

Pursuant to the Article 16, paragraph 2 of the Law on Health Care ("Official Gazette of RS", No. 107/05, 72/09 – Law, 88/10, 99.10, 57/11, 119/12 and 45/13 – Law) and Article 42, paragraph 1 of the Law on Government ("Official Gazette of RS", No. 55/05, 71/05 – correction, 101/07, 65/08, 16/11, 68/12 - US and 72/12),

The Government issues

REGULATION
ON THE NATIONAL PROGRAM FOR EARLY DETECTION OF COLORECTAL
CANCER

Article 1

This Regulation determines the National program for early detection of colorectal cancer and implementation of health care which includes activities to improve health, reduce mortality from cervical cancer and improve the life quality of people.

Article 2

Activities to promote and preserve health are conducted by the National Program referred to in Article 1 of this Regulation which contains defined goals, activities and expected results.

The national program referred to in Article 1 of this Regulation is attached hereto as its integral part.

Article 3

On the date of entry into force of this Regulation, the Regulation on the national program for prevention of colorectal cancer ("Official Gazette of RS", No. 15/09) ceases to be valid.

Article 4

This Regulation shall enter into force on the eighth day of its publication in the "Official Gazette of the Republic of Serbia".

05 No.: 110-6916/2013
In Belgrade, 16 August 2013

THE GOVERNMENT

PRIME MINISTER

Ivica Dačić

THE NATIONAL PROGRAM FOR EARLY DETECTION OF COLORECTAL CANCER

1. INTRODUCTION

In developed countries, colorectal cancer is diagnosed in 1.2 million people during their lives, or in 9.8% of all patients with malignant tumors. With approximately half a million new cases, 250,000 deceased and middle five-year survival of 54%, this disease is the second leading cause of cancer mortality in Europe.

Given the importance of the problem and the fact that in the Republic of Serbia malignant tumors of the colon are the second most frequent localization of tumors in both sexes diagnosed in around 4200 persons and 2600 die of it, the Ministry of Health, with the help of expert working groups, taking into account the recommendations of the World Health Organization (WHO), developed a program of organized screening for colorectal cancer in our country. This program was adopted by the Government, and was published in the "Official Gazette of RS", No. 20/09 as the National program for the prevention of colorectal cancer. It represented the continuity of the consensus conference "Diagnosis and treatment of colorectal cancer," the former Society of Coloproctology of Yugoslavia, held in Belgrade, in December 2003, which paved the way towards a premeditated strategy of detecting colorectal cancer in people without symptoms, the registration of all persons with increased risk and secondary prevention in these groups of patients. The program was in line with the Strategy of Health and declaration regulations: Europe against colorectal cancer (Europe against Colorectal Cancer. Declaration of Brussels. 2007) and the Resolution on the prevention and control of cancer (VHA 58.22) "Prevention and control of cancer", adopted by the the World Health Organization at the meeting in Geneva in 2005.

Improvement of the National program for prevention of colorectal cancer was done in 2012 and 2013 with the support of the EU project "Support to the implementation of the National program for the fight against cancer in Serbia", the expert team of associates and working groups at the Ministry of Health.

The National program for early detection of colorectal cancer is based on existing programs, and is in accordance with the 'European guidelines for the assurance of screening quality for colorectal carcinoma' (European guidelines) from 2010, which is used in most European countries.

2. SITUATION OVERVIEW

2.1 Epidemiological situation of colorectal cancer

Of all cancers 15% is colorectal cancer. By frequency, colorectal cancer is the third (10%) most common cancer in men and the second (9.4%) leading malignant tumor in women. Approximately 60% of cases of colorectal cancer are diagnosed in the developed regions of the world. In the world, colorectal cancer takes more than 600,000 people each year, making it the fourth (8%) leading cause of death of cancer.

With standardized incidence rate (27.0 per 100,000) and mortality (16.6 per 100,000) of malignant tumors of the colon, the Republic of Serbia has for many years been in a group of European countries with medium to high rates of morbidity and high mortality rates of these cancer localizations.

2.2. Colorectal cancer prevention

2.2.1. Risk factors

Improper nutrition (food rich with animal fat and protein, and scarce with fiber), obesity, smoking, positive family history, presence of intestinal polyps (risk increases after fifty years of age) and lack of physical activity are risk factors for developing colorectal cancer.

The risk of developing colorectal cancer increases with age and increases significantly after 40 years of age. More than 90% of all cancers are detected in persons older than 50 years. All persons older than 50 years bear 4.8% risk to by the age of 74 have colorectal cancer, or 2.3% of the risk that they will die from colorectal cancer. Symptoms that indicate colorectal cancer are concealed (occult) or visible (overt) bleeding, change in bowel patterns, abdominal pain and anemia. One quarter (25%) of patients has a positive family history of colorectal cancer, of whom more than half with the first order relatives.

2.2.2. Forms of colorectal cancer prevention

Prevention of colorectal cancer is aimed at reducing the number of patients, improving the quality of life of patients and to reduce the costs of treatment.

Primary prevention includes measures and procedures implemented before the onset of cancer with the aim of its prevention. Eliminating or reducing the extent of human exposure to risk factors for colorectal cancer (inadequate nutrition, overweight, low physical activity, smoking, excessive alcohol consumption, etc.) will contribute to reducing the incidence of this malignancy.

Secondary prevention involves detecting the disease at an early stage, which affects the success of the treatment. Detecting the disease in the precancerous stage – stage of benign polyps or stage of localized disease provides full healing in more than 85% (76-90%) of patients. Early detection of colorectal cancer (hereinafter referred to as screening) is an important component of secondary prevention.

2.2.3. The implementation of the National program for early detection of colorectal cancer

Screening represents detection of unrecognized disease, using the screening test in ostensibly healthy population with no signs of the disease. Screening is aimed to reduce the incidence and mortality of the disease the screening is organized for. Screening program can be opportunistic and organized.

Opportunistic screening represents the unsystematic application of screening tests as part of regular inspection. This includes people who themselves ask for examination or refer to a medical doctor for other reasons.

Organized screening is organized, mass calling the target population for screening mammograms and interpretation of images, accompanied by quality control and reporting.

Screening allows not only the detection of colorectal cancer at an early stage, but also the precancerous lesions (polyps), whose removing prevents the development of malignant changes. In countries, mostly developed, where the organized screening programs are successfully applied for several decades, there has been a dramatic decline in mortality from colorectal cancer.

The screening test is applied in the process of screening for early detection of disease. It should be highly sensitive, specific, easily applicable, simple, painless and relatively inexpensive. The screening test for organized screening of colorectal cancer is usually the test for the presence of occult (invisible) faecal blood (hereinafter referred to as the FOB test).

The target population in screening for colorectal cancer may be different depending on many factors: epidemiological, demographic, human, organizational and financial. European guides recommend that the target population should cover men and women between 50 and 74 years of age.

A successful screening should have:

- 1) a large population coverage (coverage should aim for at least 75% of population);
- 2) further care and monitoring of individuals with positive test;
- 3) data collection through the information system
- 4) quality control.

The above conditions can be provided only in organized screening districts, and on the whole territory of the Republic of Serbia. By reducing the mortality and morbidity, improving the quality of life of patients, human and financial resources of the health system become unburdened.

Recommendations for screening colorectal cancer are related to asymptomatic population, with expected average risk of illness. For persons with increased risk it is necessary to comply with specific rules and examinations should begin at an earlier age and be implemented in a pre-determined intervals.

Screening for colorectal cancer is meaningful because it usually arises from benign mucous growths – adenomas during the process of carcinogenesis, which lasts on average not less than ten years. This lengthy process enables timely detection and removal of these changes. Detecting the disease in the precancerous stage – stage of benign polyps or stage of localized disease provides full healing in more than 85% (76-90%) of patients.

Use of the test for the presence of occult blood in the stool as the initial test in screening of colorectal cancer led to a decline in relative mortality rates by 18-33%. The most commonly used tests that detect the presence of occult (invisible to the naked eye) blood in the stool, and less flexible rectosigmoidoscopy or colonoscopy.

The test results of screening effect the screening interval, which may be from one to several years. In case of application of more specific immunochemical stool test for occult bleeding, the cycle usually repeats every two years (Federal Republic of Germany, the Republic of Slovenia, the Czech Republic, the Republic of Finland, the Republic of France), and in the case of less specific guaiac test the cycle repeats every year (Republic of Croatia, The State of Israel).

In the case of other tests intervals are different. In Poland, the primary screening is colonoscopy, which is done once in ten years.

Other diagnostic procedures, such as the detection of specific DNA mutations in the stool and virtual colonoscopy are in the testing phase for efficiency and reliability.

2.3.1 Test for occult stool bleeding

Early detection of colorectal cancer by testing the presence of occult blood in the stool in the asymptomatic population with average risk proved to be a suitable method for its simple use and low cost. A positive test is an indication for further gastroenterological testing or colonoscopy.

In a large population and control studies (B evidence level) a positive test was reported in between 1% and 5% of asymptomatic subjects (3.6% of respondents in the pilot program on the territory of seven local communities of the municipality of Voždovac). Most population screening studies showed that newer immunochemical test (immunohistochemical FOB test) has significantly higher sensitivity and specificity for advanced adenomas and cancer than older guaiac test (gFOB test). In the guaiac test sensitivity was 37% and specificity 87%, and immunochemical test sensitivity was 69% and specificity 98%. Due to the sensitivity and particularly specificity (guaiac test does not distinguish human from animal blood), it should test three consecutive stools after the previous "white diet" (diet without meat), while the immunochemical test one sample is sufficient and no restrictions in diet are necessary.

In people with a positive test further diagnosis reveals colorectal cancer of the in 5-10% and adenoma in 20-30%.

Guided by the recommendations of the "European guidelines" this screening recommends application of immunohistochemical FOB test as a screening test in people with average risk, aged between 50 and 74 years.

A person tested for the presence of occult stool blood should be warned that a negative test does not mean security that he/she does not have a polyp or colorectal cancer.

2.3.2 Colonoscopy

Colonoscopy as the initial method is considerably more expensive, but also very sensitive in detecting even the smallest lesions. In addition to sensitivity, endoscopic methods have the advantage that the observed changes may be removed during the examination and thus save time and money, and the process itself becomes a method of treatment. Colonoscopy, if the preparation is adequate and an endoscopist trained to do a total colonoscopy, reveals 90-95% of the existing colorectal cancer.

Colonoscopy is done as the second test in screening for all persons with the positive test for the presence of occult blood, and thus determine the cause of occult bleeding.

For people with an increased risk of colorectal cancer (inflammatory bowel disease, heredity, family or personal history of adenoma and colorectal cancer) screening for colorectal cancer should begin earlier. For people with a personal history of low risk adenoma colonoscopy is performed for screening, which is administered every five years. For people with a personal history of high-risk adenoma colonoscopy is repeated every three to five years. For people with a positive family history of colorectal cancer (first-order relatives younger than 50 years or two first-order relatives of any age) primary screening is colonoscopy, and it begins in the

40th year of age or ten years before the age in which the cancer is detected in a relative, and the screening interval is three to five years. For people with a family history of familial polyposis (FAP) screening is sigmoidoscopy or colonoscopy starting at the age of 10 to 15 and is repeated annually. For people with hereditary non-polyposis syndrome screening colonoscopy is done starting from 20 or 25 years of age or ten years before the youngest diseased patient in the family. For people with inflammatory bowel disease screening colonoscopy is done every year or every other year.

2.3.3. Colorectal cancer screening in the Republic of Serbia

The Republic of Serbia has so far had a few (Vozdovac, Subotica and Zrenjanin in 2005) organized colorectal cancer screenings.

The following deficiencies were noted:

- 1) lack of information of the target population about the effectiveness of the measures of colorectal cancer prevention;
- 2) low coverage of the target population with the FOB test;
- 3) a high percentage of colorectal cancer discovered at an advanced stage;
- 4) lack of education;
- 5) inadequate data collection and reporting;
- 6) insufficient involvement of local government.

3. OBJECTIVES OF THE NATIONAL PROGRAM

3.1. General objective

Reduction of morbidity and mortality of colorectal cancer.

3.2. Specific objectives

- 1) Raising awareness of the population about the importance of regular stool examinations for hidden bleeding, and informing about the importance of screening;
- 2) strengthening the capacity of health institutions for the implementation of screening in terms of ensuring a sufficient number of trained personnel and equipment;
- 3) establishing a system of data collection and management during screening implementation;
- 4) establishment of quality control services in the implementation of screening;
- 5) involving local authorities and civil society in the implementation of screening.
- 6) providing sustainability of screening implementation by supporting society in general.

4. LEGISLATURE AND SCREENING PARTICIPANTS

4.1. The legal framework

The basis for the implementation of organized screening are the following regulations:

- Health Protection Act ("Official Gazette of RS", No. 107/05, 72/09 - dr. Law, 88/10, 57/11, 119/12 and 45/13 - dr. Law);
- Health Insurance Act ("Official Gazette of RS", No. 107/05, 109/05, 57/11, 110/12 and 119/12);
- Regulation on the national program of health care for women, children and youth ("Official Gazette of RS", No. 28/09);
- Regulations on the nomenclature of health services at primary health care level ("Official Gazette of RS", No. 24/09 and 59/12);
- Public Health Strategy of the Republic of Serbia ("Official Gazette of RS", No. 22/09)
- Decision on the plan of development of health care in the Republic of Serbia ("Official Gazette of RS", No. 88/10);
- Decision on establishing standards for accreditation of health facilities ("Official Gazette of RS", No. 28/11).

4.1.1. Social care for the health of the population in the Republic of Serbia

Within the early detection of the disease, according to the Health Protection Act (hereinafter the Act), shall be targeted at preventative care or screening, according to the respective republic programs. Implementation of screening, according to Article 11, paragraph 15 of the Act, falls within the social care for the health of the population in the Republic of Serbia, and in accordance with Article 45, paragraph 1 of the Law on Health Insurance health care is insured in full force at the expense of the budget of the Republic of Serbia as well as for persons covered by screening according to the respective republic programs.

4.1.2. Activities of the selected physician in the screening implementation

The health care system and the organization of health services are regulated by the Act, according to which the medical activity is performed at the primary, secondary and tertiary levels (Art. 79, 88, 89, 90 and 91). In the process of health care implementation at the health center physician the elected physician conducts all activities defined by the Act (Art. 95, 98 and 99), including work on the identification and elimination of risk factors for the disease and implementing screening programs in accordance with special programs issued pursuant to the Act.

Screening as an activity is mentioned in the Strategy of Public Health of the Republic of Serbia while the screening provisions are discussed in the Regulation on the national program of health care in women, children and youth, as a way of achieving the objective – preserving and improving the health of women in reproductive age.

4.1.3. Protection at work

Protection at work in the field of screening is regulated with various regulations. The ISO 15189:2008 quality standard of Medical laboratories is applied for the protection at work – special requirements for quality and competence.

Protection of carcinogenic substances and biological materials is achieved pursuant to the Law on Safety and Health at Work ("Official Gazette of RS", No. 101/05), Regulations on preventive measures for safe and healthy work when exposed to biological hazards ("Official Gazette of RS "No. 96/10), Regulations on preventive measures for safe and healthy work at the workplace (" Official Gazette of RS ", No. 21/09) and Regulations on preventive measures for safe and healthy work when exposed to carcinogens or mutagens (" Official Gazette of RS ", No. 96/11).

4.2. Participants in the screening implementation

Colorectal cancer screening is carried out on the territory of the Republic of Serbia in the form of organized decentralized program.

4.2.1. Republic Expert Board for the implementation of programs for early detection of malignant diseases

Republic Expert Board for the implementation of programs for early detection of malignant disease (hereinafter referred to as the REB), formed by the Minister of Health for expert supervision over the implementation of organized screening, which through the defined annual plan, performs the following actions:

- 1) provides guidelines for screening programs and performs expert verification of screening programs, considers and adopts models and changes in screening programs;
- 2) provides guidelines for the organization, coordination, monitoring and evaluation of screening programs;
- 3) determines the list of indicators in the process of implementing screening;
- 4) determines and approves the plans in implementing screening and adopts the report on the plan execution and submits them for approval to the Ministry of Health, as well as the models in the implementation of screening programs and their changes;
- 5) conducts the activities in accordance with the plan of activities;
- 6) establishes the draft criteria, standards and norms pertaining to screening programs;
- 7) provides technical support to the Office for the Prevention of malignant diseases;
- 8) Evaluates the screening training program;
- 9) establishes programs of promotional activities related to screening programs, as well as plans for research in the field of screening programs;
- 10) makes proposals for the engagement of individuals or groups of experts to address certain issues in the field of screening and conducts other activities pursuant to the Act and the Minister of Health;
- 11) REB submits reports on its work to the Ministry of Health on a quarterly, semi-annual and annual basis.

4.2.2. The Institute of Public Health of Serbia "Dr Milan Jovanovic Batut"

The Institute of Public Health of Serbia "Dr Milan Jovanovic Batut" provides the necessary expert and logistical (technical) support to the Office for the Prevention of malignant diseases.

The information system of the Institute of Public Health of Serbia "Dr Milan Jovanovic Batut" represents the IT support in implementing screening programs, or collects data from the institutes of public health, forms continually updates appropriate electronic databases. Updated database is available to the Office for the Prevention of malignant diseases.

4.2.3. The Office for the Prevention of malignant diseases

The Office for the Prevention of malignant disease was established at the Institute of Public Health of Serbia "Dr Milan Jovanovic Batut".

The Office for the Prevention of malignant disease is responsible for the implementation of organized screening and performs the following actions:

- 1) coordinates, organizes, monitors and evaluates the implementation of organized screening and provides technical support to other participants in its implementation;
- 2) coordinates training in the areas of screening, in accordance with the plan for the implementation of screening;
- 3) prepares the draft plan for the implementation of screening;
- 4) performs activities of the five-year and annual plans in implementing screening of its competence (education coordination in the field of screening, organizing promotional activities);
- 5) submits the proposal of five-year and annual plans in implementing screening, including a financial plan, to the Ministry of Health and REB, and submits periodic and annual reports on the implementation plan to the Ministry of Health;
- 6) suggests REB changes, additions and new screening programs and models for their implementation to REB;
- 7) prepares and proposes REB draft of criteria, standards, norms and indicators related to the implementation of screening;
- 8) prepares and proposes REB suggestions of guidelines and regulations for screening;
- 9) prepares and proposes REB single form for collecting data on screening (population, test results, etc.);
- 10) issues instructions for preparing reports of the institutes of public health and health centers on the implementation of screening;
- 11) plans and conducts research in the field of screening;
- 12) prepares proposals for the program of promotional activities related to screening;
- 13) submits reports on the screening implementation to the Ministry of Health screening at least once a month;
- 14) performs other activities in the field of screening, with the consent of the REB.

4.2.4. The institutes of public health

The institutes of public health coordinate the implementation of screening in the territory they are established for and perform the following activities:

- 1) appoint screening coordinator and his deputy;
- 2) daily communication and cooperation with representatives of health centers are provided through a designated coordinator and his deputy;
- 3) coordinate and organize health centers and local self-government (representatives of population groups) in order to educate, motivate and increase the response of the local population to screening;
- 4) appoint their representatives in the team for the coordination of screening at the level of health center;
- 5) provide assistance to health centers in the preparation of action plans for the implementation of screening and approve the action plans;
- 6) collect and update data from health facilities which conduct screening (health centers, hospitals) according to a unique pattern, process this data and transmit them in the form reports to the Office for the prevention of malignant disease at least once a month;
- 7) prepare an annual report on the implementation of organized screening and submit it to the Office for the prevention of malignant diseases.

4.2.5. Health center

Health center is the carrier of screening in the territory it is established for.

Health center forms a team to coordinate the implementation of screening, whose member and representative of the institutes of public health it is. Among the team members for coordination of screening implementation persons responsible for screening are appointed.

Health center provides information to screening participants, motivates women invited for screening, receives participants' calls and records the time of arrival to screening.

Health Center performs the following activities:

- 1) every year in collaboration with the institute or the National Institute of Public Health it issues an action plan for the implementation of screening;
- 2) organizes and conducts calling target population;
- 3) keeps call records which should contain (by date and shift) the number of: invited women, managed contacts, the women who refused to participate in screening, examined women, those who were not found at the given address and after repeated calls;
- 4) implements organized screening in separate time and/or place from providing health care to other patients;
- 5) the team for coordination and implementation of screening has a database and submits pattern reports to the competent institute or the public health department.

4.2.6. Medical institutions of secondary and tertiary health care

Colonoscopy is done in a medical institution of secondary or tertiary level, and is performed by trained medical doctors – specialists in gastroenterology, internal medicine and surgery.

Health institutions of secondary and tertiary levels of care shall perform the following activities:

- 1) carry out a complete colonoscopy with a high percentage of the cecum intubation;
- 2) record every detected lesion and remove it in the same act during the colonoscopy;
- 3) perform biopsy of each revealed lesion not suitable for polypectomy;
- 4) keep the paper and/or electronic documents required for registration of all tasks in the field of screening implementation;
- 5) send all biopted and removed changes for histopathological analysis;
- 6) reports selected physicians from the health centers of the results of colonoscopy using a single standardized report.

Men and women with positive FOB test and colonoscopy findings, which definitely is not cared for during colonoscopy, refer to the additional care in the appropriate health institution of secondary or tertiary level of care.

The time period from the issuance of referral from the health center to the visiting of a specialists should be as short as possible and not longer than six weeks.

Medical institutions of secondary and tertiary health care provide services necessary to complete the diagnosis and carry out necessary treatment. These services are not part of the screening, but part of routine health services of these institutions, but their reporting is necessary for analyzing the screening results. The institutions that provide them, fill out the appropriate paper and/or electronic documentation and forward it to the health centers, relevant institutes or public health departments in the prescribed uniform form.

Medical institutions of secondary and tertiary health care appoint a coordinator and a nurse responsible for screening implementation. They keep records of the number and outcome of examined plates, of the number referred and examined women in the screening, of the final outcome of the screening, they monitor the implementation of clinical path and report to the relevant institute or public health department once a month.

4.2.7. Local government

In coordination with the institutes and departments of public health, health centers, representatives of religious and ethnic communities, associations of citizens, the media, representatives of local governments perform actions to educate and motivate women to respond to the call for an organized screening program.

4.2.8. The mass media

In agreement with the participants of organized screening, as well as with the Ministry of Health, the mass media play an important role in the process of education, motivation and increasing response of women, through activities: national and local media campaigns ("leaflets", brochures, posters, billboards, radio jingles TV spots, contributions to the website of the Ministry of Health and the Office for the prevention of malignant diseases, social networks, etc.); press conferences; press releases; interviews; and specially designed programs.

5. METHODOLOGICAL GUIDELINES FOR SCREENING IMPLEMENTATION

5.1. Screening model in the Republic of Serbia

Cervical cancer screening is performed on the territory of the Republic of Serbia as organized decentralised program.

Target population: men and women 50-74 years of age.

Population coverage: tends to at least 75%.

Screening cycle: every other year.

Screening test: immunohistochemical FOB test

Test interpretation: health center laboratories(educated laboratory technician and medical nurses).

Further investigation in positive immunihistochemical FOB test: colonoscopy.

The end of the screening process: the screening process ends with the negative immunihistochemical FOB test, and in the case of positive immunihistochemical FOB test it ends with colonoscopy and histopathological finding in case of taking bioptic material.

Further treatment and monitoring which is not included in the screening process: general hospitals and clinical centers.

Quality control and final evaluation of screening process: the Office for the prevention of malignant diseases.

Announcing results, determining the dynamic and content of the follow-up, including referrals to further diagnostics are performed by the selected physician.

5.2. Information, education, communication and social mobilisation

Prior to the beginning of screening implementation it is necessary to define the strategy of information, education, communication and social mobilisation, operation plan for its realization and its time frame, as well as to determine persons responsible for performing the mentioned activities at the level of the Republic of Serbia and managing districts.

The strategy for municipalities covered by health center represents a part of annual action plan of the health center activities prepared by the team for screening coordination that submits it for adoption to the competent institute or public health department.

5.3. Identification of target population

At the start of the screening cycle the target population is identified. It consists of individuals between 50 and 74 years of age. The screening records are based on the list of the insured by the Republic fund for health insurance and other citizens who are entitled to health care, in compliance with regulations governing the protection of personal data.

Screening records exclude people who are already suffering from colorectal cancer, people with terminal stage of other illness and people with an increased risk of developing colorectal cancer (inflammatory bowel disease, heredity, family or personal history of adenoma and colorectal cancer) in which early detection of colorectal cancer should begin earlier, and the screening test is colonoscopy.

If this is not known, and these people were entered in the screening records, then they are excluded based on the anamnesis during the first screening.

Coordination team for screening implementation in a health center, in cooperation with the institute or public health department, prepares the target population list.

5.4. Invitation plan

The invitation plan is made by the institutes or public health departments in cooperation with health centers.

Health centers, in accordance with their personnel and spatial capabilities and the invitation plan, organize calling and testing of women, providing them the possibility of testing off working hours, as well as overtaking the FOB test.

The invitations should include at least the half of target population per year.

5.5. Invitation

The invitation letter is delivered by mail.

The invitation letter includes:

- 1) invitation with the phone number of health centers in order to make an appointment for testing;
- 2) information on the purpose and importance of screening (information leaflet).

Inviting can exceptionally be done by telephone. In this case, the woman is given an information leaflet during testing.

Coordination team for the implementation of screening in a health center in agreement with the competent institute or the public health department, periodically (every one to two months) checks women's response to calls for screening, using screening records which is constantly updated.

Repeated invitation is forwarded in a period not exceeding six months from the date of the first invitation.

In case a contact is not established even after six months, health center is required to provide a direct call along with an invitation letter. If after attempting a direct call by the health center, contact is not established, the woman is excluded from screening and is invited in the next cycle.

5.6. Determining the exact testing time

Screening participants confirm participation and testing appointment by phone, SMS, email or in person.

5.6.1. Testing

On the given date women (hereinafter referred to as screening participant) with a letter of invitation reports to the service for health care of women in a health center. Responsible health worker accepts her, takes the invitation letter, performs recording and sends her to the appropriate clinic specific for screening (or the clinic of the selected physician, doctor of medicine specialist in gynecology, but separately from regular patients).

The selected physician, doctor of medicine specialist in gynecology performs the following actions:

- 1) receives screening participants who made an appointment;
- 2) provides necessary information about screening;
- 3) gives screening participants to sign a statement if she does not want to participate in screening;
- 4) takes anamnesis and fills out a standard protocol (clinical path) in paper or electronic form;
- 5) gives an instruction set for taking stool sample and informs the screening participant to perform the test at home;
- 6) refers a screening participant to the health center laboratory where he/she brings the performed FOB test within seven days;
- 7) informs screening participants about the examination results (if the result is negative, it can be announced by phone, and the written report can be obtained in the health center; in the case of a positive result, he invites the participant for a visit within three weeks);
- 8) if the test result is not clear, he invites the participant and gives him/her another set for taking the stool sample;
- 9) if the test result is positive, he informs the participant of the necessity of colonoscopy and informs him/her both verbally and in written form about that research, necessary preparations and possible complications;
- 10) schedules colonoscopy, with maximum time between positive screening test and colonoscopy should be shorter than two months;
- 11) in case the participant rejects colonoscopy, he wants the participant to sign the statement on that;
- 12) announces the results of pathohistological analysis; if the result is negative, he monitors the patient according to the recommendation of an endoscopist and/or the protocol;
- 13) invites the participant to repeat the FOB test within two months, if he did not consent for the colonoscopy;
- 14) refers the participant to other examinations if there is an indication based on the positive colonoscopy results;
- 15) submits weekly reports to the relevant person from the coordination team for screening implementation on the health center level on meeting the dynamic of the action plan.

5.7. Interpretation of immunohistochemical FOB test

Immunohistochemical FOB test is interpreted by the responsible technician or a nurse in the health center laboratory.

The laboratory submits a report to the selected physician on the test result within two days from the sample submission.

If the test result is unclear, a participant is phoned for a re-test.

5.8. Colonoscopy

Colonoscopy is done in a medical institution of secondary or tertiary levels of care. Colonoscopy is performed by trained gastroenterologists, internists and surgeons. Each colonoscopist who participate in screening should do at least 300 colonoscopies annually to ensure the necessary competence.

A colonoscopist performs the following actions:

- 1) performs a complete colonoscopy, which involves the removal of polyps and taking a biopsy;
- 2) fill out the paper and/or electronic report in a unique part that serves for the recording of all data on colonoscopy;
- 3) sends removed changes and biopsies for histopathological analysis;
- 4) receives histopathological report and sends it along with a copy of a single standardized report to the selected physician who referred the screening participant to colonoscopy.

If more than one lesion are identified, the result of screening is the worst prognosis, or one that requires the most invasive procedure.

Colonoscopy process must record each biopsied lesion, each adenoma $\geq 10\text{mm}$, as well as any complications.

5.9. Pathohistological finding

A pathologist performs the following activities:

- 1) reviews the submitted samples taken during colonoscopy and records the histopathological finding in the report. He completes the new histopathological report for any change;
- 2) the histopathological report is sent to a colonoscopist;
- 3) if the histopathological finding is positive, the patient is referred for further treatment in accordance with the result of the medical indications;
- 4) the patient returns the histopathological findings together with the conclusion of a colonoscopist to the selected physician who, depending on the findings, acts in accordance with the recommendations of the Guide for good clinical practice.

The explanation of pathological findings, conducted interventions and guidance on further actions and monitoring interval are obligations of the specialist who did the colonoscopy or the selected physician.

5.10. Referring a patient for further diagnostics

Patients with colorectal cancer undergo additional diagnostic process (abdominal ultrasound, heart and lungs imaging, abdomen CT) and are suggested further therapy (surgery or another, at the discretion of the council).

A patient is referred for further diagnostic procedures by the selected physician, depending on the indication on the basis of the results of colonoscopy and recommendations of the Guide for good clinical practice.

Necessary diagnostic procedures must be performed no later than six weeks from the time of referral.

The maximum time between positive colonoscopy and definitive treatment should be one month.

It is extremely important to ensure adequate communication with the patient at all levels. It involves the communication of all treatment options and outcomes and obtaining the informed consent from the patient for further proceedings.

5.11. Collecting data and reporting

Data on the target population, sent invitations, response to screening, results of screening tests, all the necessary diagnostic and therapeutic procedures make a database at the health center. This database is necessary for the monitoring and estimation of screening implementation.

Records of sent invitations, given invitations and response to testing is conducted by the team for coordination of screening implementation at the health center. Mentioned activities are performed by a medical technician pursuant to the recommended standards.

5.11.1. Standard protocol (clinical path)

Reporting on the screening results is based on the minimal data set which must be collected to calculate the process and outcome indicators of the screening program.

The data necessary for the assessment of screening efficiency are created in every stage of screening implementation, thus a standardized and coordinated way of their collection is required. In order to avoid data loss, they should be collected at the time of their appearance. Thus the screening uses the standardized protocol (clinical path) that monitors the screening participant through every screening stage, from the beginning to the end, which refers to invitation, all visits to the physician and other health workers, as well as to the performance and analysis of screening tests and other procedures included in the screening process at all levels of health care.

5.11.2. Data entry

The protocol can be printed on paper, but the optimal data entry into the protocol is electronically which requires the following:

- 1) the existence of the protocol for the electronic data entry with accompanying software equipment;
- 2) the existence of computer equipment at every work place where a screening participant is;
- 3) network of all work positions, so that all screening performers have insight into the previous stage of the process;
- 4) connection with the institutes and departments for public health and the Office for the prevention of malignant diseases.

In case such system exists, all the data are entered only once at the work place where they occur, and the networking allows them to be available at all other work places, as well as to the centers for collecting data where through the databases they transform into the required indicators.

5.12. Data and indicators of program implementation

5.12.1. List of data collected in screening

All the collected data are shown in the protocol (clinical path).

5.12.2. Indicators of screening implementation

Indicators for monitoring the implementation of screening are: lower rates of population suffering from colorectal cancer, the number of reports about the performed preventive examinations by planned screening, the number of trained health workers, health facilities equipped for conducting systematic examinations, printed promotional material and number of individual invitations for screening.

For short-term assessment of overall screening the following are evaluated: response, the time from the patient's invitation for an examination, notification of the positive findings to screening (colonoscopy), what is the relationship of the people with "positive" test to further examination and what is the degree of use of hired resources (colonoscopy, analgosedation, endoscopic intervention – the success of the examination, monitoring of pathological findings and treatment).

In the long term, evaluation of program implementation concerns the assessment of the reduction of morbidity and mortality rates,

Process indicators are:

- 1) percent of people who responded to the invitation and reported to a health center after the first and following calls;
- 2) percent of people who submitted the stool sample;
- 3) percent of people with positive FOB test and who agreed for colonoscopy;
- 4) percent of people with positive FOB test and who did colonoscopy;
- 5) percent of people that did not respond to delivered invitations;
- 6) percent of people who did not agree for screening;
- 7) percent of people who did not agree for colonoscopy.

Outcome indicators are:

- 1) percent of inadequate FOB tests (of all FOB tests);
- 2) percent of positive tests (of all FOB tests);
- 3) percent of positive colonoscopies (of all performed screening colonoscopies);
- 4) presence of adenoma of any size (of all performed screening colonoscopies);
- 5) presence of not progressed adenomas (of all performed screening colonoscopies);
- 6) presence of progressed adenomas (of all performed screening colonoscopies);
- 7) presence of cancer by stage (of all performed screening colonoscopies);
- 8) percent of incomplete colonoscopies;
- 9) percent of hospitalization for unwanted reactions on the day of colonoscopy by the number of colonoscopies;
- 10) percent of unplanned hospitalizations by the number of colonoscopies within eight days from the day of screening, if it can be associated with screening;
- 11) mortality within 30 days from colonoscopy, if it can be associated with screening;
- 12) Positive predictive value of FOB test according to positive colonoscopies.

Long-term indicators:

- 1) interval cancers (percent of cancers that occur after a negative screening episode, during the period prior to the next invitation for screening);
- 2) incidence of colorectal cancer in the population;
- 3) rates of the detected progressed disease (Dukes C and D) in the population;
- 4) rates of mortality of colorectal cancer in the population.

5.13. Quality assurance

Quality and success of the whole screening program in one country depends on the high quality of every step in the organized screening.

Each step of the screening must be explained in detail through instructions so the screening organization on the territory of one country could be as uniform as possible.

Social mobilisation requires adequate professional approach to greater population synced with demographic, social, educational and religious structure of the population. Special attention must be directed to marginalized groups and minorities. Invating and informing during all screening stages must be conducted by ethnic, legal and moral principles, synced with educational and social status of women according to the instructions.

Uniform immunohistochemical FOB tests on the level of the Republic Serbia, which are generally accepted by the European countries, are necessary.

Uniform data collection through unique protocols and reports are necessary for monitoring and estimation of screening implementation.

Based on monitoring and estimation of screening implementation and the collected data, quality control is performed on all screening stages: through response, performing and interpretation of the screening tests (FOB test and colonoscopy), and education on the state level.

5.14. Monitoring and evaluation of screening

Monitoring and evaluation of screening is planned and conducted by the Office for early detection of malignant diseases through a database of organized screening and periodical reports of the public health institutes and centers. Final evaluation of the screening is done ba the Ministry of Health for each calendar year, based on the data and reports of the Office for early detection of malignant diseases.

6. FINANCING

The National program for early detection of cervical cancer is financed pursuant to the law.