NATIONAL PLAN

FOR RARE DISEASES

2009 – 2013

(Genetic, congenital malformation and non-hereditary disease)

I. Introduction

(Skiped)

II. Aim

The program aim is to create an adequate institutional framework and mechanisms for the provision of timely prevention, diagnostics, optimal treatment and rehabilitation of patients with rare diseases (genetic, congenital malformation, and non-hereditary disease).

III. Priorities

1. Provision of epidemiological data on rare diseases in Bulgaria by the establishment of a National Register.
2. Improvement of the prevention of rare diseases with genetic origin by extension of the screening programs.
3. Improvement of the prevention and diagnostics of rare diseases with genetic origin by the introduction of new genetic tests, decentralization of laboratory activities and facilitated access to genetic counseling.
4. Integrated approach to the implementation of prevention, diagnostics, treatment, and social integration of patients wuth rare diseases and their families.
5. Increase of the physicians' professional qualification in the field of early diagnosis and prevention of rare diseases.
6. Research on the necessity, opportunity, and criteria for the establishment of a reference center for rare diseases on a functional principle in Bulgaria.
7. Organization of a national public awareness campaign on the problems of rare diseases and their prevention.
8. Support and collaboration with non-governmental organizations and the associations of patients with rare diseases.
9. Close collaboration with other EU member-countries working to achieve the purpose of the program and with the Rare Disease Task Force at DG SANCO, EC.

IV. Target Groups

The National Plan for Rare Diseases (genetic, congenital malformations, and non-hereditary diseases) 2009-2013 focuses on the following target groups:

1. The country population

    - Patients with rare diseases - 6% of the country's population;
    - Families in risk of giving birth to a child with genetic problems (previous child with genetic disease);
    - Families with reproductive problems;
    - Pregnant women;
    - All newborns.

2. Medical specialists of all type of specialties on all levels of the healthcare system, involved in the program's implementation;

3. Non-governmental organizations (NGOs) active in the area of rare diseases.

V. Program Activities

1. Establishment of a National Consulting Council for Rare Diseases (NCCRD) within the Ministry of Health

A National Consulting Council for Rare Diseases (NCCRD), within the Ministry of Health, shall be established for the purposes of the National Plan for Rare Diseases (genetic, congenital malformations, and non-hereditary diseases) 2009-2013.

The members of the National Consulting Council for Rare Diseases (NCCRD) shall be appointed by an order issued by the Minister of Health and shall be presided by a Chairman specialized in social medicine and health management, also appointed by the Minister of Health. NCCRD shall draw up a Statute for its activities based on the priorities and activities set out in the program.

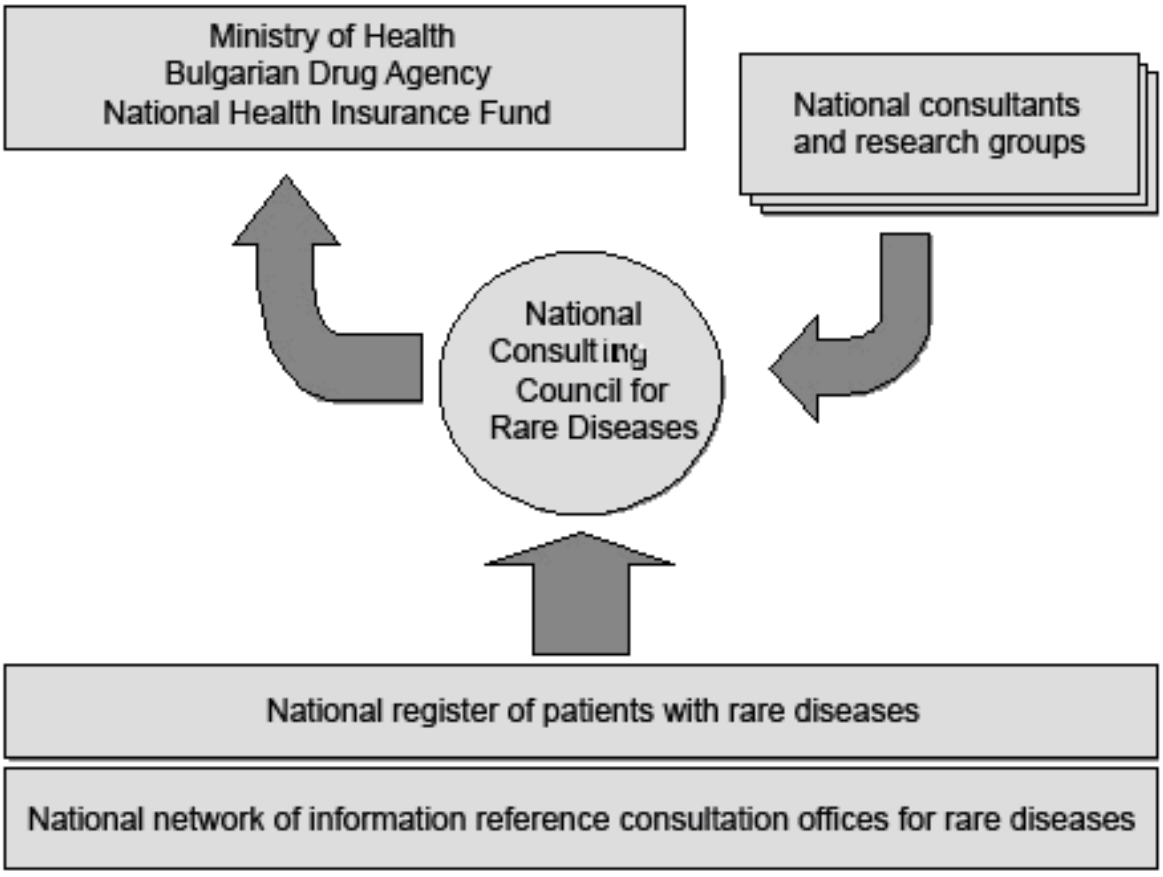

Figure 1. Institutional framework for the execution of the National Plan for Rare Diseases

The members of NCCRD shall be permanent and include:

a) national consultants and/or specialists in major program priorities;

b) representatives of governmental institutions working in the field of prevention, diagnostics, treatment and rehabilitation of rare diseases;

c) representatives of patient organizations for rare diseases.

2. Establishment of expert panels for rare diseases working with the national consultants

On NCCRD's initiative, and in close cooperation with the Bulgarian medical scientific societies, the national consultants of different medical specialties will work with the newly established expert panels that will propose to NCCRD a list of actual for Bulgaria rare diseases within the scope of their corresponding medical specialty. The panels have to prepare a rationale for each proposed disease according to the below stated criteria as well as a standard for its clinical management based on the newest achievements and good medical practices.

Criteria for rare disease proposal:

- Rarity (prevalence less than 5 per 10 000 people);
- Clinical severity;
- Degree of damage;
- Established standards for diagnosis, treatment, and rehabilitation;
- Availability of an orphan drug, approved by the European Drug Agency or other treatment significantly improving the health condition of the patient;
- Cost-benefit of the treatment.

If needed, the national consultants and the expert panels will perform other consultative functions related to work issues and activities of NCCRD.

3. Establishment of a national network of information-reference centres for rare diseases

The Ministry of Health's National Consulting Council for Rare Diseases shall propos the competition criteria applicable to the selection of healthcare facilities, where a total of 6 information-reference centres for rare diseases will be set up.

The centres are the constituent parts of the National Network for Rare Diseases and are managed and coordinated by NCCRD.

The expected flow of patients with rare diseases and the organization of the neonatal screening in Bulgaria are presented on Figure 2.

- **Tasks of the national network of information-reference centres for rare diseases**
    - Exchange and synchronizarion of information regarding the performance of the National Plan for Rare Diseases;
    - Ensure functioning of the National Register of Rare Diseases;
    - Guarantee equal access and quality of information;
    - Provision of data for planning purposes on a regional and national level

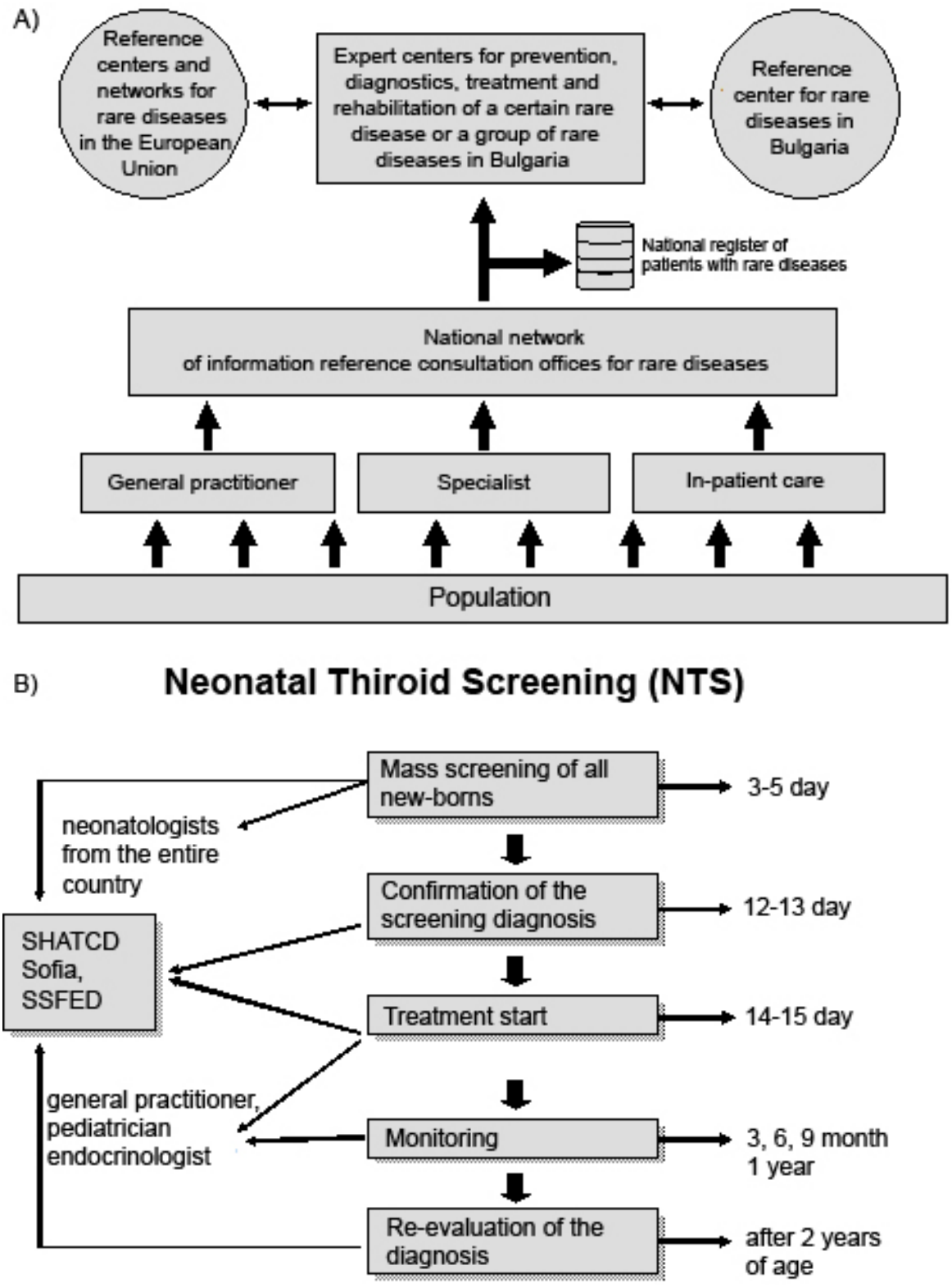

Figure 2. Expected flow of patients with rare diseases (A) and organization of a neonatal thyroid screening in Bulgaria (B)

- **Tasks of the information reference centres for rare diseases**
    - Dissemination and implementation of the NCCRD's programs on field, including the national public awareness campaign on the problems of rare diseases and their prevention;
    - Reference nodes for referral of patients with rare diseases to medical specialists working in the out- and in-patient care area;
    - Regional unit of the National Register for Rare Diseases;
    - Creation and maintenance of local registers of patients with rare diseases;
    - Creation and maintenance of local registers of clinical trials in the respective medical departments and facilities in the in-patient care;
    - Creation and maintenance of local registers of the regionally available diagnostic tests for rare diseases;
    - Interaction with the developed and functioning screening network;
    - Support of regional in-patient health care facilities through the provision of clinical protocols and standards for treatment of rare diseases;
    - Assistance and training of general practitioners;
    - Increase the awareness of patients, physicians and society of the issues of rare diseases;
    - Maintenance of a close relation and collaboration with the rest of the reference consultation offices.

4. Establishment of a national register of patients with rare diseases

The terms and registration order, processing, and storage of data in the national register of patients with rare diseases are set by the National Consulting Council for Rare Diseases, at the Ministry of Health. The register is situated in a healthcare facility selected by a competition and is maintained by 3 specialists: one of them is a physician, and the

remaining 2 are technical specialists. The prepared and approved by NCCRD reporting documentation is used for the purposes of primary epidemiologic information collection. The information in the register is submitted by the information reference consulting offices for rare diseases and exchanges epidemiological data with the National Center for Health Information. The register includes nosologic units from the National List of Rare Diseases, created and updated by NCCRD. The register observes all legal requirements applicable to the private data protection.

The register's main goals are to:

- collect, summarize, and provide epidemiologic information on the incidence and prevalence of rare diseases in Bulgaria;
- assist the preparation of diagnostic and therapeutic protocols and standards for treatment of rare diseases;
- assist the Ministry of Health, the Ministry of Labour and Social Policy, and the National Health Insurance Fund in the planning and delivery of expensive treatment and medical care to patients with rare diseases;
- improve the interaction between health services and patient organizations;
- provide and publish data needed for planning and comparison on a regional and national level.

5. Improvement of the prevention and diagnostics of rare genetic diseases, predispositions, and congenital anomalies

5.1. Improved prevention and diagnostics of rare genetic diseases, predispositions, and congenital anomalies.

5.1.1. Mass neonatal screening for congenital hyperthyroidism with an expected annual growth among new-borns of 2–4,000 cases;

5.1.2. Mass neonatal screening for phenylketonuria with an annual growth among new-borns of 2-4,000 cases;

5.1.3. Extension of postnatal endocrine screening programs through the introduction of screening practices for 21-hydroxylase deficit after 2009;

5.1.4. Training of staff for the needs of the medical genetic consultations in compliance with the requirements of the European Union and in collaboration with the European Genetic Foundation;

5.1.5. Update of the acting legislation and publication of methodology guidelines intended for general practitioners, obstetricians, neonatologists, and pediatricians, which include:

- protocol and condition for collection, storage, and transportation of blood samples of new-borns;
- protocol regarding the follow-up and treatment management of patients detected in screening procedures.

5.2. Extension of genetic disease diagnostics through the introduction of new methods for diagnostics and transfer of technologies to the genetic laboratories.

5.2.1. Extension of the postnatal selective metabolic and enzyme screening;

5.2.2. Extension of the postnatal DNA diagnostics of different multigenic diseases and transfer of technologies to other genetic laboratories – mucoviscidose, spinal muscle atrophy, muscle atrophies, Wilson's disease, hemophilia A and B, etc.;

5.2.3. Performance of postnatal cytogenic diagnosis for chromosomal diseases of healthy first-degree relatives, children with chromosomal disease, extended examinations for detection in risk families and other healthy individuals, carrying of balanced chromosomal mutations, cytogenic tests of both partners before manipulations related to an *in vitro* fertilization;

5.2.4. Medical genetic consultation of all examined patients.

5.3. Improved diagnostic of mental retardation with new technologies

5.3.1. Diagnostics with fluorescent *in situ* hybridization – FISH;

5.3.2. Diagnostics of fragile chromosome X with a DNA assay;

5.3.3. Diagnostics with a microchip technology;

5.3.4. Medical genetic consultation of all examined patients.

5.4. Improved diagnostics of congenital anomalies through the introduction of molecular cytogenetic tests and microchip analysis

5.4.1. Improved diagnostics of congenital anomalies with microdeletion syndrome tests with FISH techniques;

5.4.2. Molecular cytogenic tests of children with malformation syndromes and complex chromosome rearrangements – multicolor fluorescent *in situ* hybridization – mFISH;

5.4.3. Detection of microstructural anomalies with microchips;

5.4.4. Medical genetic consultation of all examined patients.

5.5. Decrease of the number of new-borns with severe hereditary and congenital genetic diseases (biochemical screening in pregnant women and prenatal diagnostics).

5.5.1. Extension of the prenatal biochemical screening for detection of pregnant women at higher genetic risk of delivering a child with Down syndrome, severe neural tube and abdominal wall defects with screening on the 10-14 week of the pregnancy;

5.5.2. Introduction of prenatal cytogenic diagnostics of pregnant women in all genetic laboratories;

5.5.3. Performance of prenatal enzyme diagnostics of families in high risk of схгеисшеа genetic deviations;

5.5.4. Performance of prenatal DNA diagnostics of monogenic disease in families with proven mutation;

5.5.5. Medical genetic consultation of all examined patients.

5.6. Improved diagnostics of chromosomal pathology in oncohematologic diseases.

5.6.1. Test for chromosomal anomalies in the bone marrow with a routine cytogenic analysis;

5.6.2. Test for mutations of oncogenes, tumor-suppressive genes, and specific chromosomal rearrangements with FISH;

5.6.3. Test for hidden chromosomal translocations with a multicolor mFISH;

5.6.4. Test for chimerism in the peripheral blood flow with fluorescent *in situ* hybridization with centrometic X and У FISH samples;

5.6.5 Test of specific chromosomal aberrations with a DNA assay;

5.6.6. Medical genetic consultation of all examined patients.

5.7. Improved diagnostics of genetic predispositions to some malignant conditions

5.7.1. Test for microsatellite instability and search for gene mutations related to hereditary non-polypous colorectal carcinoma;

5.7.2. Test for BRCA1 and BRCA2 gene mutations for hereditary forms of breast cancer;

5.7.3. Introduction of DNA markers for chemotherapy administration – HER2, EGFR and others;

5.7.4. Offering of a highly specialized medical genetic consultation of the examined patients.

5.8. Improved genetic diagnostics of reproductive disorders – male and female sterility, families with miscarriages and still-births.

5.8.1. Routine cytogenic diagnostics of chromosomal aberrations in the peripheral blood flow of patients with more than two miscarriages, still-born children, male and female sterility.

5.8.2. Evidence of predisposition to thrombophilias with a DNA assay.

5.8.3. Evidence of У-microdeletions with a DNA assay.

5.8.4. Offering of a highly specialized medical genetic consultation of the examined patients.

6. Improved treatment control of genetic and congenital diseases

6.1. Optimization of treatment algorithms;

6.2. Evaluation of treatment effects;

6.3. Participation in international programs and networks financed by the European Union.

7. Improved communication among the medical genetic consulting offices throughout the country

7.1. Inclusion of the medical genetic consultation offices in a unified network for information exchange in compliance with the private data protection law;

7.2. Connection and close collaboration between the medical genetic consultation offices and the information reference centers for rare diseases.

8. Improved genetic and screening network structure in the country

8.1. Consolidation and further development of the national structure of specialized genetic units through additional supply of the necessary equipment, integration of new technologies, development of collaborations with existing highly specialized laboratories in the respective healthcare facilities;

8.2. Extension and unification of the functions of the genetic laboratories through a technological interexchange;

9. Increase of the awareness, knowledge and professional qualification of the medical professionals in the field of early prevention, diagnostics, treatment, and rehabilitation of rare diseases.

An increase of the awareness of the problem during medical training and afterwards is necessary. This would lead to a shorter period between the occurrence of symptoms and the accurate diagnosis. Physicians will be informed of the available resources and paths in the healthcare system related to the prevention, diagnostics, treatment, and rehabilitation of rare diseases. The existence of standards and rare disease prevention, diagnostic, and rehabilitation guidelines will ensure an optimized management of patients with rare diseases and improvement of their quality of life.

Activities:

- Proposal for the introduction of medical genetics course as part of the General Practice specialty for general practitioners;
- Training of obstetricians and gynecologists for evaluation of fetal morphology;
- Training of pediatricians and general practitioners for identification of rare diseases;
- Publication and distribution of printed materials;
- Organization and conduct of an annual national working meeting for rare diseases;
- Organization and conduct of an annual regional seminars for the general practitioners;
- Preparation and distribution of information materials on rare diseases to medical professionals;
- Preparation and distribution of a compendium of rare diseases;
- Distribution of unified documents and forms:
    - *Informed consent* for material collection with chorionic biopsy, amniocentese, cordocentese, venous punction and DNA bank;

- *Informed consent* for DNA analysis, cytogenic test, diagnostic molecular cytogenic analysis, heterozygotic carrying, and preclinical diagnostics – different for each individual case (monogenic, chromosomal, predispositions, etc.);
- *Informed consent* for the evaluation of the risk of deliverying a child with Down syndrome and neural tube defects (spina bifida and anencephaly) and informed consent for an aneuploid DNA analysis;
- *Order for a DNA* analysis (for information purposes, post- and prenatal diagnostics); order for a biochemical analysis (post- and prenatal diagnostics); order for a cytogenic analysis (post- and prenatal diagnostics); order for a molecular cytogenic analysis (post- and prenatal diagnostics*;*
- *Filter form* for blood sample collection for the purposes of mass screening of new-borns (Directive 98/79/EO of the European Parliament and the European Council of October 27, 1998 regarding the *in vitro* diagnostic medical devices; ISO 13485:2003)

10. Research of the necessity, opportunities and criteria for the establishment of a reference center for rare diseases on a functional principle in Bulgaria.

The Public Health Department of the European Commission established the High Level Group on Health Services and Medical Care as a tool analyzing the recommendations made in the process of discussing patients' mobility. One of the work panels of this expert group is concerned with the development of reference networks for rare diseases. The principles of the European Reference Networks for Rare Diseases (ERNRD), including their role in the fight against rare diseases and other conditions requiring specialized care, patient volume, etc. are discussed. These centers have to be evenly spread throughout the EU territory.

The establishment of a reference center for rare diseases on a functional principle in Bulgaria unifying the available material and human resources in the country, will serve as a base for highly specialized training of students and physicians working in healthcare

and will create standards and guidelines for prevention, diagnostics, treatment, and rehabilitation of the patients with rare diseases. The reference center will be an important structure allowing closer collaboration and exchange with reference centers for rare disease in Bulgaria.

The Ministry of Health's National Consulting Council for Rare Diseases together with the national consultants and research groups in the country will perform a detailed study of the necessity, feasability, and criteria for the establishment of a reference center for rare diseases on a functional principle in Bulgaria observing the experiences of the other European countries and the changing legislation in this area.

Activities:

- Research of the necessity, feasability, and criteria for the establishment of a reference center for rare diseases on a functional principle in Bulgaria ;
- Organization and conduct of an annual national clinical conference for rare diseases and screening programs.

11. Promotion of an integrated approach to the implementation of prevention, diagnostics, treatment, and social integration of the patients and their families.

Article 152 from the European Community Contract requires that *„the development and execution of all policies and activities within the Community should ensure a high level of human health protection"*. The new health strategy of the European Union emphasizes the importance of health in the policies. This is covered by the Lisbon Strategy for Growth and Employment which stresses the relation between health and the economic prosperity and the Citizen program which acknowledges the right of people to be authorized on the issues of their health and healthcare.

The strategy activities represent the healthcare work done in all sectors. Articles of the Contract concerning the domestic market, environment, consumer protection, social work, including employees' safety and health, development policies, research activity and many others refer to health.

The population's health is a priority not only for the Ministry of Health. The integrated approach (Health in All Policies, HIAP) for prevention, diagnostics, treatment, and social integration of patients with rare diseases requires the attraction and effect of all policies outside the healthcare sector on the specific problems that these patients and their families have. The promotion of intersector cooperation will be achieved through the attraction of experts from the Ministry of Labour and Social Policies and the Ministry of Education and Science to NCCRD, increase of the professional qualification of the medical specialists, increase of the capacity of the NGOs and the patient associations in order to improve the dialog between the healthcare- and the other sectors, increase of the knowledge and social awareness of the rare diseases.

Activities:

- Organization and conduct of an annual national meeting for intersector cooperation on the issues rare diseases

12. Organization of a national public awareness campaign for rare diseases and their prevention

A necessary priority for increasing the public awareness of the existing rare diseases and the problems people with rare diseases and their families have. This will lead to an increased public involvement and tolerance towards the specific problems of patients with rare diseases and their infringed human rights. The population will become acquainted with the most important methods for primary prevention of the rare diseases.

Activities:

- Preparation and distribution of information materials on rare diseases to the population;
- Preparation and distribution of information materials to people with rare diseases and their families;
- National media campaign (radio and video spots);

13. Support and collaboration with NGOs and associations of people with rare diseases

Non-governmental organizations and the associations of patients with rare diseases have a significant role for the dissemination of information and provision of public support. These are important elements of the lobbying strategy for the development of adequate legal regulations for protection of the infringed human rights. They assist the turning of the patient from an object to a subject in his interaction with the healthcare system. They stimulate the clinical and scientific activities. They provide ethical, social, and legal support to people with rare diseases.

Activities:

- Organization and conduct of an annual national meeting with patients with rare diseases;
- Introduction and celebration of the European Day of People with Rare Diseases (the last day of February).

14. Establishment of close collaboration with the rest of the countries in the European Union

The close collaboration with the rest of the EU member-countries with national programs for rare diseases will ensure the transfer of knowledge and experience. It will provide access to health resources with a strategic significance for the management of rare diseases which Bulgaria does not have. Stimulation of the research activities and increase of Bulgaria's international prestige as a country that is actively involved in the problems of people with rare diseases is expected.

Activities:

- Organization and conduct of annual work expert meetings and synchronization of the national priorities in the field of rare diseases;
- Participation of Bulgarian experts in European initiatives and work panels for rare diseases.

VI. Program Performers

1. University hospitals throughout the country and their laboratories, diagnostic, clinical, and rehabilitation units;
2. Maternity and neonatologic wards in healthcare facilities for inpatient care throughout the country;
3. Genetic laboratories of healthcare facilities;
4. The Ministry of Health, the Ministry of Labour and Social Policy, the Ministry of Education and Science, the National Health Insurance Fund;
5. NGOs and association of patients with rare diseases;
6. National consultants and medical research groups;
7. General practitioners and specialists in the outpatient care;

VII. Expected Results

The implementation of the National Plan will improve the prevention, timely diagnostics, treatment, and rehabilitation of people with rare diseases:

1. National policy for the organization, planning, and financing of the prevention, timely diagnostics, treatment, and rehabilitation of people with rare diseases;
2. National network for rare diseases consisting of information reference centres in healthcare facilities;
3. National register of patients with rare diseases providing accurate epidemiologic information for the prevalence of rare diseases in Bulgaria;
4. Continuation and extension of the mass screening problems;
5. Improved prevention of:
    - Healthy individuals, carriers of recessive mutations or balanced chromosomal rearrangements posing a high risk of sick offspring;
    - Individuals with reproductive failure and an established genetic cause for their problems;
    - Pregnant women undergone biochemical screening for chromosomal anomalies;
    - Pregnant women undergone prenatal diagnostics;
6. Improved diagnostics of:
    - Treatable rare diseases with genetic preconditioning (multigenic chromosomal);
    - Mental retardation;
    - Congenital anomalies with new technologies;
    - Family forms of some oncologic diseases;
    - Individuals, included in programs for malignant disease prevention;

- Oncohematologic diseases with molecular genetic tests and molecular cytogenic analysis of chromosomal anomalies;

7. Decreased number of children born with severe hereditary and congenital genetic diseases;
8. Improvement of the treatment of oncologic diseases with genetic test markers;
9. Introduction of monitoring practices following up the effect of the oncohematologic disease therapy with bone marrow transplantation;
10. Increase of the medical genetic consultations' number ;
11. Improvement of the control on rare disease treatment;
12. Regulation and consolidation of the genetic network's infrastructure;
13. Identification and announcement of expert centers for prevention, diagnostics, treatment, and rehabilitation of a certain rare disease or group of diseases in Bulgaria;
14. Increase of the physicians' knowledge and professional qualification in the field of early prevention and diagnostics of rare diseases;
15. Research of the necessity, possibility, and criteria for the establishment of a reference center for rare diseases on a functional principle in Bulgaria;
16. Creating public awareness of rare diseases and their prevention;
17. Attraction of NGOs and patient organizations as active partners of the healthcare system;
18. Participation in European projects and networks for rare diseases involving attraction of additional sources of financing;
19. Establishment of a close collaboration with the other EU member-countries and improvement of the Bulgarian prestige.

VIII. Management and Coordination of the Program Activities

The National Plan is managed and coordinated by the National Consulting Council for Rare Diseases (NCCRD) which is:

- part of the Ministry of Health;
- appointed by the order of the Minister of Health;
- presided by a Chairman specialized in social medicine and health management appointed by the Minister and the Vice Chairman – National Medical Genetics Consultant;
- The members of NCCRD are permanent and include:

  а) national consultants and/or specialist in main program priorities;

  б) representatives of state institutions working in the field of prevention, diagnostics, treatment, and rehabilitation of rare diseases;

  в) representatives of patient organizations for rare diseases.

- NCCRD draws up a Statute for its activities based on the priorities and activities set out in the program.
- NCCRD meets at least once every two months and has the following tasks:
  - Direct responsibility for the execution and reporting on the National Plan for Rare Diseases;
  - Preparation, organization, and update of the National List of Rare Diseases proposed by the national consultant and the research groups;
  - Establishment and coordination of the National Network of Information Reference Centres for Rare Diseases;
  - Creation and coordination of the functionality of a national register of patients with rare diseases in Bulgaria;

- Provision of assistance and consultation to the Ministry of Health, BDA, MLSP, and NHIF on issues concerning the planning and delivery of expensive treatment to patients with rare diseases;
- Coordination of the screening program activities;
- Coordination of the activities related to the primary prevention and diagnostics of rare diseases with genetic origin;
- Preparation of a methodology for the identification and announcement of reference expert centers for prevention, diagnostics, treatment, and rehabilitation of certain rare disease of a group of diseases;
- Organization of a national awareness campaign for rare diseases and the existing preventive options;
- Organization of work meetings, seminars, and conferences;
- Close cooperation with similar structures in other EU countries.