs of screening.

## Registration and linkage

Effective screening management necessitates a legal mandate to register centrally all screening, diagnostic and treatment activity with a personal identifier, including negative test results, and to cover both programme-initiated and opportunistic testing. The registration must be sufficiently detailed, of high quality and complete (8,11), which precludes active consent requirements for registration.

The crucial requirement for successful implementation of quality-assured population-based screening is the possibility for linkage of at least population (target group identification), cancer and cause of death (outcome information) with and screening registers (performance information) (12,49). This requires the building of population-based cancer registries where such registries do not yet exist (26). An audit of the screening and treatment histories of all cancer cases arising in the population covered by the screening programme, and comparison of these screening histories with those of population-based controls, provides a possibility of evaluating the effectiveness of the screening programme and yields crucial information on its strengths and weaknesses. Such audits allow rational decisions to be made on modifications to screening policy and protocols, enable repeated incremental improvements to effectiveness and the prioritization of quality assurance efforts. Linkage with other registers such as vaccination and hospital episode registers can also be useful or required for adequate management, monitoring and evaluation. As for registration, such linkages should not be based on active consent. Evaluation based only on consenting individuals are likely to be biased and misleading (50). However, appropriate data protection safeguards should be in place to ensure privacy.

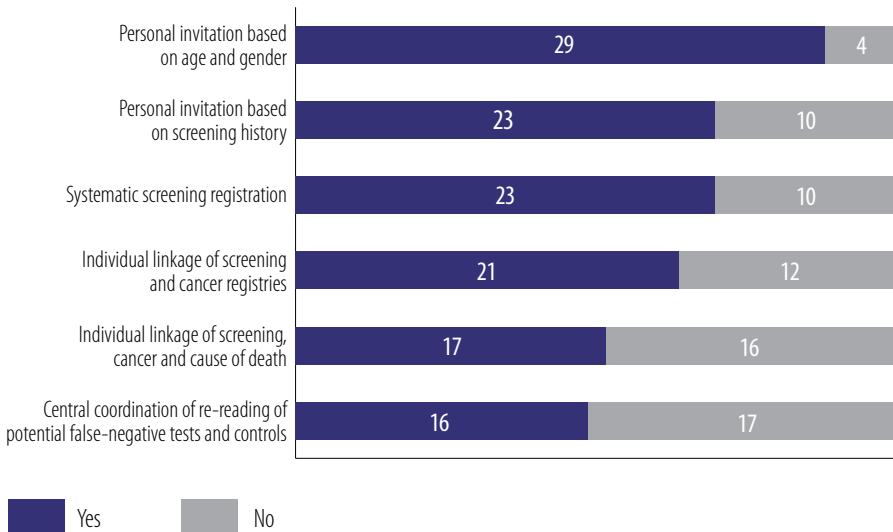
## Invitation and fail-safe monitoring

A population-based screening programme relies on the identification and personal invitation of all those in the defined target population. There must also be fail-safe monitoring to ensure adequate management of those screening positive. Consequently, those managing the screening programme must have access to a current population register with contact information and unique personal identifiers for correct linkage to screening databases and other relevant data sources. Depending on policy, invitations are sent based on a combination of age and screening or medical history. Management teams must, therefore, have the legal mandate to contact people directly based on their screening history with invitations and reminders, and to keep administrative records of this activity.

## Current status of the legal framework for screening in Europe

The lack of an adequate legal framework has been recognized as a major obstacle to effective screening programme implementation in several settings. Nevertheless, data collection and linkage must be in agreement with legal regulations. When legal barriers impede crucial data exchange operations, adaptations of local law may be required. According to results of the survey conducted in connection with the CanCon Cervical Cancer Screening Working Group, there are still significant barriers to many essential functions of population-based cancer screening in Europe (Fig. 4.4).

**Fig. 4.4** Legal frameworks for cervical cancer screening in 33 European countries



**Note:** The figure summarizes the number of countries reporting that their legal framework allows (prescribes in the case of systematic screening registration) each of six operational functions of the screening programme.

**Recommendation 4.2**

The legal code in a country should provide a specific framework for population-based cancer screening, enabling as a minimum the following basic functions: personal invitation, mandatory notification and central registration of complete screening and outcome data, individual linkage to cancer and cause of death registries for appropriate quality assurance, including audits.

**Resources for quality assurance**

Population-based programmes with appropriate quality assurance have not been fully implemented in all Member States since adoption of the recommendation on cancer screening by the Council of the European Union (5). In certain countries or regions, no such programmes exist (6,20,23,25). Integrated quality assurance has proved to be necessary to secure the potential benefits of population-based screening and limit the associated harms and costs. However, earmarked resources are needed for this activity, resources that are not always budgeted in the planning phases leading to implementation of screening. It is crucial to realize that adequate resourcing is a prerequisite for a screening programme, and that it may be better to limit the scope of the screening programme (such as number of lifetime tests) rather than neglect quality assurance if resources are scarce.

Wide variation in practices and effectiveness is observed throughout the EU, and inefficient opportunistic activities still dominate screening in several countries. A recent review on quality assurance standards and programmes in the cervical cancer screening programmes in Europe showed that organized efforts for quality assurance, including auditing, monitoring and evaluation, were carried out to a differing extent and were not standardized (Annex 4.1) (24). Most countries

found it hard to estimate the costs associated with launching and operating the organized programme. Similar systematic information on the routine audit practices of breast and colorectal screening programmes is not currently available. Nationwide, population-based registration of breast, cervical and colorectal cancer is not yet feasible in all EU Member States. In 2012, cancer registry coverage of the combined European populations was somewhat more than 60%, and systematic evaluation of cancer control and quality of care remained modest, except in a few dedicated cancer registries. Evaluation of mass screening programmes was supported more or less routinely by only 44% of cancer registries (51).

Considerable challenges, therefore, remain to bolster health equity. The lack of comprehensive quality assurance in settings relying on opportunistic testing, or even in population-based services, generally results in a less favourable benefit-harm balance compared with screening with integrated quality assurance (20,36).

Components included in comprehensive quality assurance are listed in Box 4.3. Based on the European recommendations (8,10–13), systematic quality assurance requires defined protocols for standard procedures and quality management throughout the diagnostic and patient management services within the programme. In addition, a substantial proportion of the resources in quality assurance are required for well-organized information systems that support the aims of screening registries and population-based cancer registries (10,52). This infrastructure is necessary to systematically audit the programme policies and services, as recommended in the guidelines (10,12). Adherence to these general principles and recommendations on systematic quality assurance is an ethical imperative to assure that the screening services delivered to the population are appropriate (49). Quality assurance also includes timely, prospective evaluations of modifications of existing programmes and for piloting new programmes (8).

**Box 4.3 Functions and budgetary items for the quality assurance allocation of 10–20% of total screening programme expenditure, in accordance with the European guidelines for quality assurance in cancer screening**

- Development and maintenance of well-organized information systems
- Clinical and diagnostic quality assurance and quality management
- Development of population-based cancer registration and other databases for adequate monitoring of the burden of disease and the outcomes of screening
- Development, implementation and enforcement of a quality manual based on European and national standards
- Reporting of performance and outcome indicators based on European and national standards
- Retrospective evaluation of the effectiveness of the programme and its components
- Prospective evaluation and introduction of new screening methods, policies and organizational models

Based on experience in implementing population-based cancer screening programmes in Europe, an estimated 10–20% of total screening programme expenditure should be dedicated to quality assurance (53) (Box 4.3). The lower end of the range, 10%, is more applicable to very large, less complex programmes with substantial economies of scale. In the initial years, this proportion

may be substantially higher because of the low volume of screening examinations compared with the situation after complete roll-out of a nationwide programme. If resources are scarce, a good approach may be to start with a limited target population, with the view to expand when quality is established and resources allow, rather than compromise on quality assurance. Resources spent on quality-assured screening may be largely compensated by the reduction in inefficient opportunistic overscreening and subsequent overtreatment.

A substantial proportion of the resources is required for the development and maintenance of well-organized information systems, reporting the results based on the European standards and related national quality manuals and indicators; for systematic audit programmes of cancer screening; for prospective evaluations required for modifications of existing programmes and piloting new programmes; and for building up cancer registry systems that enable monitoring and evaluation of cancer screening and its impacts on the population. Evaluation of clinical and diagnostic quality irrespective of cancer screening is also very important; there are synergies with this area of research and evaluation of cancer screening programmes. Health equity should be an integrated aspect of the regular quality assurance activities at both programme and patient management levels.

#### **Recommendation 4.3**

Successful implementation of effective cancer screening programmes requires significant resources for quality assurance that is 10-20% of the estimated total expenditure of a full-scale programme.

## **Organizational requirements**

Adequate organization and coordination of screening are important at all stages of programme development from preplanning and feasibility testing to implementation piloting, roll-out and continuous improvement.

### **Organization and infrastructure**

A programme should be thoroughly preplanned for the target ages, screening interval and tests used to identify preclinical disease. Appropriate synthesis of evidence on effectiveness, adverse effects, health-economic aspects, in combination with information on the burden of disease, is essential background information for these tasks. In this phase there should be data also for estimation of the invitational population size per year, planning for feasible schemes to cover the target population often enough (interval between invitations) and plans on how to reach a high uptake of the primary test and guarantee fully quality-assured management services ready at the time of starting.

Population-based cancer screening has infrastructure requirements that need to be verified or developed before starting to screen. First, the target population (age, region, gender) has to be individually identified to allow a call and recall system. For follow-up of screening outcomes, population-based registration of both cancer and screening is needed. Additionally, time and cause of death has to be individually linked with screening invitation information for outcome evaluation purposes. The development of a comprehensive quality assurance plan and manual needs to precede the start of screening activity. Planning includes verification of adequate

capacity through the whole screening chain from individual identification of persons to be invited to treatment and follow-up of screen-detected lesions.

A new programme and all its components, or new procedures in an existing programme, should be feasibility tested and piloted in a controlled fashion before national roll-out (Fig. 4.1). Initial training and development of competence can be focused on a developing national screening reference centre or area, where feasibility testing and piloting can be based, and where subsequent training needs for the roll-out phase can be satisfied. The invitational procedures with call and recall, acceptance of testing, communication with the screened person, delivery of further investigations (e.g. diagnostics and treatment), costs and other details not yet known at launch may provide challenges. For example, the uptake of screening may depend on the premises where samples are taken, opening hours, public traffic, personnel (women for breast or cervical cancer screening), among many other factors.

After the piloting phase, the programme can be rolled out after modifications and corrections deemed necessary based on pilot evaluation. The full implementation of the programme may take several years to achieve coverage and ensure optimal function through the screening chain. A gradual build up is usually needed to ensure practical resources, for example colonoscopy services for those who are positive for faecal occult blood test. Integrated comprehensive quality assurance allows for further incremental improvement in a continuous quality cycle.

A high level of organization with solid governance and coordinating functions also give better opportunities to stop ineffective or harmful activities in a controlled fashion. If existing screening does not fulfil quality requirements, the decision must be either to reorganize by following EU guidelines or ultimately to stop the ineffective programme. Continuation of an ineffective programme is unacceptable.

Modifications from ongoing opportunistic testing (either self-selection or general recommendations as opposed to invitation based) towards population-based programmes are encouraged.

#### **Recommendation 4.4**

Implementation of population-based screening should be a carefully managed multistep process through the phases of coordinated planning, piloting, roll-out and continuous improvement.

## **Coordination**

Following the political decision with associated budget allocations to start implementing a population-based cancer screening programme, and formulation of its goals and frameworks, the first step is to establish coordination and allocate institutional responsibilities. The institution housing the management unit should receive a clear mandate and resources to manage the entire process of programme implementation depicted in Fig. 4.1. The management unit also has to prepare the budget details through all phases, including the resources required for quality assurance, programme management and staff training. The work necessitates close collaboration with authorities and all stakeholders, preferably within a well-defined and mandated governance structure (Fig. 4.2). The mandate may also require changes in national legislation to ensure that it does not contradict effective implementation. Considerable autonomy to take organizational decisions must be allowed for coordination.

## Multidisciplinary management and evaluation teams

It is essential that a screening programme is managed by specialists with adequate knowledge and training in the subject areas of cancer screening. Specific training possibilities in the EU are available. Experience from other EU countries could be helpful; experts from other countries should be involved as consultants if local expertise is unsatisfactory.

Professional expertise should be utilized from the planning phase (development of standards and quality indicators) and throughout the implementation and for continuous evaluation. The professional and organizational management structure must be equipped with the competence and the mandate to control the quality of the entire screening process. Recent European guidelines and available European expertise should be consulted regarding questions on efficacy and effectiveness of new technologies. It may not be necessary to complete a national health technology assessment on questions related to new tests or diagnostic/therapeutic procedures if thorough international evaluations already exist. In that case national health technology assessment agencies could focus on questions related to local implementation and costs.

## Registration and information technology systems

The formation of a centralized data registration system for quality assurance is critical for the success of a programme. The format of the data follows standards developed by professionals and based on the European quality assurance guidelines. Although linkage to the screening procedure reimbursement system is desired, it is essential that the system is not limited to invitation and procedure reimbursement but also covers performance and outcome of the screening programme.

The requirements for continuous quality assurance should be considered early on and incorporated when designing the comprehensive information technology system that covers the entire screening process, including the quality of treatment of detected lesions. The established quality assurance system should also be used for procedures outside the screening programme.

In most EU countries, the screening data platform has not been embedded in a comprehensive clinical health (e-health) data system; however, this would be highly recommended.

### **Recommendation 4.5**

The mandate and resources for screening coordination and training, and for the electronic information systems necessary for quality assurance and incremental improvement, must be secured before starting the population-based screening service.

## Integrated evaluation

### Linkage and indicators for quality and effectiveness

The Council of the European Union recognized that quality screening includes analysis of the process and outcome of the screening, and that this analysis is facilitated if the screening database can be linked to cancer and mortality databases (5). The European guidelines for quality assurance in breast, cervical and colorectal screening (10,12,13) all emphasize data linkage between screening and cancer registries; implementation has, however, been limited throughout Europe (54). In this context, the FP7 European project EUROCOURSE formulated a set of recommendations for data interfaces between screening programmes and cancer registries as well as with other



information sources (26). A set of performance indicators has been generated separately for each screening programme for comparative monitoring at the European level, and the importance of linking the screening data not only with cancer registry data but also with other registries of interest (population, cause of death, diagnostic and treatment registries and, more recently, HPV vaccination and biomaterial registries) has been emphasized (26,48). While the linkage between cancer registries and mortality databases has been established in most European cancer registries, linking the data from national screening databases and cancer registries still poses a significant issue in some (Fig. 4.4).

The Council of the European Union recommendation mentions a need for monitoring specific performance indicators, without detailing the nature of these indicators. The specific guidelines discussed above describe these indicators thoroughly and set the desired levels. For example, in breast cancer screening the desired invitational coverage is 100%, the attendance rate over 75%, the rate of recalled less than 3% and first year sensitivity over 70%. The other approach to assessing performance is the rate of false positives (recalled women whose examinations end with a negative result) and the overdiagnosis rate (breast cancers that would not have come to clinical attention were it not for screening). The estimates from routine screening for the latter vary considerably (1–54%), although it is reduced to 1–10% when adjusted correctly for lead time (55).

#### **Recommendation 4.6**

To secure the benefits of screening, routine linkage between the registries containing relevant data for defining the population, performance and outcome is essential and can be considered an ethical requirement of screening.

### **Monitoring and equity**

Quality management must include both continuous monitoring of the quality indicators and programme improvement when indicated by monitoring or related evaluation projects. Quality assurance should be performed both at institutional and individual level, as appropriate. Linking indicators of quality with reimbursement of screening procedures provides a powerful tool for quality assurance and can initiate mechanisms to provide training and education to professionals failing to reach the minimum quality requirements and to exclude from participation in the screening programme any institutions and individual specialists repeatedly failing to reach agreed benchmarks of quality.

Monitoring and evaluation reports must be published regularly to inform the public and decision-makers and to permit timely modification of programme policy, if necessary (5). Because of the importance of acceptance of the programme by society, the results have to be communicated to the public on a regular basis. Collaboration between countries in monitoring and evaluating routine programmes will ensure better comparability of results and may encourage higher standards in all aspects of quality assurance. Countries with federated screening programmes need central collection of monitoring data for calculation and analysis of performance indicators and their publication and dissemination. An example of such a monitoring organization is provided by the Osservatorio Nazionale Screening (National Centre for Screening Monitoring) in Italy (56).

An important advantage of population-based screening programmes is that they can contribute to improve equity by comparison with other preventive health service modalities such as case finding or opportunistic testing (3). This is achieved by improved access to services through the

personalized invitations to all individuals in the target population and adoption of comprehensive quality assurance of services throughout the programme span (57,58). However, social inequalities in access to cancer screening can still be observed within population-based programmes, evident as lower participation in cancer screening programmes by lower socioeconomic status, within minority ethnic groups or in deprived areas (59–68). Participation in and performance and outcome of population-based screening varies remarkably also between countries (23,35–37,54,69), indicating large inequalities throughout Europe. According to a recent report on breast cancer screening, only about half of the EU Member States monitor access to screening by socioeconomic level, educational level and/or ethnicity/nationality (70). There is also some evidence on the association between cancer burden and human development index, a composite indicator of life expectancy, education and gross domestic product using aggregated data (71–73). Increases in the unemployment rates during the recent economic recession have also been associated with rises in cancer mortality (74).

Evaluation and regular monitoring of screening performance by demographic and socioeconomic groups, and in regions by their development index, is essential to verify whether screening reduces social inequalities in cancer and improves equity in health. Information on socioeconomic and ethnic or language groups, and on issues such as education level can be generated through linkages with appropriate population registries and census records. Evaluation research with experimental designs – also with qualitative components – is needed when social inequalities in cancer have been revealed (68). When attempting to correct social inequalities in cancer screening, it would be very useful to have partners from different countries and programmes with earlier experiences on the relevant interventions. Collaboration and investments in translational research are needed to develop research activities in the local, specific programme settings (e.g. in the case of poor attendance or poor adherence to quality assurance guidelines) on reasons and on how to optimize attendance and to develop balanced, appropriate information for the programme. The Council of the European Union's recommendation (5) already covers most aspects of monitoring content and aims. However, explicit address of social inequalities as an essential part and specific aim for monitoring is added here.

#### **Recommendation 4.7**

Whenever relevant, evaluation and regular monitoring of cancer screening should also detect social inequalities and trigger research and interventions on improved equity in health. Research collaboration has an added value to develop interventions and solutions in the local settings where social barriers and social inequalities in cancer have prevailed.

### **Health economy and benefit-harm balance**

According to the recommendation by the Council of the European Union from 2003 (5), it is an ethical, legal and social prerequisite that cancer screening should only be offered to fully informed people with no symptoms if the screening is proved to decrease disease-specific mortality, if the benefits and risks are well known and if the cost-effectiveness of screening is acceptable.

The balance of benefits and harms is a strongly debated topic, particularly in the field of population-based breast cancer screening. The usually considered benefits from breast cancer screening include avoiding deaths from breast cancer, achieving less invasive treatments and improving quality of life; harms include overdiagnosis, overtreatment, false-positive and false-

negative findings, anxiety, radiation exposure and pain. The recent IARC Working Group (75) stated that there is sufficient evidence of a reduction in breast cancer mortality through screening by mammography in women aged 50–74 years, to the extent that the benefits substantially outweigh the risk of radiation-induced cancer, and of the detection by screening of breast cancers that would never have come to clinical attention (overdiagnosis).

Multiple reviews have been published in this field recently; however, because of differing inclusion strategies and benefit and harm definitions, the benefit-harm ratios vary considerably. For example, for each prevented breast cancer death, one review estimates that 0.5 women are overdiagnosed per death prevented (22), another review that three are (76) and a third that as many as 10 are (77). In the last estimate, lead time was not taken into account (55), which can be done best by including observational time at least 10 years since the last screen or by modelling (75). The EUROSCREEN Working Group (a cooperative group that includes experts involved in planning and evaluating most of the population-based screening programmes in Europe) in its summary of screening outcomes estimated that for every 1000 women (screened biannually from age 50 to 69) seven to nine breast cancer deaths are prevented, four women are overdiagnosed and 200 have at least one false-positive recall (22). While the benefits are usually estimated on historical RCTs and observational studies, the harms are almost exclusively based on current screening practice and the results may differ for various technical, cultural and societal reasons and because of variation in screening performance and breast cancer risk.

Communication of benefits and harms should be central to population-based screening programmes, and those invited should be provided with the information needed to make an informed decision about participation. In a balance sheet for breast cancer screening, the absolute number of lives saved and the number of breast cancer cases overdiagnosed in a given scenario may be presented. No judgement is then made regarding the relative value of a prevented breast cancer death to a case overdiagnosed – this is left for individual judgement.

The current approach for the acceptability of an intervention demands limited adverse effects and substantial positive health outcomes (absolute or QALY gained; improvements to cognitive, motor and/or socio-emotional development; significant increase in management or treatment options) with the effects established with certainty, preferably in RCTs (see below). This should lead to a reasonable ratio between costs and benefits, with the assumptions that the implementation will not lead to substantial unintended effects and that other developments do not change this ratio in the short term (4). The incremental cost-effectiveness ratio indicates the additional cost necessary per QALY gained and can be used as an indicator of cost-effectiveness of new methods in comparisons with already existing ones.

#### **Recommendation 4.8**

Benefits and harms of screening need to be clearly communicated to the public as the appropriate balance may be judged differently by individuals; scientific consensus on the appropriate estimation method and estimate would be of great value.

#### **Recommendation 4.9**

The cost-effectiveness of a programme or a specific modification of it should be evaluated prior to deciding on full implementation; Member States should define a threshold value relevant for decisions on cancer screening, considering affordability and available resources.

## Evidence of effectiveness and harms

The evidence for effectiveness indicators comes from either experimental or observational studies, with experimental studies typically perceived to provide higher-quality evidence based on traditional evidence hierarchy. A recent review, using only data from RCTs on breast cancer screening, has estimated that European population-based programmes achieve a breast cancer mortality reduction of 20% (76). However, the relevance of including breast cancer screening trials run in the 1960s to 1980s should be questioned when assessing current services given the large-scale improvements since then in both mammographic equipment and treatment for breast cancer (75). More recent, high-quality observational studies are considered to provide the most robust data with which to evaluate the effectiveness of mammographic screening (75) and new evaluation trials (e.g. on novel methods) are needed. Mortality reduction estimated from observational studies yields somewhat different results, depending on their design, and these results should be interpreted with caution both concerning the type of design and the possible biases that could be introduced; incidence-based cohort mortality follow-up studies are considered most relevant (75). It should be noted that varying protocols (e.g. infrastructure, technology, personnel, target age, invitational protocol, registration, and availability of data) and actual attendance rate may reflect the level of effectiveness, and that available, high-quality evidence tends to come from higher income countries.

Effectiveness of Papanicolaou (Pap) smear screening for cervical cancer was demonstrated by cohort follow-up studies on cervical cancer incidence and mortality (78), and efficacy trials have become increasingly available for novel methods such as HPV testing (8,79,80).

For colorectal cancer screening, recent RCTs have demonstrated efficacy of sigmoidoscopy screening; corresponding trial-based evidence on current immunochemical faecal blood tests, which have improved clinical accuracy compared with guaiac-based faecal occult blood testing, is not available (13,17–19). Efficacy of screening with the guaiac-based faecal blood tests has been demonstrated from RCTs (16) and there are two mortality studies on routine screening programmes using this test system (81,82). In the first study, there was a 10% relative reduction in colorectal cancer mortality in a routine screening programme in Scotland for those invited for screening, rising to 27% for those who completed the test (81); the second study did not find any effect in a randomized health services study in Finland (82). In both studies, the follow-up times are still rather short. Information on the effectiveness of the colorectal cancer screening programmes started during the 2000s and so appropriately long follow-up time is not yet available.

### **Recommendation 4.10**

Indicators for quality and effectiveness based on most recent evidence-based reviews should be monitored for informed decision-making and acted upon regularly by updating the screening programme.

## Potential new cancer screening programmes

### Criteria for implementing cancer screening

The current criteria for new cancer screening programmes (for primary sites other than breast, cervix and colorectum) or for programmes utilizing completely new screening methods that

are not understood as modifications to the current method include synthesis of the evidence of effectiveness: benefits, harms and their balance. The overall benefits should outweigh the expected side-effects and the harm, and the potential programme should satisfy the requirements of cost-effectiveness, based on evaluations from appropriate RCTs (3–5). To gather the required evidence, the Council of the European Union has also recommended that such trials need to be actively run and has proposed also pooling of relevant trials from representative settings in order to help with evidence assessments. Once evidence exists to support these criteria, implementation research in each country is needed to assess the feasibility of fulfilling the national requirements in practice (Fig. 4.1).

So far, evidence on the above aspects has not been considered adequate in the EU to recommend screening for cancers other than breast, cervix and colorectum. Yet only a few such trials and/or pooling exercises have been carried out. The potential to gain further improvement in cancer control through new cancer screening programmes is vast. This section deals with current information from trials on potential new cancer screening programmes for four cancer sites (prostate, lung, stomach and ovaries). These are used as examples to highlight key policy-making aspects. There are also other primary sites potentially relevant for screening and prevention interventions for which no or few trials are available.

### Key criteria for a decision whether to implement

Based on criteria for screening of WHO and others (1,3,4), it can be concluded that there are three key criteria for deciding whether a screening programme should be adopted: (i) is there evidence for the effectiveness of screening; (ii) is there evidence that the benefits of screening outweigh the harms; and (iii) is screening cost-effective (4). These three steps will be described in more detail below. The remaining criteria are relevant for the subsequent process of implementation, monitoring, evaluation, affordability and sustainability of the programme. In addition to evidence criteria, other aspects affect policy-making, such as prioritization because of the burden of disease, feasibility, affordability and availability of resources to organize the programme adequately. These are important in the national decision-making context, but are not discussed further here.

#### **Step 1: effectiveness**

The first step is to determine whether screening is effective, that is, does it reduce mortality from the target disease. This can only be done by means of RCTs with disease-specific mortality as the primary end-point. Observational studies (case-control studies or cohort studies) should be interpreted with caution since they are prone to selection bias: because individuals participating in screening are almost invariably healthier than those who do not, they are likely to have better outcomes, even in the absence of screening. Studies comparing survival rates between screen-detected and clinically detected cases are hardly informative, since in addition to selection bias they are prone to two other forms of bias: lead-time bias and length bias. As a result, screening seems to prolong survival even if it does not extend life.

Because cancer is just one cause of death and because of the inherent time lag between a screening intervention and its effect on mortality, RCTs evaluating screening have to be large and follow-up has to be long. As a result, screening trials are relatively expensive. Still, it is important to realize that they are indispensable. No alternatives (e.g. by using proxy end-points and/or simulation) are acceptable as primary evidence on the effectiveness of a new screening programme (83,84).

### **Step 2: benefit-harm ratio**

The second step is to determine whether the benefits of screening outweigh the harms. A frequently used method to value the health effects of screening is by using utility weights. These weights correct the time spent in a certain disease state for the quality of life experienced in that state. The valued effects can be summed up as the number of QALYs gained. Possible benefits of a screening programme are a reduction in disease-specific mortality or all-cause mortality, a reduction of advanced disease and aggressive treatment, and QALYs gained. Possible harms of screening are pain and stress of the screen test and diagnosis, false-positive tests results, more life living with the knowledge of the disease, false reassurance, overdiagnosis, overtreatment and treatment-related adverse events (4,83,84).

### **Step 3: economic evaluation**

The third step is to determine whether the effects of screening justify costs. The basic economic problem states that wants are infinite, while resources are limited. This problem, scarcity, implies that choices on how to deploy resources have to – and will be – made. All choices involve a trade-off. If a government decides to use resources to implement a national colorectal cancer screening programme, it may not have sufficient funds to simultaneously implement HPV vaccination for adolescent girls.

In general, three types of economic evaluation are distinguished: cost-effectiveness, cost-utility and cost-benefit. For all types of evaluation, the costs of screening, diagnosis and treatment have to be determined. Screening is regarded as cost-effective if the costs per QALY gained are lower than a predefined cost versus effectiveness threshold. A threshold of €20 000 or €30 000 per QALY gained is often used in Europe. National values vary and there are countries, particularly within the middle-income settings, where national values have not been formally decided. The threshold in some countries (e.g. in North America) is higher than in Europe.

While RCTs are indispensable for evaluating screening, they have their limitations. First, RCTs are relatively expensive and time consuming, limiting the number of RCTs that have evaluated screening. Second, RCTs usually have a limited follow-up time. As a result, they cannot be used to determine lifetime health effects and costs, which is necessary to directly determine the cost-effectiveness of screening. Third, the effectiveness of screening might differ between settings. Sources for variation in the results include background risk, quality and costs of screening and management in a given health care system, use of services outside the screening programme and methods in the health-economical evaluation itself. Decision models provide a useful tool to extrapolate evidence from RCTs and address the question of which screening strategy is optimal given local conditions, life expectancy, costs, resource availability and population preferences.

No detailed criteria for assessing health-economical methods or for relevant thresholds when using a given methodology have been included in the above references (1,3,5). WHO-CHOICE has suggested classifying interventions as cost effective if they yield one healthy year of life for one to three times the gross domestic product per capita and very cost effective if below the gross domestic product per capita (85). However, these thresholds are arbitrary and do not address budgetary constraints that may force a choice between several “cost-effective” interventions. The resources available for health care vary greatly between EU Member States, as reflected by an almost seven-fold difference in national gross domestic product per capita in 2014 between

Member States when corrected for purchasing power (86).<sup>1</sup> Health care expenditure per capita varied from €400 to €5500 (87). The national choices for the threshold values for cost-effectiveness vary as a result of variation in the resources available for health care. There is no common threshold value proposed for the EU. The health care resources should be taken into account in the health-economical and inequity analyses and when preparing European-level recommendations.

## Screening for prostate cancer

The current evidence is that the European Randomized Study of Screening for Prostate Cancer has showed that screening using levels of prostate-specific antigen (PSA) results in a 21% prostate cancer mortality reduction in an intention-to-treat analysis (88–90). The trial efficacy point estimates varied between participating countries because of differences in length of follow-up, underlying test and referral rates and contamination for PSA in the control arm. No mortality difference was found after a median follow-up of 11 years in a trial in the United States, failure to do so likely attributable to heavy contamination of the control arm (91,92). Although there are particularly concerns on the harms of overdiagnosis and overtreatment resulting from screening (93,94), it has been shown, based on the European trial results, that the benefits still outweigh the harms (95). Based on assessment utilizing the European Study results on cause-specific mortality, the cost-effectiveness of a screening programme with three screens at age 55–59 years with a two-year interval is at US\$ 45 600 and with four screens at age 55–67 years with a four-year interval at US\$ 92 000 (96). Cost-effectiveness with a single screen at age 55 years was estimated at US\$ 31 500. These cost-effectiveness ratios apply to health care costs as incurred in the United States and may be lower in European settings. For the Netherlands, cost-effectiveness has been estimated at €19 000 per QALY (H. de Koning, personal communication). In future, further improvements are expected because of more use of active surveillance and improved discrimination between indolent and significant disease through use of new biomarkers and magnetic resonance imaging (97–99). Hence, in some wealthy settings with a considerably high threshold value, the cost-effectiveness criteria for some policy options may already be satisfied based on current knowledge. In less affluent countries with less available money for health care, affordability issues and the prioritization of several potentially cost-effective health care interventions certainly need more deliberation before decisions can be made.

## Screening for lung cancer

In the RCTs on lung cancer screening published in the United States, the study populations at baseline consisted of current tobacco smokers or ex-smokers. In a large trial on chest radiography, no effect on lung cancer mortality by chest radiography in comparison with non-screened controls was reported (100). In another large-scale trial on low-dose computed tomography compared with chest radiography screening, annual screening was associated with a 15–20% decrease in lung cancer mortality and about a 7% reduction in overall mortality (101,102). Possible associations of lung cancer screening with smoking behaviours after screening have not been assessed systematically (103). There are several trials ongoing or under follow-up in European countries (104,105). Some variation in the nodule management protocols and of the definition of the high-risk population expected to benefit from screening may translate into variable results on efficacy. Risk

<sup>1</sup> Variation by the gross domestic product per capita ranged in 2014 from US\$ 7800 (Bulgaria) to US\$ 56 100 (Denmark) and US\$ 111 700 USD (Luxembourg), with the average in the EU approximately US\$ 35 000 (87).

stratification is important in lung cancer screening because nodules detected in those without important risk factors tend to be of low malignant potential. A recently reported Italian trial did not provide further support on efficacy of lung cancer screening, but the statistical power was very limited (106). The largest European trial, the "Nederlands Leuven Longkanker Screenings Onderzoek" (NELSON), examined the impact of low-dose computed tomography screening in association with active intervention to quit tobacco smoking (107,108). Outcome results are not yet available. The harms of lung cancer screening include false-positive results, complications from invasive follow-up and overdiagnosis with associated overtreatment. Performance characteristics of screening tools, particularly specificity and false positives, are associated with the algorithms and protocols (109). In the currently available health-economical assessments, the cost per QALY gained in annual screening with low-dose computed tomography in the tobacco-related risk groups has been estimated to vary between about US\$ 13 000 and US\$ 81 000 (110–112). At present, the high referral rates seen in the United States do not seem feasible in Europe, and mortality results are, therefore, needed from the European trials with lower referral rates.

## Screening for gastric cancer

The screening strategies for gastric cancer are targeting different lesions and conditions: (i) screening for gastric cancer itself by endoscopy or fluoroscopy, (ii) screening for precancerous lesions by detecting the ratio between pepsinogen I and II or other biomarkers in the circulation, and (iii) screening for *Helicobacter pylori*, the major carcinogen for gastric cancer, with the aim to eradicate it in those testing positive (search-and-treat strategy) (113,114). The results of randomized trials, performed mainly in Asian countries with a very high background risk of gastric cancer, indicate that *H. pylori* eradication lowers gastric cancer incidence by 30–40% (78,115,116). Endoscopy screening has been suggested to be cost-effective only in high-risk areas of Asia (117,118). The accuracy of pepsinogen testing alone is restricted for precancerous lesion (atrophy) rather than for gastric cancer detection (119–121); furthermore the sensitivity for detecting either precancerous lesions or cancer is limited. Search-and treat in healthy asymptomatic adult populations has been suggested to be cost-effective by considering the reduction of gastric cancer-caused burden as well as other diseases related to this microorganism (122–124).

However, the potential long-term adverse effects have not been considered sufficiently. At the population level, a programme of population screening and treatment for *H. pylori* with antibiotics could plausibly increase the prevalence of antibiotic-resistant pathogens within the community (125). Furthermore, strategies for the age groups to be subjected for eradication are not well defined. Uncertainties remain about the generalizability of results on various strategies and about the benefit-harm balance of programmes applied in community settings. The IARC has therefore recommended exploring implementation of population-based *H. pylori* eradication strategies by the means of well-designed implementation studies, such as the GISTAR study in Europe (78,126). In European populations, the rationale for endoscopy and serology screening for gastric cancer and the associated risk-lesions require more research. Additional clinical trials should help to clarify whether and how to implement population-based *H. pylori* screening and treatment programmes. Support to these trials is key to develop European cancer control policies.



## Screening for ovarian cancer

The poor prognosis for ovarian cancer has motivated initiating screening research. Cell-surface glycoprotein CA125 has been reported to be elevated prior to clinical diagnosis of primary and recurrent ovarian cancer (127). A randomized trial of screening with CA125 in postmenopausal women of average risk demonstrated a survival benefit for those with ovarian cancer (128). Two large-scale trials have reported their results on mortality outcomes and adverse effects of CA125-based screening for ovarian cancer. Among women in the general United States population, simultaneous annual screening with CA125 and transvaginal ultrasound, compared with usual care, did not reduce ovarian cancer mortality (mortality relative risk, 1.18; 95% confidence interval (CI), 0.82–1.71) (129) but about 15% of women with surgical follow-up after a false-positive screening test did experience serious complications. In the United Kingdom Collaborative Trial of Ovarian Cancer Screening, the primary analysis of ovarian cancer mortality gave a cancer-specific mortality reduction of 15% (95% confidence interval, 3–30;  $P = 0.10$ ) over a 15-year follow-up for screening with annual multimodal screening with repeated serum CA125 interpreted with use of the Risk of an Ovarian Cancer algorithm; and a cancer-specific mortality reduction of 11% (95% confidence interval, 7–27;  $P = 0.21$ ) for screening with annual transvaginal ultrasound screening compared with no screening (130). Although the mortality reduction was not significant in the primary analysis, a significant mortality reduction was observed for the multimodal screening when prevalent cases were excluded. The authors concluded that there was also some encouraging evidence of a mortality reduction in the late years of the follow-up period, and further follow-up is still needed before firm conclusions can be reached. False-positive surgery was less frequent in the multimodal screening than in the transvaginal ultrasound screening (131) or using a fixed cut-off for CA125 (132).

### Recommendation 4.11

Quantitative estimates of the benefits, harms and cost-effectiveness of possible new cancer screening programmes are needed to decide on implementation. It is essential that the EU Member States finance randomized trials designed to produce the information necessary for policy-making, and investments are needed so that results become available in as early a phase as possible.

### Recommendation 4.12

Active European research collaboration and pooling of results from RCTs and related health-economical assessments are necessary in order to obtain evidence relevant for the different settings, with potential variations in the burden of disease, health priorities, effectiveness, and resources and affordability, found among the European countries.

## Summary and conclusions

Most EU countries are planning, piloting or implementing population-based screening programmes for breast, cervical and colorectal cancers. However, there are deficiencies and barriers in many of these programmes, as indicated in a recent implementation report (6), for example in access to screening and in systematic quality assurance throughout the screening chain. Challenges in screening implementation are related in early phases to issues in planning and gradual well-controlled introduction of currently recommended programmes in regions or settings where effective and cost-effective programmes do not yet exist; in later phases challenges relate to modifying and reorganizing currently running programmes with new tests, treatments, policies or working models (Fig. 4.1). Developing key strategic tools on evaluations needed for policy-making on possible new cancer screening programmes (other than for breast, cervical or colorectal cancer) is also essential.

Considerable deficiencies in the governance structures of population-based screening were identified during the development of this chapter (Fig. 4.3), which may severely impede the full implementation of effective population-based cancer screening programmes in Europe. Key functions of screening governance are to secure political and professional commitment to an agreed screening policy with common targets; adequate legal, financial and organizational frameworks and resources to coordinate, evaluate and continuously improve the programme; and a transparent and well-informed decision mechanism for starting, modifying or stopping population-based screening (Recommendations 1–3).

Coordination of a multifaceted screening programme with a number of stakeholders by a competent management team needs to be established immediately following the decision to implement. The management is responsible for the planning and organizing of feasibility studies, piloting, roll-out, training of staff, development of information technology systems capable of population-based invitation and monitoring, comprehensive quality assurance functions and manuals in collaboration with the clinical specialties (Recommendations 4.4 and 4.5). This work starts in the preplanning phase of programme implementation and continues through to the continuous quality improvement of the established programme (Fig. 4.2). Recognition of the human and financial resources needed for this activity is important at the point a decision is made to start a programme.

Routine monitoring and evaluation of the performance and outcomes of screening can be considered an ethical imperative of population-based screening, and allow its maintenance and gradual quality improvement (Recommendations 4.6 and 4.10). The ability to individually link screening and cancer records is required. In addition to continuous quality assurance, essential parts of population-based screening are periodic evaluation of the effectiveness, benefit-harm ratio and health economy of screening; prospective evaluation of new screening methods; and dissemination of the results (Recommendation 4.8). There is a continuing need to develop further research and interventions to ensure equal access to quality screening, irrespective of socioeconomic status, ethnic background or domicile (Recommendation 4.7).

There is untapped potential for cancer prevention through extending population-based screening to new cancer sites beyond breast, cervix and colorectum. However, solid evidence on the effectiveness of new programmes from randomized trials is needed. These trials are necessarily large, time-consuming and, therefore, relatively costly; hence financing mechanisms through pan-European cooperation are recommended (Recommendations 4.11 and 4.12). Such

cooperation is particularly relevant since cost-effectiveness can vary between disparate regions of Europe and cannot always be directly transferred across different economic, epidemiological and organizational settings. At present, evidence on the effectiveness of prostate cancer screening is available; evidence on lung cancer screening is expected in the near future, but acquisition of evidence is still in its infancy for other cancer sites. All new potential cancer screening programmes require investment in research on optimal strategies for acceptable benefit-harm ratios and cost-effectiveness in different settings (Recommendation 4.9).

Cost-effective screening programmes need good governance, monitoring with standard key indicators throughout the screening chain and evaluation of outcome. Establishing sustainable models for funding is still in focus in many Member States. The wide variation in resources for health care between Member States should be taken into account when planning for Europe-wide recommendations and research strategies. Cancer control plans provide an essential mechanism where these issues can be elaborated and integrated into the planning and development of the health service.

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## Annex 4.1

A review on quality assurance standards and programmes in cervical cancer screening programmes in Europe provided data on case audit and its use in 10 out of 19 EU countries or regions (Table 4A.1).

**Table 4A.1** Cervical cancer case audits occurred in cervical cancer screening in 10 out of 19 EU survey respondent countries or regions

| Country         | Audits | Results used programmatically | Notes   |
|-----------------|--------|-------------------------------|---|
| Denmark         | Yes    | Not specified                 | National numbers will be published for the first time in 2014, with data from the year 2013   |
| England         | Yes    | Yes                           | Audits are completed annually; the results are used programmatically with the aim being to monitor and improve the programme locally  |
| Finland         | Yes    | No                            | Audits have been completed through research projects but not regularly scheduled within the programme; results have been used for laboratory quality assurance and policy discussions                           |
| Hungary         | Yes    | Not specified                 | Audits are completed and published by the National Audit Office   |
| Ireland         | Yes    | No                            | Audits are completed through ongoing incident case review with the aim of determining why the cancer developed and to inform any necessary improvements to the screening programme; results are not made public |
| The Netherlands | Yes    | No                            | Audits completely annually, results have yet to be used programmatically and are not available to the public  |
| Scotland        | Yes    | Not specified                 | Audits have been completed at the regional level and a national pilot has been underway since 2011; results are collated annually, used locally and made public in regional annual reports                      |
| Slovenia        | Yes    | Yes                           | Audits are completed annually and results presented in programme training days and will be published in the next programme report   |
| Sweden          | Yes    | Yes                           | Audits have been completed through research projects with the intention of making them annual; results are used programmatically through the regional cancer centres and professional organizations             |
| Wales           | Yes    | Not specified                 | Audits are completed ongoing, with results disseminated in local meetings and through direct communication; results have been used for educational and service improvement                                      |

Source: Elfström KM et al. Cervical cancer screening in Europe: quality assurance and organisation of programmes. *European Journal of Cancer*, 2015;51(8):950–968.

