NAMSE

National Action League for People with Rare Diseases

National Plan of Action for People with Rare Diseases

Action Fields, Recommendations, Proposed Actions

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Founders of NAMSE

Federal Ministry of Health

Federal Ministry of Education and Research

achse
Allianz Chronischer Seltener Erkrankungen

Note concerning use of sexist language according to the Sex Discrimination Act

For reasons of legibility the authors do not necessarily distinguish between male and female forms. The terms employed always refer to both sexes.

Preface

In Germany, more than four million people are afflicted with rare diseases, of which there are some 8,000 types worldwide. It is a paradoxical situation. Rare diseases are in fact so numerous that a quarter of all diseases occurring in humans may be subsumed into this category and, taken together, they are as prevalent as any one of the major chronic diseases. However, the fewer the number of persons suffering from any one of the rare diseases, the less knowledge is available about its causes, symptoms and treatment options. In recent years, awareness of the challenges posed by rare diseases has risen tremendously both in Germany and in the entire European Union. Indeed, it is primarily through greater cooperation at national and European level in this area that increased value added can be expected.

Rare diseases are characterised by a number of peculiarities. These include, first and foremost: the small number of patients who suffer from any one rare disease; the broad regional distribution of these persons, which hinders their participation in appropriate studies; the small number of geographically scattered experts trained to address these diseases. Moreover, the path to good treatment and care is frequently all but clear. The result is that persons living with rare diseases often feel left alone to cope with their disease.

In 2010, the German Federal Ministry of Health (BMG), together with the German Federal Ministry of Education and Research (BMBF) and the Alliance for Chronic Rare Diseases (Allianz Chronisch Seltener Erkrankungen, ACHSE e.V.), founded the National Action League for People with Rare Diseases (Nationales Aktionsbündnis für Menschen mit Seltenen Erkrankungen, NAMSE). NAMSE's goal is to improve the life situation of each and every individual with a rare disease through a concerted effort. At the end of a three-year co-ordination process, which required the commitment of all of those involved in the healthcare sector, a total of 52 proposals for action were compiled and included in a National Plan of Action for People with Rare Diseases. From the very beginning of this process, it was possible to increase awareness for the plight of persons with rare diseases. The implementation of the National Plan of Action guarantees an equal place in day-to-day medical practice for these persons.

The policy proposals are based on a broad consensus among the participants and reflect a wide spectrum of tasks to be executed. They include concrete recommendations for action on information management, possible paths to diagnosis, care-giving structures and on the conduct of research into rare diseases. This is the result of the unrelenting commitment of the many experts who participated in the working groups and of those who were members of the Steering Committee.

There is much to be learned from rare diseases. They pose a challenge that requires our collective efforts. As clear symptoms are often lacking, complex, interdisciplinary and multiprofessional diagnosis and treatment become necessary. These are the challenges that are to be met by the creation of centers of expertise so as to concentrate the know-how in the field and to support further research into rare diseases. The goal is to have patients referred as quickly as possible to the center that is right for them. The targeted transfer of knowledge lies at the heart of the efforts on both the national and the European level, in order that those affected may receive competent medical care, preferably near to their loved ones and in their native tongue.

Research into rare diseases remains of great interest because their study often unearths many basic biomedical relationships that serve to identify the causes of other, more common diseases. It will thus remain an important goal to intensify the research in this area. The Action Plan provides an essential contribution to the goals of the Health Research Framework Program of the Federal Government.

The important role of patient organizations among those afflicted as well as among others active in the healthcare system becomes especially striking in the case of rare diseases. Here, patients and their relatives often represent important bearers of knowledge in their respective area. Connecting their knowledge with the expertise present among the healthcare providers is possible only by linking them together in large organizations such as the Alliance of Chronic Rare Diseases (ACHSE e.V.).

This publication of these policy proposals concludes the first phase of the National Action Plan. Thereafter the real work begins – implementing and monitoring the suggested proposals. The NAMSE coordinating office intends to continue its support to all of the NAMSE's partners. The common goal of all partners in this effort should be to ensure that NAMSE and its coordinating office become a sustainable, self-supporting structure in the future. This in turn would serve to guarantee that the key actors in the German healthcare system cooperate in the future to shoulder the common responsibility of caring for persons with rare diseases.

We would like to especially thank all participating experts in the working groups and the members of the Steering Committee for their excellent work in realizing the National Plan of Action. The fact that Germany now also has its own National Plan of Action for People with Rare Diseases is the joint achievement of all involved.

We wish all the best for the implementation phase!

Daniel Bahr
German Minister
of Health (BMG)

Johanna Wanka
German Minister of
Education and Research (BMBF)

Christoph Nachtigäller
President of ACHSE e.V.

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List of Abbreviations

ACHSE e.V.	Allianz Chronischer Seltener Erkrankungen e.V.
AOLG	Arbeitsgemeinschaft der Obersten Landesgesundheitsbehörden
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.
AWMF-IMWi	AWMF -Institut für Medizinisches Wissensmanagement
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
BAG SELBSTHILFE e.V.	Bundesarbeitsgemeinschaft Selbsthilfe von Menschen mit Behinderung und chronischer Erkrankung und ihren Angehörigen e. V.
BÄK	Bundesärztekammer
BMAS	Bundesministerium für Arbeit und Soziales
BMBF	Bundesministerium für Bildung und Forschung
BMFSFJ	Bundesministerium für Familie, Senioren, Frauen und Jugend
BMG	Bundesministerium für Gesundheit
BPI	Bundesverband der Pharmazeutischen Industrie e.V.
BPtK	Bundespsychotherapeutenkammer
BVA	Bundesverwaltungsamt
BVMed	Bundesverband Medizintechnologie e.V.
BZÄK	Bundeszahnärztekammer
DFG	Deutsche Forschungsgemeinschaft
DGKJ	Deutsche Gesellschaft für Kinder- und Jugendmedizin
DIMDI	Deutsches Institut für Medizinische Dokumentation und Information
DKG	Deutsche Krankenhausgesellschaft e.V.
DNebM	Deutsches Netzwerk Evidenzbasierte Medizin
DPR	Deutscher Pflegerat e.V.
EBM	Einheitlicher Bewertungsmaßstab
ELSA	Ethische, rechtliche und soziale Aspekte der modernen Lebenswissenschaften und der Biotechnologie
E-Rare	ERA-Net für Forschungsprogramme zu Seltenen Erkrankungen
EU	Europäische Union
EUROPLAN	European Project for Rare Diseases National Plans Development
EURORDIS	European Organisation for Rare Diseases
G-BA	Gemeinsamer Bundesausschuss
GKV	Gesetzliche Krankenversicherung
GVG	Gesellschaft für Versicherungswissenschaft und -gestaltung e.V.
ICD	International Classification of Diseases
IIT	Investigator-Initiated-Trials
IMPP	Institut für medizinische und pharmazeutische Prüfungsfragen
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IRDiRC	International Rare Diseases Research Consortium
KBV	Kassenärztliche Bundesvereinigung
KZBV	Kassenzahnärztliche Bundesvereinigung
MDK	Medizinischer Dienst der Krankenversicherung
MDS	Medizinischer Dienst des Spitzenverbandes Bund der Krankenkassen
MFT	Medizinischer Fakultätentag der Bundesrepublik Deutschland
MVZ	Medizinisches Versorgungszentrum
NAMSE	Nationales Aktionsbündnis für Menschen mit Seltenen Erkrankungen
NCBI	National Center for Biotechnology Information
NGS	Next Generation Sequencing

NIH	National Institutes of Health
NKLM	Nationaler Kompetenzbasierter Lernzielkatalog Medizin
NKLZ	Nationaler Kompetenzbasierter Lernzielkatalog Zahnmedizin
PKB	Patientenorientierte Krankheitsbeschreibungen
PKV	Verband der privaten Krankenversicherung e.V.
SE	Seltene Erkrankungen
SGB	Sozialgesetzbuch
SOP	Standard Operating Procedure
TMF	Technologie- und Methodenplattform für die vernetzte medizinische Forschung e.V.
UPD	Unabhängige Patientenberatung Deutschland
VDGH	Verband der Diagnostica-Industrie e.V.
VF	Versorgungsforschung
vfa bio	Biotechnologie im Verband der forschenden Pharma-Unternehmen (vfa)
VUD	Verband der Universitätsklinika Deutschlands e.V.
WHO	World Health Organization

1. Introduction

Rare does not always mean rare: In Germany alone some four million persons suffer from so-called "rare diseases" – in the EU the number is estimated to lie at around 30 million.[1] According to the definition now valid in Europe, a disease is deemed "rare" if it afflicts no more than 5/10,000 persons in the general population.[2] The rare diseases comprise a very heterogeneous group of mostly complex syndromes that are generally chronic and reduce the quality of life and/or the life expectation of the persons afflicted. Some 80 percent of these diseases are genetic, and most are incurable.[3] Characteristic of these diseases is also that they are usually systemic, i.e., they affect multiple organs. In many cases they first appear during childhood or adolescence. Because of the severe course these diseases often take and the (relatively) high number of persons affected, rare diseases are considered to be of major significance.

Today, the awareness of the challenges posed by rare diseases is increasing both in Germany and in the rest of Europe. The crucial insight is that, because of the low overall number of persons afflicted by the estimated 7,000 to 8,000 different rare diseases, substantial improvement to the health situation of persons with rare diseases can occur only through a concerted cooperation at the European level. The Council of the European Union has thus recommended that each member country prepare its own respective national action plan as well as establish national centers for research and treatment. The goal is the targeted transfer of knowledge among the various countries of the EU to ensure proper local medical competence in the patient´s home country and native language. Establishing centers of expertise should serve to concentrate existing expertise and support in the field of rare diseases. This goal represents one of the major objectives of the German National Plan of Action presented in this publication.

The fact that the diseases in question rarely exhibit is a detriment to the establishment of research and medical care from both medical and economic vantage points. Persons with these diseases are thus confronted with a number of difficulties surrounding both the diagnosis and therapy of their diseases.

[1] Kaplan, W. & Lang, R. (2004), p. 95.
[2] Decree (EG) No. 141/2000 (2000), Preamble Para. 5
[3] Wetterauer, B. & Schuster, R. (2008), p. 519

1.1 The Overall Health Situation of Persons with Rare Diseases

In 2009, the German Federal Ministry of Health (BMG) published a research report entitled "Measures to improve health in people with rare diseases."[4] The goal of this study was, first, to analyze the care presently afforded to persons with rare diseases in Germany and, second, to develop ways and means as well as concrete suggestions and solutions for improving their lot.

This report reached the following conclusions:

- The situation surrounding rare diseases is highly important and relevant.
- Only little information is presently available concerning many forms of rare diseases, and even this limited information is not widely available.
- Patients with rare diseases are in need of comprehensive and specialized care.
- With many rare diseases there are no safe diagnostic methods, and information about the disease is not readily available.
- It would appear that the complexity and heterogeneity of rare diseases are not properly reflected in the existing remuneration system for outpatient medical care.
- For many rare diseases no adequate medication therapy is available.
- Intensive research into rare diseases is paramount to the future care of afflicted persons.
- A National Action Plan for People with Rare Diseases should be prepared by a National Action League.

1.2 Development and Methods of a National Action League

The results of this research report point clearly to the need to improve the pluralistic health care system in Germany to include the prevention, diagnosis and therapy of rare diseases. This is possible only through the concerted efforts of existing initiatives and the establishment of common, coordinated and targeted actions of all involved. To this end, in order to create this crucial prerequisite for improving the health situation in the area of rare diseases, on 8 March 2010 the National Action League for People with Rare Diseases (Nationales Aktionsbündnis für Menschen mit Seltenen Erkrankungen, NAMSE) was founded at the behest of the German Federal Ministry of Health. Together with the German Federal Ministry for Education and Research (BMBF) and the Alliance of Chronic Rare Diseases (Allianz Chronischer Seltener Erkrankungen, ACHSE e.V.), NAMSE became a national council responsible for coordinating and publishing the common efforts. The primary goal of NAMSE is to prepare suggestions for establishing a National Action Plan for People with Rare Diseases by 2013 as well as supporting the establishment of national centers of expertise. With this step Germany will have fulfilled the respective recommendation of the European Union for an Action in the Field of Rare Diseases.[5]

[4] Bundesministerium für Gesundheit (2009): Maßnahmen zur Verbesserung der gesundheitlichen Situation von Menschen mit Seltenen Erkrankungen. Available online at http://www.bmg.bund.de/fileadmin/dateien/Downloads/Forschungsberichte/110516_Forschungsbericht_Seltene_Krankheiten.pdf

[5] Recommendation of the Council of the European Union of 8 June 2009 on an Action in the Field of Rare Diseases (2009/C 151/02).

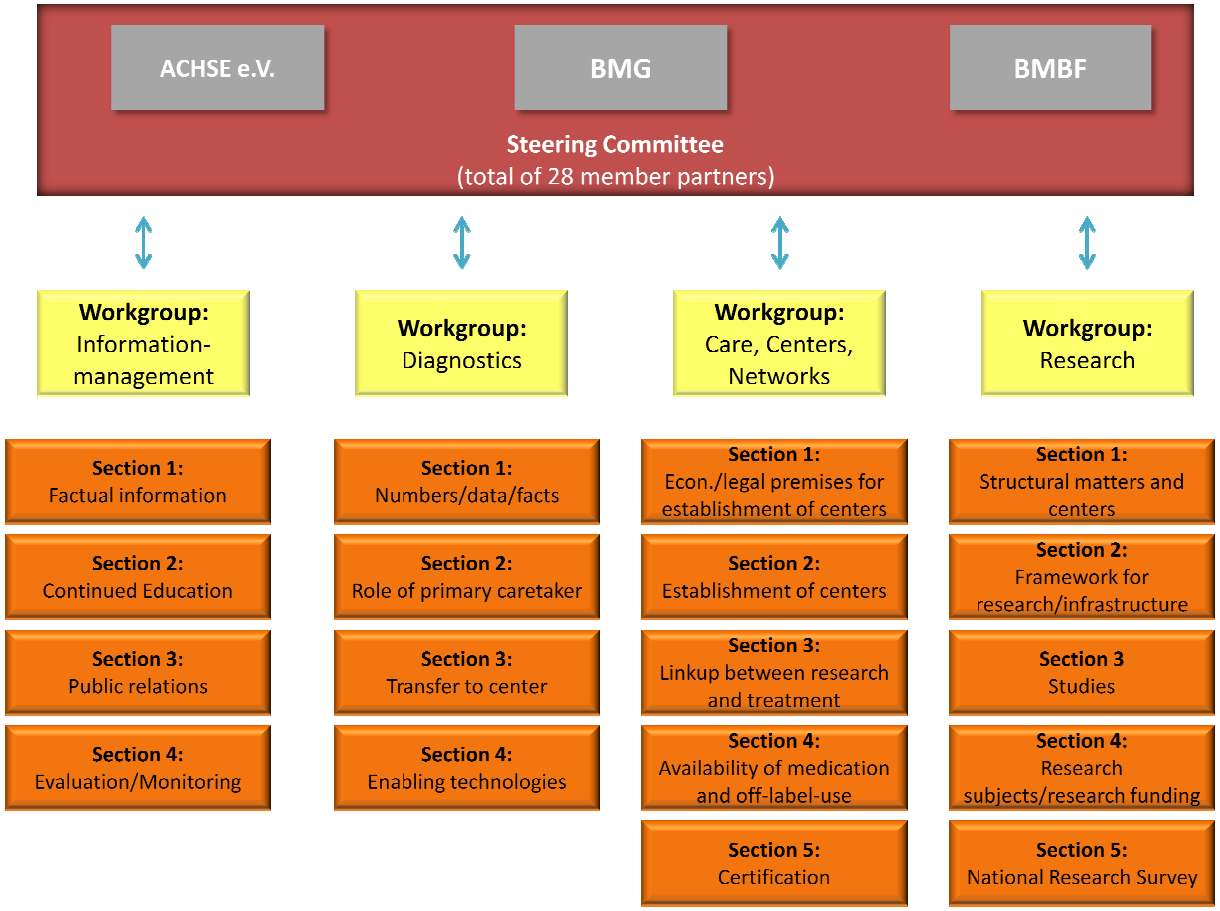
All essential partners from the health care system involved with rare diseases (both central and umbrella organizations) are participants in the National Action League. By accepting the common declaration (cf. Appendix 1) they have reinforced their will to establish the necessary prerequisites to ensure a long-term and effective improvement in the health situation of persons with rare diseases.

Partners of NAMSE:

- Allianz Chronischer Seltener Erkrankungen e.V. (ACHSE e.V.)
- Arbeitsgemeinschaft der Obersten Landesgesundheitsbehörden (AOLG), represented by the respective federal state holding the chair
- Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften e.V. (AWMF)
- Beauftragter der Bundesregierung für die Belange der Patientinnen und Patienten
- Bundesarbeitsgemeinschaft Selbsthilfe von Menschen mit Behinderung und chronischer
- Erkrankung und ihren Angehörigen e.V. (BAG SELBSTHILFE e. V.)
- Bundesärztekammer (BÄK)
- Bundesministerium für Arbeit und Soziales (BMAS)
- Bundesministerium für Bildung und Forschung (BMBF)
- Bundesministerium für Familie, Senioren, Frauen und Jugend (BMFSFJ)
- Bundesministerium für Gesundheit (BMG)
- Bundespsychotherapeutenkammer (BPtK)
- Bundesverband der Pharmazeutischen Industrie e.V. (BPI)
- Bundesverband Medizintechnologie e.V. (BVMed)
- Bundeszahnärztekammer (BZÄK)
- Deutsche Forschungsgemeinschaft (DFG)
- Deutsche Krankenhausgesellschaft e.V. (DKG)
- Deutscher Hausärzteverband e.V.
- Deutscher Pflegerat e.V. (DPR)
- Gemeinsamer Bundesausschuss (G-BA)
- GKV-Spitzenverband
- Kassenärztliche Bundesvereinigung (KBV)
- Kassenzahnärztliche Bundesvereinigung (KZBV)
- Medizinischer Fakultätentag der Bundesrepublik Deutschland (MFT)
- Orphanet-Deutschland
- Verband der privaten Krankenversicherung e.V. (PKV)
- Biotechnologie im Verband der forschenden Pharma-Unternehmen (vfa bio)
- Verband der Universitätsklinika Deutschlands e.V. (VUD)
- Verband der Diagnostica-Industrie e.V. (VDGH)

NAMSE consists of a Steering Committee and four workgroups. The Steering Committee in turn consists of the representatives from the 28 member partners of NAMSE. This committee set the goals and defines the methods in accordance with the results of the research report. Thus, the four workgroups were founded to implement the four major action fields “information management,” “diagnostics,” “care/centers/networks” and “research.” Members of these workgroups are high-ranking experts from the respective fields.

Figure 1. Organizational structure of NAMSE



1.3 Action Fields and Goals of the National Plan of Action

The National Action Plan has two main goals: to prepare policy suggestions and proposed actions. The policy suggestions and proposed actions contained in this publication were prepared by the workgroups and adopted by common accord by the Steering Committee. In addition, a number of background publications were prepared during this process in order to further explore the respective action fields and to intensify the work with the individual issues. These background publications stem from the consultation process that took place in the respective workgroups. They serve as a basis for preparing the decisions in the Steering Committee to accept or reject policy suggestions and proposed actions. They do not necessarily reflect the position of all persons involved.

At the beginning of the process, the workgroups received their mandates in the form of a manual describing the respective action fields and goals, as follows:

Action field: Care/centers/networks
Goals:

- Define the various steps to be taken by the centers and networks and prepare their implementation

- Define the range of tasks and methods to be employed by the centers and networks as well as the criteria for identifying and designating these organizations
- Develop suggestions for the long-term funding of such centers and networks
- Optimize the supply of both approved medicines and off-label-use medicines

Action field: Research
Goals:

- Improve the overall conditions for research and development in the area of rare diseases
- Accelerate the transfer of research knowledge to practical applications
- Improve research on optimizing therapy
- Improve health services research

Action field: Diagnostics
Goals:

- Accelerate the diagnostics of rare diseases
- Develop strategies for dealing with an unclear diagnosis
- Improve the design of guidelines

Action field: Information management
Goals:

- Increase awareness for rare diseases in both the general public and among experts
- Improve the level of information available to and information procurement by those afflicted, their relatives, doctors, therapists and caretakers
- Improve the training and further education of medical, therapeutic and caretaking personnel

These action fields and goals were modified and adapted in the course of the work process. The final goals are contained in the catalogue of proposed actions of the National Action Plan.

The members of the Action Coalition have come to the conclusion that patient organizations to improve the medical treatment situation of persons with rare diseases should play a central role in all further actions and become a cross-sectional issue within the National Action Plan. This subject is elaborated on in Chapter 2 concerning the importance of patient organizations. Further, the area of "**Patient Orientation**" was adopted as an independent field of action across all workgroups. The action field "**Registries**" was also recommended as a further cross-sectional theme.

2. The Importance of Patient Organizations in Patient-Oriented Care

Patient organizations are becoming an increasingly important factor in the health care system. They now play an important role in sustaining health, dealing with problems and fostering healthy ways of living, in particular for persons living with chronic diseases, disabilities or a chronic rare disease. The greatest advantage of patient organizations lies in the mutual help offered in support of those directly affected (and their relatives) by other affected persons, in order to better deal with the specific disease or disability.

Patient organizations are characterized by the intensive exchange of information and the bilateral support they afford. They offer qualified counseling, organize informational and training events, publish relevant informational materials and join in local and national debates at both the technical and political level. Since 2004, such organizations have also become directly involved in the health care system through what is known as 'structured patient participation'. In this scheme, representatives of the various patient organizations introduce the knowledge they have gained, through a regular exchange of ideas and opinions with affected persons, into the various committees that play a role in the health care system, in particular in those of the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA). The joint aim of all involved is the improvement of patient orientation throughout the health care system.

Vigorous activity on the part of patient organizations serves to empower those affected, to improve the quality of care and to strengthen research activities

Patient organizations are particularly welcome in situations in which there are deficits in the existing care or where research in rare diseases is lacking. Patient organizations for persons with rare diseases arose primarily because detailed information concerning these illnesses and their care was lacking. They have since provided many impulses for continued research efforts, for example in the form of scientific studies.

People with rare diseases are well aware of the fact that it is essential for research to be carried out in order to develop treatments to extend their lives and improve their quality of life. Persons suffering from a rare disease and their representatives emphasize the need to strengthen research in this entire area. This is particularly the case with the ethical questions that arise, for example, with regard to diseases that tend to manifest during childhood. When assessing ethical issues, the personal situation and perspective of those affected by a rare disease plays a special role in the weighting of the various interests. Thus, from the patient organization's point of view, it would be desirable for ethics committees to consider including a representative of the relevant patient organization (or of the patient organization for all rare diseases) in each of the committees. In particular it is recommended that a patient representative be heard on opinions regarding the conduct of clinical studies.

In a situation in which hardly anything is known about a particular disease, patient organizations are especially important as their great strength lies in mutual support. Those affected by a rare disease are often the only ones who can truly understand what someone else is going through and giving that person the assurance that they are not alone with their fate. The reciprocal exchange of information serves to gather and expand the knowledge available about a particular disease, its treatment and experts who can potentially help to deliver treatment. Patient organizations offer the best opportunity to bring together people who are dealing with a particular disease, such as doctors, therapists and scientists, from the various disciplines and from different parts of the country. The knowledge accumulated in this manner and the expertise provided by those living with a rare disease, as well as the networking among the various patient organizations, fosters general awareness and increases the quality of the healthcare provided and the research into rare diseases. Thus, the support of patient organizations is also a service to all persons who will be affected in the future.

To be effective, patient advocacy requires a framework that provides sufficient support

Persons with rare diseases are confronted with the large breadth and complex nature of their disease while also having to deal with a wide range of persons who are involved with their care. Sources of information and support are difficult to find. The rareness of the specific disease may make it extremely difficult to find a sufficient number of representatives willing to serve in the various political, self-administration and patient organization bodies; the networking of research, healthcare professionals and industry may prove insurmountable. Anyone who in addition to coping with their own disease, or that of their relative, while securing their own livelihood finds the time and energy to become involved, politically or professionally, on a voluntary basis clearly needs support. Competent participants require good further education to acquire the many skills and competences that are necessary and they also need adequate financial support to master the multitude of tasks before them. A health care system that makes the patient its focal point needs the self-help activities of those directly affected in order to guarantee proper patient orientation. Good patient advocacy needs a proper framework to be effective. Very often, assuring the long-term participation of patient organizations at a high level of competence is possible only with the support of qualified, full-time employees at the patient organizations.

3. Action Fields, Recommendations and Proposed Actions

This chapter deals with the various action fields of the National Action Plan which provide concrete proposed actions to ensure long-term improvements in the prevention, diagnosis and treatment of rare diseases. The description of these action fields follows a set structure. First, at the beginning of each subject area, the current situation, including any existing problems, are outlined in a short introductory text. Then, recommendations and concrete proposed actions are delineated. The proposed actions also include a timeline[6] that specifies when the action is to commence and which institutions and bodies are to participate in its execution.

For better comprehension, a glossary of terms has been added to the individual action fields to explain the relevant terminology.

3.1 Action Field: Care, Centers, Networks

Rare diseases are often systemic, that is, they manifest in multiple organ systems simultaneously. Sometimes clear guiding symptoms are missing, so that complex, interdisciplinary and multi-professional diagnostic and treatment procedures become necessary. The rarity of these individual diseases renders their treatment and the research into their nature difficult, for both medical and economic reasons. This situation confronts patients affected by these diseases with special problems as they are dependent on receiving highly qualified and specialized care.

Even though, in many cases, the necessary expertise is available, often transparent opportunities for patients and their doctors, as well as a concept for a needs-based creation of centers of expertise and networks are lacking. Rather it is the case that access to care opportunities is largely accidental. The goal of NAMSE is to further the establishment of centers of expertise and to facilitate the financial framework conditions.

Medication therapy also plays a major role in the care of persons with rare diseases. Even though many rare diseases cannot, or can only marginally, be treated with medicinal products, the provision of medicines is frequently the only potential line of treatment. In principle, medication therapy can take the form of medicinal products specifically authorized for the disease, so-called orphan drugs, or the form of medicinal products approved for other indications - so-called off-label use.

For many of the rare diseases, however, no drug treatment is available owing to the lack of incentives for research and development. Furthermore, the off-label use of medicinal products brings with it a number of uncertainties with regard to their use and reimbursement by the health insurance system, since clear evidence for their efficacy is often lacking. Chapter 3.1.2, which deals in greater detail with the role of orphan drugs, off-label use and evidence generation, will be presenting recommendations

[6] Short-term = 1 to 2 years; medium-term = 3 to 5 years; long-term = over 5 years.

and proposed actions aimed at mitigating the most urgent problems outlined above and improving the availability of medicinal products to treat rare diseases.

3.1.1 The Center Model for Rare Diseases

The identification of centers of expertise is one of the main proposals contained in the Council Recommendation on an Action in the Field of Rare Diseases. In particular, it recommends that Member States: (a) identify or create appropriate centers of expertise (b) foster the participation of national centers of expertise in existing European reference networks, (c) create structures that facilitate the cooperation of specialists and the exchange of experts and expert knowledge in this area, on both the national and international level, (d) consider the use of modern information and communication technologies to enable all necessary special medical treatment to be provided, where necessary from a distance, (e) create the requirements for the dissemination of the expert knowledge necessary to treat rare diseases patients locally, (f) encourage the treatment of all persons with rare diseases to be based on a multidisciplinary approach.

Some centers of expertise have a special role to play since, as reference centers, they are a fundamental component of a Europe-wide reference network for rare diseases, as called for in Directive 2011/24/EU on the application of patients' rights in cross-border healthcare. The European Union Committee of Experts on Rare Diseases (EUCERD) published a recommendation on quality criteria for centers of expertise for rare diseases in Member States in October 2011.

Recommendation: NAMSE recommends the establishment of centers for rare diseases at three different, cross-linked levels of specialization. These levels are not to differ in the quality of the care they provide, but only in the spectrum of services they offer. They are to be embedded in the local healthcare structures in both primary and specialist care. The three levels of specialization in the model of cross-linked centers for rare diseases are to be differentiated according to whether the treatment they offer is outpatient/inpatient or disease (group) specific/non-disease specific. [7]

The type C centers (cooperating centers for a specific rare disease/disease group x)[8] are to be responsible for disease-specific or disease-group specific, interdisciplinary and multiprofessional outpatient care. A type C center (cooperating center) is to be primarily concerned with delivering concrete care for patients with a confirmed diagnosis or a clear suspected diagnosis. Type C centers may include non-hospital subspecialized practices, group practices, medical care centers or hospitals.

Type B centers (centers of expertise for a specific rare disease or disease group x)[9] are also to be organized around certain specific rare diseases or rare disease groups for patients with a confirmed diagnosis or a clear suspected diagnosis. However, they are to offer not only outpatient but also inpatient, interdisciplinary and multiprofessional care. Thus, the type B center (center of expertise) is to be an established hospital that is equipped to deal with a specific rare disease or rare disease group both on an inpatient and an outpatient basis.

[7] The main precondition for establishing a center model is an official statement concerning financing. Thus, any measures of the National Action Plan that are concerned with the establishment of centers of expertise can be implemented only after the center model has been firmly established. Such measures are denoted in the following by the use of an asterisk (*).
[8] Hereinafter type C centers (cooperating centers).
[9] Hereinafter type B centers (centers of expertise).

Type A centers (reference centers for rare diseases, with centers of expertise for xyz)[10] are to consist of more than two type B centers (centers of expertise) and offer, in addition, special non-disease specific structures (e.g. for the treatment of patients with unclear diagnoses, patient guides, interdisciplinary case conferences, innovative special diagnostics). Type A centers (reference centers) are to be the referral center for patients with an unclear diagnosis; they are also to do basic and clinical research and they are entitled to provide training tools and training sessions covering the medical dimension of care for undergraduate medical students at medical school.

The **individual non-disease specific interdisciplinary tasks** of the type A centers (reference centers) are to be as follows:

- To guide patients with specific diagnostic or therapeutic needs to their proper place within the system (seamless patient pathway and, if necessary, national and Europe-wide routing).
- To provide standardized methods of diagnosis for patients with an unclear diagnosis who demonstrate a high probability of having a rare disease. Type A centers also participate in remote diagnostic procedures (e.g., telemedicine, teleconsultation, symposia to review unclear diagnoses and standard operating procedures between the centers; the latter are especially important with respect to the role of the European reference networks).
- To provide comprehensive resources that can be used centrally for multiple medical facilities and multiple rare diseases, such as patient registries, biobanks, innovative special diagnostics, etc.
- To offer a range of continuing medical education courses for the specific rare diseases in cooperation with the patient organizations.
- To participate in the European reference networks for rare diseases in accordance with the provisions of Directive 2011/24/EU of the European Parliament and the European Council.[11]
- Together with the type B centers (centers of expertise), to develop uniform recommendations for the diagnosis and therapy of rare diseases, which are regularly updated in accordance with the newest scientific evidence. These recommendations are then to form the basis for patient care at all three levels (types A, B and C).
- Together with type B centers (centers of expertise), to support the work of the type C centers (cooperating centers) with special diagnostics and procedures for confirming diagnoses.
- To provide a multidisciplinary research infrastructure where both basic and clinical research as well as research into healthcare provision can be carried out.

Because of the large number of rare diseases, no single type A center (reference center) will be able to cover the entire spectrum of possible diseases. So as to be able to cover as many rare diseases as possible, a national network of type A centers (reference centers) is necessary to provide a coordinated effort for the diagnosis of unclear cases, to conduct training, continuing and further medical education and to develop quality standards for documentation.

Further, type A centers (reference centers) should be cross-linked to all type B centers (centers of expertise) and type C centers (cooperating centers). They could provide support for activities such as patient documentation (registries), diagnosis confirmation, counseling and consultancy, and compliance with the newest therapy recommendations and integrate the type B centers (centers of exper-

[10] Hereinafter type A centers (reference centers)

[11] Directive 2011/24/EU of the European Parliament and the European Council of 9 March 2011 on the application of patient rights in cross-border healthcare. Available online at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:088:0045:0065:DE:PDF

tise) and the type C centers (cooperating centers) in research activities, in particular in clinical studies and health services research. To this end they are to provide the necessary infrastructure (e.g., software). A preliminary list of the criteria to be met can be found in Appendix 2 to this publication. Of course, this list is not final and needs to be further developed, concretized and operationalized in order to serve as a basis for any future designation process.

Any facility seeking to belong to one of the three levels of care described above will have to provide proof that it fulfills the criteria listed in the then finalized list of criteria. This assumes the development of a transparent and replicable method of designating the three different types of rare disease centers. Such proof of competence will serve as a signal to both providers and patients that the institution has been designated based on objective criteria. It can be assumed that, in the first phase, the designation will be based on a self-declaration by the applicant center, which the NAMSE Coordinating Office will examine for completeness and plausibility based on the documents submitted along with the self-declaration. In the beginning, no further examination, such as on-site inspections or the review of the fulfillment of criteria, is foreseen. However, a proper designation body will have to be created as soon as possible to ensure compliance with the criteria. The structures for the certification of cancer centers in Germany may serve as a model in developing this designation body. The designation awarded by this body is to be valid for 3 years.

NAMSE has already described the existing possibilities for funding outpatient care structures in the German healthcare system. Funding options were outlined for all three types of centers within the existing legal framework. The following were discussed in detail with respect to their suitability for funding the three types of centers of expertise: (1) Highly specialized outpatient care (§116b Social Code Book V), (2) care by panel doctors and dentists (§§95ff Social Code Book V) including care provided by hospital physicians or clinics authorized to provide outpatient care (§§116, 116a Social Code Book V), (3) enabling provisions for university outpatient clinics (§117 and 120 Social Code Book V) as well as social-pediatric centers (§119 Social Code Book V). In addition, besides the collective agreements, there are the selectively contracted conditions for remunerating special services within the framework of integrated care (§§140a ff Social Code Book V) or specialized medical care (§73c). However, selectively contracted solutions have proven to be unsuitable for ensuring universal access to care for the small numbers of persons affected because of the specific challenges faced in the area of rare diseases. Instead, the existing funding possibilities offered by collective contracts are to be used to finance the systematic implementation of the three-tiered structure of centers for rare diseases. The NAMSE partners will urge that the necessary funds that are not already included in the existing standard remunerations be made available by the payers.

Proposed action 1:

Existing funding options are to be used to ensure funding for the three-tiered structure of the centers for rare diseases. Special healthcare services for treating persons with rare diseases, in particular type A centers (reference centers), are to be taken into account within the framework of the negotiations for the remuneration of inpatient and outpatient care. In an advisory capacity, representatives of patient interests will work together with representatives of both the healthcare providers and the third-party payers to clarify the common criteria and requirements for funding the centers. They shall work together to ensure that the third-party payers can agree locally to provide the funds not already included in the existing standard remunerations. Once questions of funding and implementation have been resolved, it is recommended that the care providers implement the three-tiered model of “Cen-

ters for Rare Diseases (A, B, C)" in accordance with the suggested definition, taking into account the agreed preliminary list of the criteria to be met[12] (see Appendix 2).

Implementation: short-term
Responsible bodies: DKG (German Hospital Federation), VUD (Association of University Clinics in Germany), GKV-Spitzenverband (Federal Association of Statutory Health Insurance Funds), healthcare providers

Proposed action 2:

Suitable healthcare providers desiring to be designated as centers of expertise for rare diseases type A (reference center), type B (center of expertise) or type C (cooperating center) according to the proposed definition of the NAMSE three-tiered model of centers for rare diseases and taking into account the commonly agreed upon criteria[13], should make this known to the NAMSE Coordinating Office. In the course of a transparent preliminary procedure that must be equally accepted by all parties involved, including the patient representatives, the NAMSE Coordinating Office will examine the declaration of intent, substantiated by the evidence submitted, to determine completeness and plausibility. A central designating body analogous to that found in the certification procedure for the German cancer centers should be set up as quickly as possible. The designating body will issue designations valid for 3 years. In this entire process, the establishment of standards, the inspection of conformity to these standards, designation by an appropriate coordinating office, as well as an independent committee structure should be kept as separate from one another as possible. The designated centers of expertise are to be listed in an overview on the homepage of the coordinating office with reference linking for both providers and patients.

Implementation: short-term
Responsible bodies: NAMSE partners

Proposed action 3:

Two years after the implementation of the National Action Plan, the German Federal Ministry of Health (BMG) shall, together with the other NAMSE partners, evaluate the designation process and determine whether the funding elements contained in the existing standard remunerations are sufficient to fund the centers of expertise or whether new legislation is necessary.

Implementation: medium-term
Responsible bodies: German Federal Ministry of Health, NAMSE partners

3.1.2 Orphan Drugs, Off-Label Use and Evidence Generation

Once a diagnosis has been established, the ensuing decisions regarding further treatment, including initial dosage determination in the context of medication therapy as well as regular reviews of treatment outcomes should take place, where possible, in the center in question. Insofar as regular administration of the prescribed, authorized medicinal product by a physician is necessary, and the feedback to the center is guaranteed, the administration of the medicinal product should be carried out by a

[12, 13] The catalogue of criteria is preliminary and serves as a guide only. It must be updated and further developed as necessary.

physician, in keeping with the desire to provide high-quality care for patients with a rare disease in their proximity. In the process, it should be borne in mind that, hitherto, the various interfaces in the treatment chain (inpatient, outpatient, rehabilitation) have caused interruptions in the care provided, with negative repercussions for patient welfare. Further to the problem of interface management, difficulties may arise with the subsequent prescriptions in the context of outpatient care by the physician responsible for further care, following initial treatment at the center. The question of whether regulations should be expanded to allow the certification of special services in the non-hospital/ outpatient sector such as private practices for the care of rare diseases should be taken up after monitoring how the system works in practice. In the context of inpatient care in hospitals and in rehabilitation facilities, financing the supply of orphan drugs may also be a problem, regardless of whether or not this inpatient care was due to a rare disease.

With rare diseases, it can naturally be expected that medication therapy will, of necessity, involve off-label prescribing. Since both the statutory and the private health insurance, as well as the agencies providing health insurance assistance for civil servants, are accustomed to bearing the costs of off-label use in cases of rare diseases (although frequently little empirical evidence is available for such off-label use), the third-party payers have an inherent interest in eliminating this lack of evidence, and therefore an interest in the conduct of methodologically appropriate studies. Thus, the goal should be to generate the best possible evidence of the effectiveness of the off-label use of these medicinal products.

Recommendation: NAMSE supports guaranteeing and optimizing the quality-assured treatment of patients with authorized medications for rare diseases, including the local care of patients in everyday life. It must be ensured that, following initial prescribing and regular monitoring of the treatment at a center of expertise, follow-up prescribing by office-based panel doctors (non-hospital physicians) or local hospitals should be possible.

In order to improve the availability of medicinal products for rare diseases and to provide evidence supporting this use, NAMSE further recommends the generation of the necessary data documenting the extent of off-label use of medicinal products for rare diseases.

Proposed action 4:

Given the problematic situation described in the Introduction to this publication, efforts are being made to determine whether further measures for procuring medicinal products for persons with rare diseases are still necessary once the center model for rare diseases has been implemented.

Implementation: medium-term*[14]
Responsible bodies: BMG (German Federal Ministry of Health), the self-administration structure, ACHSE e.V., type A centers (reference centers), type B centers (centers of expertise) or type C centers (cooperating centers)

Proposed action 5:

Within the framework of a health services research study based on the available data, a first step will seek to describe the care of patients with rare diseases using orphan drugs during inpatient care in a

[14] Once the center structure has been established.

hospital as well as during inpatient rehabilitation, regardless of whether or not this inpatient care was due to a rare disease. In the process, special attention should be given to the potential problems with the funding of orphan drugs, as well as the approach taken hitherto with the problems encountered. On this basis, the need for supplementary measures should also be investigated.

Implementation: Short-term
Responsible bodies: GKV-Spitzenverband (Federal Association of Statutory Health Insurance Funds), DKG (German Hospital Federation), BMG (German Federal Ministry of Health)

Proposed action 6:

An expert opinion is to be commissioned to examine the possibilities of gleaning knowledge from the routine provision of patients with authorized medicinal products and the off-label use of medicinal products. This should include investigating in advance which data from routine use can be put to good use. Worthy of consideration would be data from healthcare providers, which are gathered as part of the statutory obligation to document treatment, as well as data transmitted to the statutory insurance funds in the course of the invoicing process. In the latter case, use can be made of the data that are transmitted by the Federal Office of Administration (BVA), in compliance with the Ordinance on Data Transparency, to the German Institute for Medical Documentation and Information (DIMDI), which places them in anonymous form at the disposal of specific user circles. However, these data are not likely to be available before the end of 2013.

The expert opinion in question should, in particular, address the question of which of the data that are currently being collected can be used for this purpose, how data collection can be expanded and, if necessary, medical documentation standardized in such a way as to generate such information from the day-to-day provision of medical care. In addition, the usefulness of this additional knowledge (for example, in generating new hypotheses or controlling the flow of patient care) should be weighed against the necessary expenses. Note that this shall be without prejudice to the evidence hierarchy established by the Federal Joint Committee of Physicians and Health Insurance Funds (G-BA).

Implementation: Short-term
Responsible bodies: BMG (German Federal Ministry of Health)

Proposed action 7:

(a) A study to determine the extent of off-label drug use in rare diseases, based on the data gathered pursuant to §303a ff Social Code V (SGB V) in conjunction with the Ordinance on Data Transparency of the German Federal Ministry of Health of 10 September 2012, to be carried out by one of the institutions empowered pursuant to § 303e sub-sect. 1.
(b) Ranking of rare diseases according to their in terms of treatment with off-label drug use, based on the data gathered pursuant to §303a ff Social Code V (SGB V) in conjunction with the Data Transparency Act of the German Federal Ministry of Health of 10 September 2012, to be carried out by one of the research institutions empowered to do so.
(c) Evaluation of the results pursuant to Chapter 4 of the Rules of Procedure of the Federal Joint Committee of Physicians and Health Insurance Funds (G-BA) and, where applicable, commissioning by the G-BA of the expert commissions according to § 35c sub-sect. 1 Social Code V (SGB V) to determine the status of the existing scientific knowledge. If necessary, additional expert commissions according to § 35c sub-sect. 1 SGB V may have to be set up.

(d) Establish the infrastructure for clinical trials with medicinal products approved for human use that could be carried out at clinical trial centers specializing in rare diseases, particularly with respect to off-label use.

Implementation: Short and long-term*[15]
Responsible bodies: BMG (German Federal Ministry of Health), type A centers (reference centers), type B centers (centers of expertise), type C centers (cooperating centers), G-BA (Federal Joint Committee of Physicians and Health Insurance Funds), pharmaceutical companies

[15] Once the center structure has been established.

3.1.3 Glossary

Term	Definition
Evidence	Irrefutable fact
Expertise	Competence, expert knowledge
Hypothesis	Assumptions that are as yet unproved, but free of contradictions
Indication	Reason for administering a treatment or applying a diagnostic measure
Interdisciplinary	A merging of methods, approaches and opinions from different medical disciplines and/or professionals
Guide	Guide or helper through a healthcare system
Multiprofessional	Treatment by a number of different medical disciplines and/or professionals
Off-label use	Use of an authorized medicinal product beyond the intended and approved indication
Orphan drug	Medicinal products for rare diseases
Pharmacotherapy/Medication therapy	Treatment of a disease through the administration of medicinal product(s)
Systemic	Affecting the whole organism
Transsectoral	Beyond sectoral boundaries
Unclear diagnosis	An unclear diagnosis is defined as follows in this publication: (1) the existing symptoms do not allow for a clear diagnosis; (2) the main criteria for reaching a diagnosis are not fulfilled; (3) additional, significant symptoms not typical of the diagnosis are present.

3.2 Action Field: Research

Rare diseases comprise a very large field of research with a very heterogeneous state of knowledge. Nevertheless research into rare diseases is often an important entry point to gain knowledge of very basic biological processes and their pathomechanisms. In contrast to more widespread diseases, rare diseases may often be traced back to a few individual factors that are then in need of intensive and comprehensive study. In this sense research into rare diseases may also exert a profound influence on our general understanding of disease processes and thus be very important to our insights into more common diseases. The research landscape in Germany with respect to rare diseases has many facets but lacks a consistent structure. Research is presently done where local interests call for it and is directed mainly toward individuals and not toward structural units. There are indeed a number of good and very good initiatives, harboring local expertise and activities; yet there is little overarching coordination of these activities. A further important phenomenon is that only a marginal part of the estimated 7,000 to 8,000 known rare diseases have been researched to any depth. The following actions serve to intensify general research into rare diseases in the areas of fundamental research, clinical research and health services research as well as to improve the overall structural conditions of research into rare diseases.

3.2.1 Etiology and Genome Analysis

Generally speaking, rare diseases tend to be genetic. Over the past 25 years the genes responsible for about one fourth of the known 8,000 rare diseases have been identified. New methods of genome analysis (next generation sequencing, NGS; array comparative genomic hybridization or array-CGH to discover variations) have served to speed up the identification of the responsible genes considerably and provide completely new approaches to researching and identifying mutations in genetic diseases. These methods are complemented by other high-throughput methods, such as proteome analysis.

With these methods researchers are now in the position to drastically reduce the number of unknown rare diseases, to enable ever more targeted molecular diagnostics and to develop new diagnostic procedures and therapeutic agents. Comparing genetic norm variants (so-called polymorphisms) will also allow us to further investigate genetic factors for the variability of their morbidity and course of disease. This development should enable us to establish greater diagnostic and therapeutic differentiation. The goal is to identify the causes of most genetically determined rare diseases by the year 2020, analogous to the goals of the International Rare Diseases Research Consortium (IRDiRC).

However, high-throughput techniques to discover disease etiology and for genome analysis are complex, expensive and demand special expertise. Thus, to ensure their efficient application, it is paramount that the methods be concentrated and be made available at select centers.

Recommendation: NAMSE recommends that selected sequencing centers for rare diseases be established or supported, primarily in type A centers (reference centers). These sequencing centers should pursue the following tasks:

a) Do research into the genetic causes of previously unresolved rare diseases in order to improve their diagnostics
b) Join in national and international networks of clinical workgroups and coordinate the collection and preparation of biological material to resolve the question of phenotypes
c) Do research into and improve the techniques for using next generation sequencing (NGS) data in this context

d) Consolidate national and international databases on NGS diagnostics and phenotyping
e) Do research on and instigate discussions surrounding the medical-ethical conditions for carrying out research projects that involve genome information

Proposed action 8:

Set up and expand sequencing centers for rare diseases.

Implementation: short-term*[16]
Responsible bodies: German Federal Ministry for Education and Research (BMBF), type A centers (references centers), type B centers (centers of expertise) or type C centers (cooperating centers)

3.2.2 Pathophysiology and Disease Mechanisms

Because of the often monogenetic nature of rare diseases, they are particularly appropriate for determining causal mechanisms. Conclusive evidence on their molecular function as well as on the organ-specific effects and the pathophysiological relevance of the affected genes or the metabolic pathway(s) involved can usually be determined. Further, research into rare diseases can subsequently provide additional insight into other more common, in part multifactorial diseases – creating scientific findings that go far beyond the immediate goal of addressing rare diseases.

Research into the pathophysiology of unresolved rare diseases often begins by applying screening techniques independent of any hypotheses, e.g., the detection of differentially regulated mRNAs, microRNAs, lipids and proteins (so-called omics analysis) or the discovery of changes in the genetic material of cells or diseased tissues. The next step is to do in vitro and in vivo analyses, for which, according to the procedures of research, animal models are necessary. NAMSE supports this appraisal.

Proposed action 9:

Support research projects on rare diseases that comprise the use of animal or cell models to elucidate the pathophysiology of rare diseases.

Implementation: short-term
Responsible bodies: German Federal Ministry for Education and Research (BMBF), German Research Foundation (DFG), other research sponsors

3.2.3 Development of Diagnostic Test Systems

Because of the often monogenetic nature of rare diseases, they are particularly appropriate for developing diagnostic test procedures. Herein lies an enormous potential for developmental progress presently being driven by advances made in the fields of genomics and bioinformatics. New techniques of genome analysis will someday make it possible to determine the molecular causes for nearly all monogenic rare diseases. This in turn will lead to a massive increase in our knowledge of both the causes behind these diseases as well as in our ability to predict and treat them differentially. The knowledge won through translational research can be directly applied to existing problems. Nongenomic test procedures will also play an important role. However, commercial CE-labelled IVD kits will

[16] Once the center structure has been established.

not be available for the purpose of in-vitro diagnostics on the part of the manufacturers because of the low number of submitted samples and the lack of appropriate clinical material. For this reason, many test systems developed and employed at the research level will have to be funded through public subsidies. The development of biomarkers, for example, for follow-up purposes, will also pose a challenge because of the low number of relevant cases.

Proposed action 10:

Intensify research to develop diagnostic procedures for rare diseases.

Implementation: short-term
Responsible bodies: German Federal Ministry for Education and Research (BMBF), German Research Foundation (DFG), other research sponsors, diagnostics industry

3.2.4 Investigator-Initiated Trials: Prospective, Controlled Clinical Studies

Investigator-initiated trials (IIT) are presently being funded by the German Federal Ministry for Education and Research (BMBF) and the German Research Foundation (DFG). The pharmaceutical industry is also contributing considerably to this end. Preparing and carrying out IIT for rare diseases – in the hopes of developing new forms of therapy – is a more difficult task than with more prevalent diseases. Particularly with respect to funding, regulatory procedures as well as statistical planning and analyses, the demands are complex and require considerable additional and detailed knowledge not necessarily available in the individual centers. For this reason units dedicated to specialized clinical research in rare diseases are necessary.

Proposed action 11:

Specialization of clinical research units dedicated to the study of rare diseases.

Implementation: short-term*[17]
Responsible bodies: Type A centers (reference centers), German Federal Ministry for Education and Research (BMBF)

3.2.5 Health Services Research

In Germany, health services research has become an important interdisciplinary and transdisciplinary field of research in recent years. It is dedicated to the study of the medical and social care provided to persons with rare diseases. Its goal is to describe, analyze and evaluate such care using scientific methods as well as to map the further development, to provide counseling and, where needed, to intervene on an experimental and scientific basis. These efforts are carried out with the regular consultation of the patients themselves and their patient organizations. Among other things, health sciences research on rare diseases serves to determine the care needs of the various groups of rare diseases, to analyze existing care provisions for over- and undersupply as well as inappropriate approaches, and to suggest remedies to improve existing care. Studies on the psychosocial problems faced by patients with rare diseases as well as on possible new approaches are of particular importance.

[17] Once the center structure has been established.

It may be assumed that the extent, frequency and quality of care provided to patients with rare diseases in Germany varies considerably. In order to identify the most urgent research concerns in the care of patients with rare diseases in Germany and to expand the capacities in the area of health sciences research into rare diseases, NAMSE suggests the following policy proposals:

Proposed action 12a:

Induce a multidisciplinary discussion on the state of health services research in order to take stock of and identify gaps in the research on the care of rare diseases as well as possible solutions.

Implementation: short-term
Responsible bodies: German Federal Ministry for Education and Research (BMBF), German Federal Ministry of Health (BMG), ACHSE e.V.

Proposed action 12b:

Based on the results of the above-mentioned multidisciplinary discussion, support the set up and expansion of the appropriate scientific personnel base in the field of health sciences research in rare diseases through the establishment and integration of such research in the centers for rare diseases.

Implementation: short-term*[18]
Responsible bodies: Type A centers (reference centers), type B centers (centers of expertise) or type C centers (cooperating centers), German Federal Ministry for Education and Research (BMBF)

3.2.6 Ethical, Legal and Social Aspects

Because of the increasing demands being made on research into the ethical, legal and social aspects (ELSA) of modern life sciences and biotechnology, the German Federal Ministry for Education and Research (BMBF) has funded ELSA research since 1997. The focus of ELSA is part of the Framework Program of the German Federal Government on health research. This program addresses questions concerning political and societal dimensions as well as medical ethics. NAMSE thus recommends continuing this path and including the viewpoint on rare diseases. as a further focal point.

Proposed action 13:

Continuation of the ELSA funding program.

Implementation: short-term*[19]
Responsible bodies: German Federal Ministry for Education and Research (BMBF)

3.2.7 Cooperation Between Academia and Industry

The development of any new drug depends on knowledge emerging from preclinical research. The goal is to understand the biological mechanisms behind the respective diseases as well as to identify and describe points at which to apply therapeutic principles. This means setting up a targeted search for appropriate treatments. Such an extensive undertaking is fraught with the danger of setbacks since

[18] Once the center structure has been established.
[19] Once the center structure has been established.

it is not restricted to discovering simple agents, but also entails examining biologics as well as any number of new treatments such as genetic therapeutics, somatic cell therapeutics and biotechnologically manufactured tissues. Preclinical research lies in the domain of the pharmaceutical industry as well as academic institutions. The latter are increasingly becoming involved in joint ventures with the pharmaceutical companies.

Because it is important to stabilize and expand this cooperation, there is a need for a platform for linking up such partners. Such a platform serves to better enable preclinical research, the goal being the development of pharmacotherapies. This should also include regular workshops and partnering events as well as the initiation of joint projects.

Proposed action 14:

Implementation of a cooperative platform to broker the engagement between academia and industry. This should include patient patient organizations as well as small and medium-sized companies as part of a multistakeholder process.

Implementation: short-term*[20]
Responsible bodies: NAMSE coordinating office, German Federal Ministry for Education and Research (BMBF), industrial partners (vfa = German Association of Research-based Pharmaceutical Companies and BPI = Federal Association of the German Pharmaceutical Industry), academic partners including type A centers (reference centers), type B centers (centers of expertise) or type C center (cooperating centers), research associations of rare diseases

3.2.8 Cooperation with International Partners

The problems surrounding rare diseases are, of course, not limited to Germany. Adequate research into many rare diseases demands pooling the capacities and resources beyond national competences. Increased international cooperation is thus paramount to successful research into rare diseases.

The German Federal Ministry for Education and Research (BMBF) is participating in the ERA-Net Initiative “E-Rare” since 2003. This organization has the goal of coordinating research funders in the European Union and EU-associated countries. A continuation through 2014, E-Rare-2, is also in place. This cooperation serves to collect information about research going on into rare diseases in these countries, to strategically coordinate these activities and to fund transnational research projects.

Rare diseases are a key priority in the 7th Framework Program (2007-2013) of the European Commission. In the first four calls for proposal in the years 2007 through 2010 some 50 joint projects were funded with over EUR 237 million; ca. EUR 100 million were foreseen for further projects in the 2011 call. In addition, together with the US National Institutes of Health (NIH), the EU Commission founded the Rare Diseases Research Consortium (IRDiRC) in 2010, the goal of which is to develop 200 new therapiesand diagnostic procedures for most rare diseases.

NAMSE recommends supporting and continuing the initiatives mentioned above.

[20] Once the center structure has been established.

Proposed action 15:

Continued strategic development of research funding of international cooperation in the field of rare diseases.

Implementation: short-term
Responsible bodies: German Federal Ministry for Education and Research (BMBF), German Research Foundation (DFG), other research sponsors

3.2.9 Establishing Centers for Rare Diseases

Research and patient care for persons with rare diseases has long been one of the major tasks and areas of interests at the university level. Rare diseases demand highly specialized treatments and medical expertise that are often found only in university facilities. At the same time rare diseases are often of particular interest to research institutions in general because of their important biomedical background. Research into rare diseases has thus become an important component of the biomedical scientific research done at the university level.

Research on patients with rare diseases is presently insufficiently structured in Germany. It is often directed not toward the existing needs, but rather determined by other criteria such as local competence. Such fragmentation leads to basic research becoming separated from clinical research, thus preventing the expedient translation of the results to applied treatment.

Better structures can be achieved through the establishment of Centers for Rare Diseases. Based on existing excellent research results, type A centers (reference centers) can pool their relevant clinical and research competences drawn from a specific area of rare diseases; this would further the knowledge gained on specific diseases in conjunction with basic, applied and patient-oriented research already being done. Closely enmeshing all forms of clinical research as well as ensuring proper networking among all activities concerned with the treatment and teaching of as well as research into rare diseases would serve to clear the way for a balanced utilization of research and treatment activities. This would be one of the main characteristics of type A centers (reference centers).

Setting up type A centers (reference centers) would increase scientific competitiveness, ensure the intensive use of existing resources for rare diseases and also promote the effective translation of research results to the realm of treatment. A close cooperation between type A centers (reference centers) and more research-oriented type B centers (centers of expertise) and type C centers (cooperating centers) will be necessary for completing clinical studies and health care research studies with a sufficient number of patients in order to identify real-life problems and investigate these within scientific projects. The goal is to transfer the results of such research to the actual treatment of persons with rare diseases on a national level.

The establishment of centers can lead to the setup of scientific and diagnostic platforms to be used by other laboratories and clinics as reference points as well as provision of advanced technology for the study and development of diagnoses. Competence centers could be developed to deal with specific themes and to become internationally competent both scientifically and in their interaction with basic research, the goal being to transfer the results of this research to more practical applications. This would necessitate intensive networking of the centers among themselves as well as with other centers within the European Union. The required platforms should be set up and implemented.

Setting up the centers would also serve to address one of the central problems in the realm of rare diseases: the low number of patients. The coordinated establishment of a database (registry and biotissue bank) allows patients to be properly guided to the center appropriate for them, where they can be included in the respective studies and find targeted treatment. This constellation would close a further gap in the research.

NAMSE considers the establishment of centers for persons with rare disease and the inclusion of research activities in the criteria for their approval as such centers to be a central action for strengthening the research on rare diseases in Germany. The research done at the various centers could be weighted depending on the type of center.

In addition, it is paramount that the funding for research into rare diseases be established so as to enable the close long-term cooperation of fundamental research with clinical research and patient care. Such funding would also comprise setting up national and international networking of the competences and synergies present at the centers and at the various research locations.

Proposed action 16:

Provide support for innovative concepts to connect the patient care and research at the individual locations in order to enable a close cooperation between fundamental research on the one hand and clinical research on the other as well the effective translation of research results into actual care. This would be especially aimed at the type A centers (reference centers).

Implementation: medium-term*[21]
Responsible bodies: German Federal Ministry for Education and Research (BMBF), German Federal Ministry of Health (BMG), NAMSE partners, university clinics, non-university research facilities

[21] Once the center structure has been established.

3.2.10 Glossary

Term	Definition
Animal model	Model research done on animals in order to gain insight into the causes of and means of treating human diseases.
Array-comparative genomic hybridization (array-CGH)	A technique to detect losses and gains at the genomic DNA level. It allows discovery of even the smallest changes in the chromosomes throughout the entire genome.
Basic research	The scientific assembly, testing and discussion of fundamental principles of science. This forms the basis for advanced research.
Biobank	A collection of biological material (e.g., tissue samples) linked to clinical data.
Bioinformatics	The interdisciplinary science of doing research into problems from the natural sciences with theoretical, computer-assisted methods.
Biomarkers	Measureable products or substances of an organism that provide evidence of the existence/manifestation of a disease or how a certain drug works.
Biomedicine	A branch of human biology situated between medicine and biology.
Biotechnology	An interdisciplinary science in which knowledge from the life sciences is linked to that of process engineering, the goal being the development of new techniques.
CE	Sign used in Europe to denote that a product meets the requirements established by the European Union for manufacturers of such products.
Cell model	Exemplary basic research using cells.
Center of expertise	A network of qualified, interdisciplinary and transsectoral facilities that cover, as far as possible, the entire healthcare supply chain for patients.
Expertise	Competence, expert knowledge.
Gene therapy / Gene therapeutics	The insertion of nucleic acids such as DNA and RNA into the body cells of an individual using certain drugs.
Genome analysis	The examination of the complete set of genetic substance with regard to its structure and/or function.
Genome information	The entire hereditable information of a living creature.

Term	Definition
Genomics	Study of the all hereditable information (genomes) and the interactions among the individual segments of genetic information.
High throughput technique	A method whereby thousands to millions of biochemical, genetic or pharmacological tests are carried out in rapid sequence.
In vitro	Literally "in glass," refers to experiments done under controlled and artificial circumstances outside of a living organism.
In vivo	Literally "within the living," refers to organic processes that take place within a living organism.
Interdisciplinary	A collection of methods, approaches and strategies from various medical fields and/or professional groups.
Investigator-initiated trial (IIT)	A noncommercial clinical trial carried out by scientists not associated with the pharmaceutical industry.
IVD kits	Kit for doing in-vitro diagnostics.
Lipids	Fats (and other fat-soluble substances)
Micro RNAs	Short, well-preserved, noncoding ribonucleic acids (RNAs) that play a role in gene control.
Molecular	Pertaining to the molecule, the smallest unit of a chemical compound and consisting of different atoms
Monogenetic	Controlled by a single pair of genes or alleles.
mRNA	Messenger ribonucleic acid (RNA), which serves to translate the genetic information present in the deoxyribonucleic acid (DNA) into a protein structure.
Multifactorial	Dependent on or influenced by many factors.
Mutation	Change(s) in genetic material.
National Institutes of Health (NIH)	Agency of the United States Department of Health and Human Services
Next Generation Sequencing (NGS)	State-of-the-art (third-generation) method for deciphering genetic information (DNA sequencing)
Pathomechanism	The scientifically proven course of a disease process.
Pathophysiology	The science of how the human body functions in the presence of a disease.

Term	Definition
Phenotype	The appearance of an organism based on a multifactorial combination of genetic traits and environmental factors.
Polymorphism	The appearance of one or more genetic variations within a single population.
Preclinical research	The phase of pharmacological research in which studies are carried out at the cell level or on animal models.
Prospective	Likely or expected to happen.
Protein	Biological molecules consisting of one or more chains of amino acids.
Proteome analysis	A method permitting creation of a protein pattern that ideally is characteristic of a particular disease.
Somatic cell therapy	A method of treating or diagnosing a disease with body cells through the targeted use of characteristics and functions inherent in these cells.
Stratification	Dividing the overall population into parts from which samples are then taken, which in turn make up the total sample. This method is used whenever the population is not homogeneous and it is feared that only partial aspects may be discerned from a random sample.
Tissue products	The implementation of human tissue and cells for therapeutic purposes.
Translation / translational	The transferral of the results of clinical research to the treatment of patients.

3.3 Action Field: Diagnostics

The correct and prompt diagnosis of a rare disease is one of the most important demands for understanding and treating these diseases. But even for patients who suffer from rare diseases with no treatment options, early detection is of the utmost importance: A precise diagnosis is often the final link in a long chain of uncertainty and clinic visits. Also, a correct diagnosis is the prerequisite for determining the prognosis or the expected course of the disease. Further, the existence of a precise diagnosis affects many social aspects of a patient´s life such as schooling, career choice, partner choice, family planning and legal manifestations, including the funding of therapy attempts or social/medical expert opinions. The existence of an exact diagnosis is thus vital to those afflicted by rare diseases.

There are a number of reasons why diagnoses today are still often delayed or false, including the heterogeneity and high number of undiagnosed illnesses as well as the general lack of knowledge about rare diseases among the medical profession. The following recommendations and proposed actions serve to discover the reasons behind the deficits in diagnostics and to develop strategies to remedy these deficits. The focus will be on supporting the search for diagnostic methods through the input of diagnostic procedures as well as the establishment of guidelines.

3.3.1 Initial Contact: Primary Care

Medical diagnostics outside of centers of expertise play a decisive role in determining which patients have rare diseases. This is the level that normally initiates further tests in cases suspected of being rare diseases. Based on the results of the research publication[22] commissioned by the German Federal Ministry of Health (BMG) as well as additional random surveys carried out by NAMSE, we today possess indications that a number of factors contribute to delays in diagnosis at the primary-care level.

Recommendations: In order to formulate concrete solutions, NAMSE recommends initiating a survey among primary-care providers to determine the reasons behind the causes of delays in diagnosis at the primary-care level[23]. NAMSE also recommends that the patients´ path to diagnosis be documented at the centers in order to gain insight into how a diagnosis is reached, the goal being to obtain concrete information on how to expedite diagnostic means.

Proposed action 17:

Initiate as part of a pilot project an analysis of what is necessary to ensure cooperation between the centers and primary-care providers (e.g., the interface between the centers and primary-care providers).

Implementation: short-term*[24]

[22] Bundesministerium für Gesundheit (2009): Maßnahmen zur Verbesserung der gesundheitlichen Situation von Menschen mit Seltenen Erkrankungen. Available online at http://www.bmg.bund.de/fileadmin/dateien/Downloads/Forschungsberichte/110516_Forschungsbericht_Seltene_Krankheiten.pdf

[23] The workgroup defined three levels of primary care: (1) family physicians or specialists in general medicine, internists without specialization, pediatricians, obstetricians/gynecologists, dentists; (2) specialists (in private practice or in general hospitals); (3) maximum-care hospitals and special units at clinics with no further connection to rare diseases (e.g., emergency care).

[24] Once the center structure has been established.

Responsible bodies: German Association of General Practitioners, German Society of Pediatrics and Adolescent Medicine (DGKJ)

Proposed action 18:

Initiate as part of a pilot project at the centers for rare diseases a questionnaire to document the path to diagnosis from initial contact at the primary-care provider to the respective center. The goal is to improve the database in order to identify roadblocks in the process and find appropriate solutions.

Implementation: short-term*[25]
Responsible bodies: Type A centers (reference centers)

3.3.2 Diagnostic Software Technologies

Because of the small number of cases of rare diseases one may fairly assume that primary-care providers do not see many such cases in the course of their professional career.

Most rare diseases are very complex illnesses that can often afflict several organs at once. Unlike other more common diseases, they do not have a pronounced set of symptoms. Making a diagnosis/suspected diagnosis of "rare disease" is in fact rather difficult. Thus, the goal is to facilitate the formulation of a valid suspected diagnosis in order to initiate further diagnostic steps, preferably to be undertaken in a center appropriate to this cause.

Recommendations: NAMSE assumes that technical aids will serve to facilitate the recognition of patients with rare diseases within primary care as well as to allow the ascertainment of suspected or confirmed diagnoses for a number of rare diseases. For NAMSE this means that, in order to develop such technical aids, it will be necessary to create a complete and uniform coding of rare diseases. It is the hope and expectation of NAMSE that the introduction of the future ICD-11 will proved to be a major step on the road to encoding the majority of these diseases.

Until the ICD-11 becomes available, however, NAMSE recommends developing resource-low solutions. A project should investigate the possibility of automatically linking or coupling the alpha-ID of the ICD-10 to the Orpha code number provided by Orphanet. The goal would be to have a clear and uniform codification of the rare diseases available at the Centers for Rare Diseases to be used in research and care activities. In this sense it might also be possible that software algorithms be implemented as part of existing medical practice software in order to point toward rare diseases in the light of certain symptom constellations. NAMSE suggests testing which of the existing software packages would be suitable and how the software manufacturers could integrate rare diseases into their software.

NAMSE further recommends the development of research tools for primary-care providers to employ when confronted with certain typical syndromes in order to better classify the disease. In this manner they can point to unusual syndromes early on as being possible rare diseases.

[25] Once the center structure has been established.

Proposed action 19:

A uniform coding scheme for all patients with rare diseases employing the Orpha diagnostic coding system in conjunction with ICD-10 GM and in anticipation of the publication of ICD-11.

Implementation: short-term
Responsible bodies: Orphanet Germany, German Institute of Medical Documentation and Information (DIMDI, part of the German Federal Ministry of Health)

Proposed action 20:

A pilot project to validate software used in primary-care private practices to provide differential diagnostic tools for the diagnosis of rare diseases in addition to more common diseases. Subsequently, existing algorithms need to be (further) developed and implemented into existing software packages.

Implementation: Pilot project: short-term, implementation: medium-term
Responsible bodies: German Association of General Practitioners, German Society of Pediatrics and Adolescent Medicine (DGKJ)

Proposed action 21:

Solicitation of a project for developing a web-based diagnostic tool for primary-care providers. This tool should utilize existing information sources, in particular Orphanet Germany and the foreseen mapping of care facilities for persons with rare diseases (cf. proposed action 38 below).

Implementation: short-term
Responsible bodies: Open solicitation

Proposed action 22:

Once the factors leading to delays in the assessment of a diagnosis have been resolved and concrete provisions have been implemented to ensure rapid diagnosis, it should be assessed whether the care given by primary-care and specialist-care providers to persons suspected of having rare diseases but without a confirmed diagnosis is sufficiently reflected in the German Uniform Fee Scale for Medical Procedures (EBM, part of the Statutory Health Insurance system).

Implementation: medium-term
Responsible bodies: Evaluation Committee on the Uniform Fee Scale for Medical Procedures

3.3.3 Innovative Sequencing Technologies for Molecular Diagnostics

The present methods employed in molecular-genetic diagnostics with rare diseases are expensive because of the genetic heterogeneity involved; relevant results are often achieved only after months of trials with so-called staged diagnostics (Gen1 > Gen2 > Gen3 …). With some types of rare diseases, staged diagnostics using the Sanger method in fact fails to produce any useful results because even rarer genes leading to disease are not studied. The Sanger method has been further developed and modified in recent years. Today, so-called “next generation sequencing” (NGS) is employed instead of staged diagnostics since it allows parallel analysis to be done of many or even all genes relevant to a particular disease. Besides addressing specific genetic modifications (so-called germline mutations),

this technology can also be used to recognize segmental aneuploidy (e.g., subchromosomal deletions) of tissue-specific genetic mutations (e.g., genetic mosaics/somatic mutations in tumors) and transcription profiles. It is generally expected that the NGS technology will lead to more precise, speedier, cheaper and overall more efficient and universal means of diagnostics than the previous Sanger methods of sequencing. In addition, this technology can be expedient with dealing with unclear diagnoses or syndromes. Thus, overall this technology represents a major breakthrough in the diagnostics of genetic-related rare diseases.

Recommendation: Because of the major importance of genetic diagnostics in the field of rare diseases, patients should have access to the newest methods, inasmuch as these methods can ensure or accelerate the availability of diagnostic means to achieve the patient-oriented optimization of health-care. NGS technologies should be introduced into the molecular diagnostics of rare diseases once a proper list of indications as well as a specification of services have been prepared and tested to show the conditions and indications under which optimal care can be provided.

Proposed action 23:

Take up consultations in the Evaluation Committee on the Uniform Fee Scale for Medical Procedures on the introduction of NGS technologies.

Implementation: short-term
Responsible bodies: Health-care providers (preliminary stage), Evaluation Committee on the Uniform Fee Scale for Medical Procedures

3.3.4 Guidelines

Evidence-based guidelines form the core demand for improving the quality of diagnostics and therapy. With rare diseases there are generally few guidelines due to the small number of cases. The Rapid Report[26] prepared by the Institute for Quality and Efficiency in Healthcare (IQWiG), commissioned by the German Federal Ministry of Health (BMG) notes that there is presently no gold standard for establishing guidelines for rare diseases.

Recommendation: NAMSE recommends resorting to existing structures and employing these "pragmatically" in order to prepare guidelines for rare diseases. First, a prioritization based on prevalence, medical necessity and feasibility should be established to determine the available expert knowledge of rare diseases. Because the Association of Scientific Medical Societies (AWMF) and the AWMF Institute for Medical Science Management (AWMF-IMWi) are largely responsible for developing guidelines in Germany, it would seem logical to create any new structures within these institutions to prepare guidelines for rare diseases. NAMSE recommends that the respective professional association be appointed to be responsible for the interdisciplinary preparation of such guidelines. In addition, NAMSE suggests that the absorption of costs involved in preparing such guidelines for rare diseases be examined by the proper entities.

NAMSE further suggests that, as a rule, some aspects of the diagnostics or therapy involved in the differential diagnostics of relevant rare diseases be incorporated into existing or new guidelines for

[26] Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (2011): Welche Evidenz wird für die Erstellung von Leitlinien für seltene Erkrankungen derzeit herangezogen? [What evidence do we presently have to help us prepare guidelines for rare diseases?] Rapid Report.

widespread diseases. Whenever such guidelines are set to be revised or rewritten, NAMSE recommends that peculiarities or subtypes of existing diseases (or pathophysiologically or symptomatically related rare diseases) be included in the new guidelines. The goal should be that the AWMF, being the leading organization responsible for such guidelines, address this demand as part of all future guidelines.

Proposed action 24:

In order to support the development of guidelines for rare diseases, an electronic platform should be established with the expressed intent of setting up such guidelines. These guidelines should be adapted to the needs of the field of rare diseases in consultation with the AWMF. The implementation of an electronic platform serves to save both time and costs, increase the transparency of the procedure and reflect the special needs of patients with rare diseases.

Implementation: short-term
Responsible bodies: Technology, Methods, and Infrastructure for Networked Medical Research (TMF, sponsored by the German Federal Ministry for Education and Research, BMBF), Association of Scientific Medical Societies (AWMF)

Proposed action 25:

Carry out a methodological project to develop criteria for the assessment and evaluation of scientific studies with few participants with regard to establishing guidelines.

Implementation: short-term
Responsible bodies: Association of Scientific Medical Societies (AWMF), Institute for Quality and Efficiency in Healthcare (IQWiG)

Proposed action 26:

Set up a standard procedure for including rare diseases in the administration of guidelines for widely prevalent diseases. In this case, the professional medical associations that are to list the differential diagnosis methods for rare diseases that are to be taken into consideration

Implementation: short-term
Responsible bodies: Association of Scientific Medical Societies (AWMF)

3.3.5 Glossary

Term	Definition
Algorithm	A clear and executable, step-by-step procedure for solving a problem.
Alpha ID	According to the alphabetic index of the ICD-10-GM every entry of the alphabet has its own consecutive identification number. The alpha ID thus provides a unique identification of each entry.
Aneuploidy	The designation for a combination of chromosomes that deviates from the norm by the absence or doubling of chromosomes or chromosome sections (e.g., trisomy 21).
Genetic mutation	A change in the genetic makeup caused by a change in the genome.
Germline mutation	Changes in the genetic makeup that may be passed on to the next generation.
Guideline	An aid systematically developed by a scientific medical association to help physicians reach a decision in certain situations. Guidelines are by nature not legally binding or enforced.
Hypothesis	Assumptions that are unproved, yet free of contradictions.
ICD-10 GM	International Classification of Diseases and Related Health Problems, 10th revision (German Modification). This is the official classification of diagnoses for use in inpatient and outpatient care in Germany.
Medical practice software	Software used in the administration, organization and business operations of a medical practice.
Next-Generation Sequencing (NGS)	Third-generation method for sequencing DNA.
Orpha code number	Classification system of rare diseases hosted by Orphanet.
Orphanet	Databank founded in 1997 by the French Ministry of Health and the Institute national de la santé et de la recherche médicale (INSERM) to gather resources on rare diseases in order to improve diagnostic and therapeutic procedures.
Sanger technique	A method of sequencing nucleic acids.
Transcription profile	Transcription is the first step of gene expression, whereby DNA is copied into RNA.

3.4 Action Field: Registries

Registries serve to support research into the pathogenesis, therapy and care of diseases. They also help in recruiting participants for clinical studies and for analyzing collected research and care data across multiple diseases.

In Germany there is presently no central coordinated registration of patients with rare diseases. Patient registries for specific rare diseases are also seldom. Those that do exist often do not cover large geographic areas and are not uniform in their data structure or data safety. No long-term plan presently exists for guaranteeing the long term financing and maintenance of such a registry.

The assimilation of patient registries in superordinate and/or international platforms is urgently necessary because of the low number of patients involved. To this end the EU has envisaged support for a Europe-wide registration platform for rare diseases. The standards and recommendations of this platform should be implemented in German registries in order to ensure a complete European information network. The prerequisite for the cooperation between German entities and international networks would, for example, be the at least partial introduction of existing data in the form of a mandatory minimal data set in a stepwise process

Together with experts from the Robert Koch Institute, the Epidemiological Cancer Registry of Lower Saxony and the Tumor Center in Regensburg, NAMSE has prepared the following recommendations and actions with the goal of establishing access to existing registries, for example, through a web-portal – a “telephone book” of such registries as it were. Further, assistance such as establishing a minimal set of data elements should be provided to help in the setup and management of disease-specific registries for rare diseases.

3.4.1 Web-Portal of Registries of Rare Diseases in Germany

All existing registries that refer to the phenomenon of rare diseases should be registered in a special web-portal. Such a “National Registry of Rare Diseases” should be maintained by a central organization and comprise only few elements. This would be a sort of “telephone book” of all registries of rare diseases; synergies with Orphanet should be exploited inasmuch as possible.

Proposed action 27:

Set up a web-portal of registries concerning rare diseases in Germany.

Implementation: short-term
Responsible bodies: Orphanet Germany, Technology, Methods, and Infrastructure for Networked Medical Research (TMF)

3.4.2 Steering Committee of Registry Operators for Exchanging Information on “Registries on Rare Diseases”

In order to set up, develop and operate such a central registry, experiences from past initiatives, like those found in existing documents on organizational concepts and requirements for data privacy and data protection, must be considered. In order to establish them in a concerted action and have them

applied as the standard, it is necessary for a regular and personal exchange of information to take place among the various registry operators. The goal is to increase the overall quality of such registries. The documents emerging from such cooperation should be made available gratis on the Internet. This committee should also be responsible for linking the biomaterial databases with existing registries.

Furthermore, any developments emerging from European and international initiatives should be reflected at the national level. To this end a national panel should be established to promote and coordinate future developments and and to evaluate the success and necessity of such initiatives.

Proposed action 28:

Establish a steering committee "Registries of Rare Diseases" (e.g., operators of registries, experts) in collaboration with the Technology, Methods, and Infrastructure for Networked Medical Research (TMF) and the NAMSE coordinating office.

Implementation: short-term
Responsible bodies: German Federal Ministry of Health (BMG), German Federal Ministry for Education and Research (BMBF), NAMSE partners, Technology, Methods, and Infrastructure for Networked Medical Research (TMF)

3.4.3 Development of Software for Establishing a Databank Prototype to Implement and Manage a Disease-Specific Registry for Rare Diseases

This project serves to develop condensed aids for establishing and managing a disease-specific registry for rare diseases. Open source and modifiable software should be used to develop such a database structure that may serve as a model for future registries and cover the basic minimum standards for the foreseen network structure. In addition to such software, the following instruments should be developed or integrated:

- Quality criteria and standards
- Legal premises
- Possibilities for maintaining registries
- National and international linking of multiple registries
- Repository of metadata (MDR - databank tables for the management of metadata) to prevent semantic problems (i.e registries must understand the questions)

Further, it would be advantageous if existing registries were to adapt their conditions to the recommendations prepared by NAMSE, in particular that all registries on rare diseases integrate the basic data scheme developed in the prototype into their own databank and export their data accordingly or allow their data to be automatically examined electronically.

In addition, a virtual national network of registries ("meta-registry") shall work together based on a compact and set of minimal data elements unsusceptible to data-security problems. In light of the planned Europe-wide networking of registries for rare diseases, the recommendations and standards established for this purpose should be implemented, inasmuch as possible.

For optional cooperation going beyond this basic level, a decentralized search engine should be developed and implemented to allow data to be created at the original location and still be retrieved by all registries via modern information technology.

Proposed action 29:

Develop a prototypical registry for a "Disease-Specific Registries of Rare Diseases" (including a standardized registry for patients without a disease-specific registry, see Proposed Action 32 below) based on the provisions outlined in the draft by the NAMSE working group 'Registries'. This prototype – or individual software modules contained therein – should be adaptable for existing registries. A standardization of all existing registries is desirable.

Implementation: short-term
Responsible bodies: German Federal Ministry for Education and Research (BMBF), German Federal Ministry of Health (BMG)

3.4.4 Registry of "Patients with an Unclear Diagnosis"

A common problem lies in reaching a correct and early diagnosis of a rare disease. For this reason it is sensible to have patients with an unclear diagnosis entered into a comprehensive registry for unclear diagnoses. This registry, however, should differentiate between patients with an tentative diagnosis and patients with a heretofore unknown rare disease. Unanswered questions concerning a registry for patients with an unclear diagnosis should first be discussed and resolved during a workshop. A development project to set up a registry for patients with unclear diagnoses should then be based on the results of such a workshop and then implemented.

Proposed action 30:

Organize a workshop to gather and solve open questions concerning a registry for patients with an unclear diagnosis.

Implementation: short-term
Responsible bodies: Board of spokespersons of the networks for rare diseases sponsored by the German Federal Ministry for Education and Research (BMBF), Technology, Methods, and Infrastructure for Networked Medical Research (TMF)

Proposed action 31:

Depending on the results of such a workshop outlined in proposed action 30 above, implement a project to establish a registry for persons with an unclear diagnosis.

Implementation: medium-term
Responsible bodies: NAMSE partners

3.4.5 Project "Non-Disease-Specific Registry"

Some rare diseases are so rare (so-called ultra-rare diseases) that establishing a separate registry is not worth it; or no one is available to responsibly establish and maintain such a registry. For such cases

a non-disease-specific registry should be established that should be maintained using the technology created for the prototype registry above.

Proposed action 32:

Establish a project “non-disease-specific registry” based on (and thus subsequent to) the development of a prototype registry as suggested in proposed action 29.

Implementation: long-term
Responsible bodies: Steering committee of the previously mentioned registry for rare diseases (proposed action 28)

3.4.6 Glossary

Term	Definition
Basic data scheme	The datasets contained within a metaregistry reflect the “smallest common denominator” emerging from the participating registries. They are called basic datasets and in turn comprise the basic data scheme, which is narrower than the data scheme of a disease-specific registry.
Metaregistry	A metaregistry supplies information as well as controlled access to the contents of existing disease-specific registries containing data ordered according to a basic data scheme. A metaregistry is concerned less with providing information for concrete, disease-specific evaluations than with being a focal point for anyone interested in obtaining an overview of existing cases including the contact data of data suppliers capable of providing further information.
Registry, dataset, data scheme	A registry is a database containing a systematic collection of structured data. The structure employed, i.e., the values and their possible characteristics, is called the data scheme. The data themselves are called datasets or contents. When managing datasets in a table the data scheme thus corresponds to the table heading (“Name; First Name”), the dataset to the individual row (“Doe; John”). Registries may serve any number of different purposes, such as epidemiological registries, healthcare registries, registries with regional or international datasets, etc. They also differ in the way they are structured, particularly how the data scheme is set up.
Unclear diagnosis	In this document an unclear diagnosis is defined as follows: (1) the existing symptoms do not allow a clear diagnosis; (2) the main criteria for a particular diagnosis are not fulfilled; (3) additional significant symptoms not typical for the diagnosis are present.

3.5 Action Field: Information Management

People with rare diseases have a tremendous need for disease-specific information. In those who have not yet received a clear diagnosis, this information serves as a general orientation guide, whereas patients who have already received a diagnosis and are now searching for proper treatment and therapies are dependent on receiving qualified information about their alternatives. Although extensive information is available on many rare diseases, it may not be adequately used by both patients and medical personnel. Furthermore, the quality of the contents may vary. For this reason it is necessary that existing information portals be examined and expanded, and that afflicted persons be made aware of existing information sources.

To guarantee long-term improvement in the knowledge about and awareness of rare diseases, further measures are required in the field of medical training and continued education.

3.5.1 Adequate Patient Information on Rare Diseases

NAMSE believes that all information offers on rare diseases for patients must meet strict standards. For this reason, NAMSE has evaluated existing patient information based on a summary of the ACHSE criteria for patient-oriented disease descriptions (PKB), the Orphanet France Guidelines for Patient Information and the "Good Practice Health Information." The results of this survey were discussed during the 2012 Annual Congress of the German Network on Evidence-Based Medicine (DNebM). Based on this analysis, NAMSE has developed new criteria for preparing adequate patient information on rare diseases.

Recommendation: NAMSE recommends preparation of a checklist based on previous criteria in order to examine whether existing information on rare diseases is purposeful, standardized and of high quality. This checklist should serve as the basis for developing patient information for rare diseases. Above all NAMSE recommends revising existing information based on this checklist.

Proposed action 33:

Develop a checklist "Criteria for Good Patient Information on Rare Diseases" based on the draft paper prepared by NAMSE.

Implementation: short-term
Responsible bodies: ACHSE e.V., Agency for Quality in Medicine (ÄZQ)

Proposed action 34:

Prepare a concept for establishing and implementing a checklist "Criteria for Good Patient Information on Rare Diseases" among a broad selection of organizations offering patient information on rare diseases.

Implementation: short-term
Responsible bodies: ACHSE e.V., Agency for Quality in Medicine (ÄZQ)

Proposed action 35:

A joint project by Orphanet Germany and ACHSE e.V. should be conducted to prepare a format for disseminating German-language patient information based on the checklist “Criteria for Good Patient Information on Rare Diseases.”

Implementation: short-term
Responsible bodies: Orphanet Germany, ACHSE e.V.

3.5.2 Joint Communications on the Subject of Rare Diseases

NAMSE recommends that the league partners remain responsible for joint public relations on the subject of rare diseases. Joint communications and procedures for the various groups should be developed in support of this venture in order to establish decentralized but coordinated public relations activities.

Proposed action 36:

Develop and implement a concept for joint communications and procedures for public relations in the realm of rare diseases.

Implementation: short-term
Responsible bodies: NAMSE coordinating office, ACHSE e.V.

3.5.3 Central Information Portal

In Germany, there are presently some 4 million persons afflicted by about 8,000 different rare diseases. These patients as well as their relatives, attending physicians and nonmedical personnel working in the area of rare diseases require information concerning the respective diseases, their diagnostic and therapeutic possibilities, and the associated social and legal questions. Much information is already available on the Internet; however, not all information is readily available or uncertainties may exist about its reliability. NAMSE believes this situation could be improved through the establishment of a central portal to handle enquiries about these matters and to focus existing quality-tested information on rare diseases. This would promote a major improvement in both the quality and quantity of information offers.

Recommendations: NAMSE recommends setting up a central and integrated information portal on the Internet for rare diseases to disseminate both existing and future information offers on this subject. This portal should meet the following prerequisites:

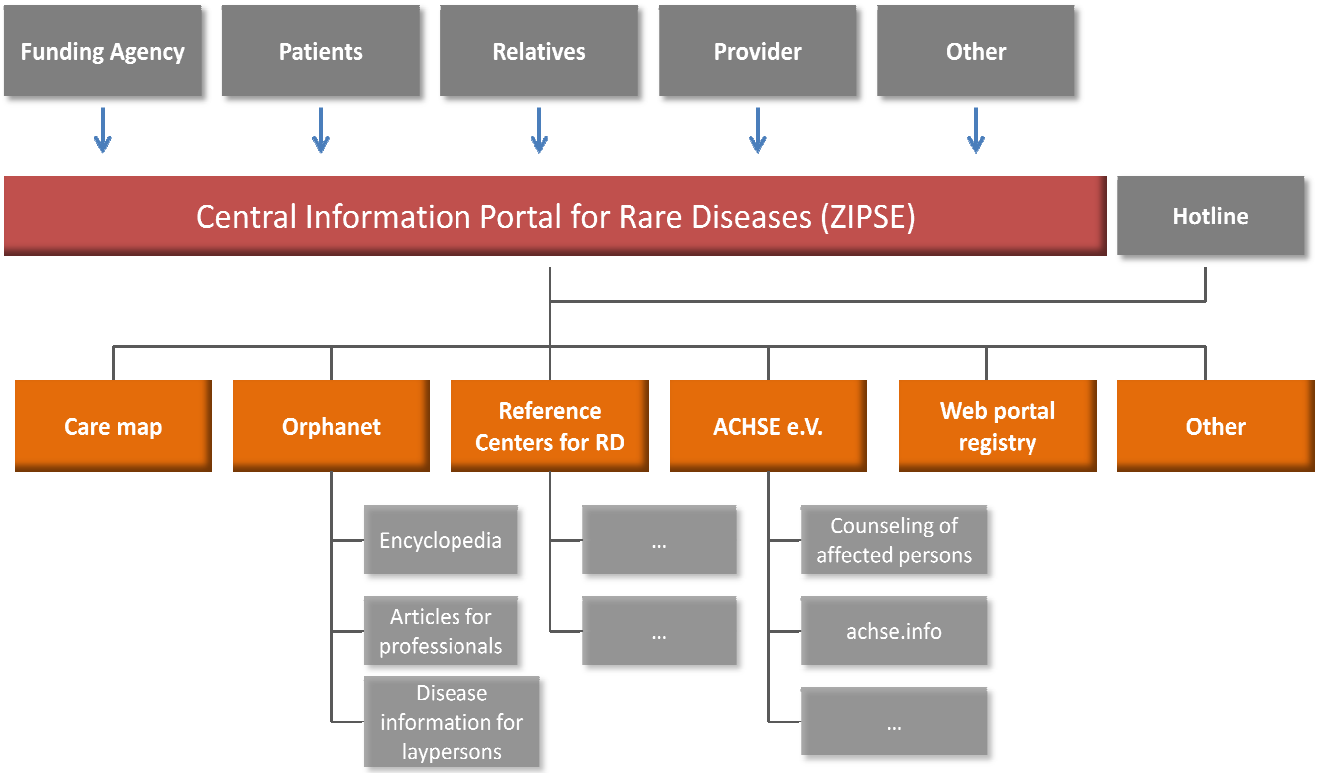
a) Provide existing information on rare diseases, including diagnostic and therapeutic means, patient organizations, treatment and research centers, registries, etc.
b) A hotline for persons seeking immediate information could provide a vital service alongside the online opportunities.
c) Provide a map of all care offers for persons with rare diseases as part of the information portal.
d) Orphanet Germany operates the information platform for rare diseases and delivers information concerning services (expert centers, diagnostic services, patient organizations, clinical studies, patient registries, mutation databases, biobanks, research projects, networks, etc.). In

addition, the platform contains articles for both professionals and laypersons with descriptions of rare diseases. Orphanet is an encyclopedia of relevant disease information.

e) Provide all pertinent links to scientific associations, patient organizations, diagnostic or therapeutic facilities (centers).

f) The portal (and the hotline) should not provide original materials, but rather refer to the relevant information sources through an appropriate and intuitive user guidance system.

Figure 2: Example of setup of an information portal



Proposed action 37:

Draft a concept including suggestions for funding for the establishment of a central information portal for rare diseases with the aid of Orphanet resources.

Implementation: short-term
Responsible bodies: Orphanet Germany, ACHSE e.V.

NAMSE also expressly recommends that Orphanet should further on be the central information platform for all information concerning rare diseases.

Proposed action 38:

Orphanet, with the participation of ACHSE e.V. (www.achse.info), should be set up in an information portal to serve as central information platform providing all quality-tested information available on rare diseases.

Implementation: short-term
Responsible bodies: Orphanet Germany, ACHSE e.V.

NAMSE maintains that a hotline can become an important, low-threshold part of an internet-based information portal on rare diseases. NAMSE recommends setting up a pilot project to determine which target groups would make best use of such a hotline, what types of questions would most often be posed and what answers can best be delivered to these questions. This information would serve to determine the probable frequency and type of questions and how to plan to best meet these demands.

Proposed action 39:

Determine the need for a central information hotline as well how which reference system would best meet that need and how much such a system would cost (both with and without the hotline).

Implementation: short-term
Responsible bodies: German Federal Ministry of Health (BMG), Orphanet Germany, ACHSE e.V., Independent Patient Counseling Centers of Germany (UPD), Federal Association of Self-help Organizations of People with Disabilities and Chronically People and Their Relatives in Germany (BAG SELBSTHILFE e.V.), NAMSE coordinating office

3.5.4 Medical and Dental Training and Continued Education

A number of studies (Research Report of the German Federal Ministry of Health (BMG)[27], EUROPLAN, EURORDIS) have determined that the delayed diagnosis of rare diseases is a major problem for those affected and for the healthcare system in general. NAMSE sees the reasons for this delay, among other things, in the insufficient level of knowledge and the lack of experience with rare diseases among the medical community. For this reason, NAMSE advocates improving medical and dental training and continued education to prioritize knowledge of rare diseases. First and foremost, NAMSE recommends emphasizing the peculiarities in the area of differential diagnosis, disease course and possible therapeutic routes. Special information sources should particularly be tapped when diagnoses are unclear or when specific knowledge about the diagnosed disease is absent.

Specifically, NAMSE suggests that medical and dental training in the future include general knowledge about rare diseases in its normal curricula. In addition, rare diseases should be made part of the National Competency-based Catalogue of Learning Objectives for Undergraduate Medical Education (NKLM) and the National Competency-based Catalogue of Learning Objectives for Dentistry (NKLZ), which is scheduled to be implemented beginning in 2014 by medical and dentistry faculties as an orientation guide for preparing the curricula and examinations in medical and dentistry schools.

In a further step, nonmedical personnel and other healthcare workers should be included in this objective.

[27] Bundesministerium für Gesundheit (2009): Maßnahmen zur Verbesserung der gesundheitlichen Situation von Menschen mit Seltenen Erkrankungen. Retrievable under: http://www.bmg.bund.de/fileadmin/dateien/Downloads/Forschungsberichte/110516_Forschungsbericht_Seltene_Krankheiten.pdf

Proposed action 40:

Establish a national, competence-based catalog of learning objectives such that students of medicine and dentistry become so thoroughly acquainted with the special characteristics of rare diseases with respect to their symptoms, physiology, diagnostics, therapy and care that they acquire the necessary medical competence in all respects (cognitive, applied and emotional/reflective). In addition, students of medicine and dentistry should have all necessary information sources on rare diseases at their disposal.

Implementation: short-term
Responsible bodies: German Association of Medical Faculties (MFT)

The German Federal Ministry for Education and Research (BMBF) is presently sponsoring a joint research project entitled "Competence-Oriented Learning, Teaching and Testing in Medicine," which has as its goal the prototypical implementation of a demand from the National Catalog of Competence-Based Learning Objectives for Medicine (NKLM) that rare diseases be included in the curricula of all medical faculties based on best-practice examples.

Proposed action 41:

As part of the joint project sponsored by the German Federal Ministry for Education and Research (BMBF) in the Competence Network for Medicine in Baden-Wuerttemberg, rare diseases with their specific characteristics should be introduced into the curricula of the medical faculties. The results and experiences gathered from this joint project should then be made available to all other federal states so that such actions can then also be implemented by other faculties.

Implementation: medium-term
Responsible bodies: Project management of joint project, German Association of Medical Faculties (MFT)

The basis for written examinations according to the German Medical Licensure Act is presently the Comprehensive Subject Catalog of the Institute for Medical and Pharmaceutical Examination Questions (IMPP). In the opinion of NAMSE, including questions on rare diseases (differential diagnosis, definition and peculiarities) would spur increased interest among medical students for this area. General knowledge of the special demands posed by rare diseases on diagnostics and therapy should thus be made part of the examination process. NAMSE recommends creating a greater awareness of rare diseases in the examination questions developed by the IMPP.

Proposed action 42:

Inclusion of questions on rare diseases in the examination questions of the IMPP.

Implementation: medium-term
Responsible bodies: German Federal Ministry of Health (BMG), Association of Scientific Medical Societies (AWMF)

In order to increase knowledge about the peculiarities of rare diseases among primary healthcare providers, NAMSE recommends the increased transfer of information about rare diseases, including existing offers of patient organizations, and special regard for the problems experienced by persons with rare diseases during medical and dental training.

Proposed action 43:

The guidelines for continued and advanced training of physicians prepared by the German Medical Association (BÄK) and the German Dental Association (BZÄK) as well as those prepared by the individual state medical associations (LÄK) and the individual state dental associations (LZK) should generally contain information concerning how to address rare diseases.

Implementation: short- to medium-term
Responsible bodies: German Medical Association (BÄK), German Dental Association (BZÄK), state medical associations (LÄK), state dental associations (LZK), professional societies

NAMSE believes that the situation surrounding rare diseases should occur regularly in medical and dental (continuing) education. Because physicians and dentists in Germany are required to attend continuing education courses, this is an ideal way to improve their overall knowledge of rare diseases. Cooperation with the patient organizations in this area can also be advantageous to physicians and dentists and would generally serve to improve medical and dental care. The partners of NAMSE are requested to organize courses in continuing education that have been approved by the state medical associations (LÄK) and the state dental associations (LZK). Contained therein should be, besides medical and dental professional knowledge, aspects brought to the forefront by the respective patient organizations.

Proposed action 44:

Type A centers (reference centers) and type B centers (centers of expertise) should provide courses in continuing education approved by the state medical associations (LÄK) at regular intervals and in association with the respective patient organizations (inasmuch as present). The goal of these courses is to provide physicians with information on rare diseases and to inform them of existing information sources as well as how to deal with a lack of information.

Implementation: short-term*[28]
Responsible bodies: Type A centers (reference centers) and type B centers (centers of expertise), professional societies

Proposed action 45:

Expand the existing courses in continuing education approved by the respective patient organizations to include other rare diseases.

Implementation: short-term
Responsible bodies: ACHSE e.V., patients´ representatives

[28] Once the center structure has been established.

3.5.5 Public Relations

NAMSE believes that the introduction of a National Action Plan should be accompanied by intensive public relations activities

Recommendations: NAMSE recommends regular public relations activities be centrally organized to inform about the progress of the National Action Plan.

Proposed action 46:

Develop and implement a concept for public relations activities with respect to NAMSE and to the realization of a Nation Action Plan.

Implementation: short-term
Responsible bodies: NAMSE coordinating office

3.5.6 Telemedicine

According to the German Society for Telemedicine, telemedicine is "the delivery of concrete medical services by bridging spatial distances with the help of modern information and telecommunication technologies." The goal of telemedicine is to ensure a high quality of healthcare independent of the location by providing all necessary information.

With rare diseases the importance of the location-independent availability of broad medical knowledge is great since there are only few experts on each of the many rare diseases. Particularly patients who, because of their disease, cannot travel great distances profit from the advantages of telemedicine. This also corresponds to the demand made by the European Union that "expertise make the journey, not patients." Below are two examples of how telemedicine can concretely be employed.

The Paediatric Hodgkin Network connects experts from the areas of oncology, radiology, nuclear medicine and radiology, on both a national and international level. The goal of this network is to better treat children with Hodgkin lymphomas by developing uniform diagnostic methods and therapeutic decision-making processes. Image data are transferred over the Internet in encrypted form. It also is concerned with providing second opinions. Medical findings are discussed via teleconferencing and deposited in a central registry. For German patients, the costs involved with this service are borne by the Statutory Healthcare System, as are costs necessary to maintaining the system as such. Especially the ability to transfer medical imaging data quickly and fluidly to other partners for their perusal is a major advantage over all other previous methods.

The German project AmbulanzPartner (Outpatient Partners) assists in coordinating the outpatient treatment of patients. Initially, it concentrated on patients with the rare disease amyotrophic lateral sclerosis (ALS), but in the meantime the project has been expanded to cover the care and treatment of other complex diseases within the standard care. AmbulanzPartner is a healthcare concept combining social-medical services (case management) with Internet technologies (www.ambulanzpartner.de). AmbulanzPartner assumes the complex tasks of organizing and coordinating the work of outpatient care facilities, specialized medical practices and specialized providers, all of which is coordinated, documented and visualized on their Internet portal. The emphasis lies on transferring care to more differentiated forms and on providing highly specialized care with the necessary aids and medicines.

How much telemedicine can contribute to healthcare depends largely on the respective situation, the technical and financial means available and on its implementation. It is recommended that all technical means be exploited. In addition to the examples given above, there are of course many other scenarios imaginable where modern information and telecommunication technologies could play a valuable role. The possible applications of telemedicine are very broad, as the examples show.

Telemedicine in the sense of the definition given above is, with some exceptions (e.g., in the care of stroke patients), not yet an integral part of the standard care. In the past it was not always the case that the advantages of telemedicine for improving the quality and efficiency in healthcare came to the forefront, and it is as yet unclear what influence it will have on existing procedures in the health care system where many different partners are involved. This is also true for the ongoing process in the scope of the German Medical Care Structure Act (§87, sect. 2a SGB V) of integrating telemedical applications into outpatient medical care. The responsibility for this has been placed upon the individual administrative organizations and thus concerns both rare diseases and non-rare diseases.

Proposed action 47:

Identify and evaluate telemedical offerings for rare diseases.

Implementation: short-term
Responsible bodies: Joint representatives from the various centers, Technology, Methods, and Infrastructure for Networked Medical Research (TMF), Association of Insurance Science and Practice e.V. (GVG): Committee on Telemedicine

3.6 Action Field: Patient Orientation

Patient organizations comprise the backbone of the caretaking system of persons with rare diseases. Not only do they make a major contribution to the direct support of individual patients, they also collectively act to achieve long-lasting improvements in the care and therapy of patients living with a rare disease. In order to support the role of these organizations, the participation of patient organizations has also been formulated in the Council Recommendation as a central goal of action in the field of rare diseases. The following recommendations for actions and proposed actions as part of this draft for a National Action Plan serve to promote this important matter on the national level.

3.6.1 Research

The patient organizations can play a supportive role in research enterprises, especially by presenting the specific patient-oriented perspectives. The existing patient expertise also provides impulses for future research. NAMSE recommends a better perception and application of their competence and important role in research ventures.

Proposed action 48:

Include as appropriate the experiences gathered by patient organizations in the development and implementation of patient-oriented research and healthcare projects on rare diseases.

Implementation: short-term
Responsible bodies: German Federal Ministry for Education and Research (BMBF), German Research Foundation (DFG), German Federal Ministry of Health (BMG)

3.6.2 Expert Opinions by the Medical Advisory Service of the German Statutory Health Insurance

Expertise on rare diseases is still limited in the health care system. Thus, a major challenge is posed by the need to have expertise available for areas where rare diseases occur. This is also true for the preparation of expert opinions by the Medical Advisory Service of the German Statutory Health Insurance (MDK).

Proposed action 49:

Improve the transparency surrounding the role and advisory capacity of the Medical Advisory Service of the German Statutory Health Insurance (MDK). To this end, the Medical Advisory Service of the Federal Association of Health Insurance Funds (MDS) can serve as contact point for patient organizations at the national level and can assume any necessary coordinating functions in the MDK community.

Implementation: short-term
Responsible bodies: Central Association of Statutory Health Insurance Funds, Federal Association of Health Insurance Funds (MDS)

3.6.3 Support and Qualification of Patient Organizations

In order for the patient organizations for rare diseases to participate as envisaged in the National Action Plan, it is necessary to provide direct support for their activities, including sufficient training and educational programs for qualification purposes.

Proposed action 50:

Within the limits of existing legal regulations, the NAMSE partners shall work to ensure the appropriate support for the activities of the patient organizations and their qualification.

Implementation: short-term
Responsible bodies: German Federal Ministry of Health (BMG), ACHSE e.V., Federal Association of Self-help Organizations of People with Disabilities and Chronically People and Their Relatives in Germany(BAG SELBSTHILFE e.V.)

3.6.4 European Networks

The patient organizations of people living with a rare disease feel the need for international networking sooner and on a more thorough level, e.g. in order to find a sufficient number of patients for exchange programs as well as in receiving proper information or gaining access to the relevant expertise. Hereto patient organizations strive for the foundation of international disease specific organizations.

Proposed action 51:

Provide support for integrating national patient organizations into Europe-wide cooperations concerning rare diseases.

Implementation: short-term
Responsible bodies: German Federal Ministry of Health (BMG), the Patient organizations

3.7 Action Field: Implementation and Future Development

This catalogue of recommended policy suggestions and proposed actions completes the initial phase of the NAMSE process. The next step is to implement the actions and accompany their further development.

In order to better evaluate the success of the National Action Plan, a number of appropriate indicators must be established. These indicators should address whether the goals of the individual actions have been met as well as whether the desired effect of the entire National Action Plan has come about. For determining whether the National Action Plan generally led to an improvement in the healthcare situation of persons with rare diseases, these indicators as well as the insights gathered in the research report "Measures to improve health in people with rare diseases" sponsored by the German Federal Ministry of Health (BMG) can be applied. Also, the so-called EUROBAROMETER Study "European Awareness of Rare Diseases"[29] may be employed as a basis for evaluating individual actions and their results.

To ensure the long-term implementation and continual further development of the Action Plan as well as the integration of the proposed actions into the German healthcare system, the proper structural prerequisites must be set in place. NAMSE bears a special responsibility for the field of rare diseases and thus recommends that the Action Coalition be continued for this purpose.

Proposed action 52:

Even after passage of the National Action Plan NAMSE should continue its efforts with the collaboration of all previous partners, the goal being to evaluate and follow-up in due time the implementation of the Action Plan. To this end, the necessary structures and processes (e.g., Steering Committee, coordinating office, means of communication) should be addressed in a separate organizational concept.

Implementation: after passage of the National Action Plan
Responsible bodies: German Federal Ministry of Health (BMG), German Federal Ministry for Education and Research (BMBF), ACHSE e.V.

[29] Europäische Kommission (2011): EUROBAROMETER Spezial 361. Bekanntheit seltener Erkrankungen unter den Europäern. Available online at http://ec.europa.eu/health/rare_diseases/docs/ebs_361_de.pdf

4. Appendices

4.1 Appendix 1: Joint Declaration

Approximately 7,000 to 8,000 out of the ca. 30,000 known diseases are classified as rare diseases. In the European Union, a disease is deemed to be rare if it affects not more than 5 out of 10,000 persons in the EU. An estimated 4 million people suffer from a rare disease in Germany, and approx. 30 million throughout the European Union.

It is the rarity of the individual diseases that renders research and the medical care of those affected difficult for both medical and economic reasons. Therefore, the diagnosis and therapy of these diseases are fraught with particular challenges.

In Germany's pluralistically structured health care system that is characterised by diverse levels of competencies, long-term improvements in the prevention, diagnosis and therapy of rare diseases can only be accomplished if we succeed in assembling initiatives and making all actors involved cooperate in a coordinated and goal-oriented manner that consistently puts patients' care needs first.

The parties to this agreement support the initiative for the formation of a National Action League for People with Rare Diseases. They share the opinion that joint action can create the prerequisites for an enhancement of the health situation of people with rare diseases that is effective over the long term. They declare their willingness to contribute towards the implementation of the established goals through their active participation in the **Action League.**

The Action League shall contribute to implementing the Recommendation of the Council of the European Union. This includes:

- drafting a National Action Plan for Rare Diseases,
- implementing and monitoring this Plan,
- supporting the establishment of centers of excellence.

The Action League is intended to coordinate measures for improving the health situation of persons with rare diseases and initiate pilot projects and further action in the field of rare diseases.
The Action League works to the following principles:

It does not pursue any economic interests.

- The Action League works from a patient-centred approach. The patients and their concerns are paramount for the activities of the Action League.
- The specific requirements involved in rare diseases are taken into consideration.
- The Action League is expected to work in an efficient and transparent manner.

With the adoption of this Joint Declaration, the partners in the Action League document their commitment to achieving the goals established and the implementation measures by means of their active participation. The following are the partners in alphabetical order:

ACHSE e.V.
Allianz chronischer seltener Erkrankungen
(Alliance for Chronic Rare Diseases)

Arbeitsgemeinschaft der Obersten Landesgesundheitsbehörden (AOLG)
vertreten durch das jeweilige Vorsitzland
(Working group of the highest health authorities of the Federal Laender, represented by the Federal Land chairing the Group)

Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften (AWMF)
(Association of the Scientific Medical Societies)

Beauftragter der Bundesregierung für die Belange der Patientinnen und Patienten
(German Federal Government Commissioner for Patients' Affairs)

Bundesarbeitsgemeinschaft Selbsthilfe von Menschen mit Behinderung und chronischer Erkrankung und ihren Angehörigen e. V. (BAG SELBSTHILFE e. V.)
(Federal Association of Self-help Organizations of People with Disabilities and Chronically Ill People and Their Relatives in Germany)

Bundesärztekammer
(German Medical Association)

Bundesministerium für Arbeit und Soziales
(Federal Ministry of Labour and Social Affairs)

Bundesministerium für Bildung und Forschung
(Federal Ministry of Education and Research)

Bundesministerium für Familie, Senioren, Frauen und Jugend
(Federal Ministry for Family Affairs, Senior Citizens, Women and Youth)

Bundesministerium für Gesundheit
(Federal Ministry of Health)

Bundespsychotherapeutenkammer
(Federal Association of Psychotherapists)

Bundesverband der Pharmazeutischen Industrie e. V. (BPI)
(Federal Association of the German Pharmaceutical Industry)

Bundesverband Medizintechnologie e.V.
(German Medical Technology Association)

Bundeszahnärztekammer
(German Dental Association)

Deutsche Forschungsgemeinschaft

(German Research Foundation)

Deutscher Hausärzteverband e.V.
(German Association of General Practitioners)

Deutsche Krankenhausgesellschaft e.V.
(German Hospital Federation)

Deutscher Pflegerat e.V.
(German Council of Nursing)

Gemeinsamer Bundesausschuss
(Federal Joint Committee)

GKV-Spitzenverband
(Federal association of Statutory health insurance funds)

Kassenärztliche Bundesvereinigung
(Federal Association of Panel Doctors)

Kassenzahnärztliche Bundesvereinigung
(Federal Association of Panel Dentists)

Medizinischer Fakultätentag der Bundesrepublik Deutschland e.V. (MFT)
(German Association of Medical Faculties)

Orphanet-Deutschland
(The Portal for Rare Diseases and Orphan Drugs Germany)

PKV Verband der privaten Krankenversicherung e. V.
(German Association of Private Health Insurance Funds)

Verband der Diagnostica-Industrie e.V. (VDGH)
(German Association of Diagnostics Industry)

Verband der forschenden Pharmaunternehmen - vfa bio
(German Association of Research-based Pharmaceutical Companies)

Verband der Universitätsklinika Deutschlands e.V. (VUD)
(Association of University Clinics in Germany)

4.2 Appendix 2: Preliminary List of Criteria to be met in the Three-tiered Center Model

		Type A (reference centers for rare diseases, with centers of expertise for xyz)	Type B (centers of expertise for a specific rare disease or disease group x)	Type C (cooperating centers for a specific rare disease or disease group x)
		Role: Non-disease specific: several rare diseases or groups of rare diseases, several type B centers work together under an overarching center Actor: generally university clinics	Role: Disease specific (single rare disease or group of rare diseases): clear diagnosis or suspected diagnosis Type B centers fulfill the requirements of type C centers Actor: hospitals with specialized outpatient and inpatient departments for rare diseases	Role: Disease specific (single rare disease or group of rare diseases): clear diagnosis or clear suspected diagnosis, particularly well suited for providing care close to home Actor: subspecialized outpatient practices, group practices, medical care centers, hospitals with specialized outpatient clinics
Disease or disease group specific	Care	Task: Availability of special non-disease specific healthcare services for several rare diseases or groups of rare diseases Criteria: 1. Proof of special expertise, special expert knowledge, international expertise 2. SOPs for seamless care pathways between the individual, integrated type B centers 3. Guarantee availability of SOPs for seamless care pathways in integrated type B centers 4. SOPs for the structural cooperation of the individual, integrated type B centers (common use devices, infrastructure, IT platforms, joint case reviews, etc.) 5. SOPs for patient care across sectors 6. SOPs for confirmation of diagnosis 7. Access to innovative special diagnostic methods 8. Availability of necessary team for dealing with the specific rare disease in acc. with guidelines or	Task: Outpatient and inpatient care of patients with a clear diagnosis or a clear suspected diagnosis, multiprofessional and interdisciplinary Criteria: 1. Proof of special expertise for the specific rare disease 2. Availability of a coordination office within the center to guide patients through the center and if necessary to refer them to another facility specialized for that specific rare disease 3. SOPs for seamless care pathway within the center 4. SOPs for confirmation of diagnosis 5. Availability of necessary team for dealing with the specific rare disease in acc. with guidelines or consensus papers 6. Proof of proper composition of team, SOPs for case reviews within the team; regular,	Task: Outpatient care of patients with clear diagnosis or clear suspected diagnosis, multiprofessional and interdisciplinary; first contact for patients with clear diagnosis or clear suspected diagnosis; cooperation with further local care providers (e.g., primary care physicians, pediatricians, outpatient care services, social services, counseling services and other specialists such as radiologists and psychotherapists) Criteria: 1. Proof of special expertise for the specific rare disease 2. SOPs for cooperation with primary care providers (with quality and documentation standards) 3. SOPs for seamless care pathway within the center 4. Availability of a necessary team for dealing with the specific rare disease in acc. with guide-

Notation: The catalogue of criteria is preliminary and serves as a guide only.
It must be updated and further developed as necessary.

		Type A (reference centers for rare diseases, with centers of expertise for xyz)	Type B (centers of expertise for a specific rare disease or disease group x)	Type C (cooperating centers for a specific rare disease or disease group x)
Disease or disease group specific	Care	consensus papers 9. Proof of the composition of /co-operation within the team, (SOPs for case reviews within the team; regular, documented team meetings) 10. Concept for psychosocial care 11. Transitional concept Task: Availability of a quality-assured, innovative genetic diagnosis and interpretation above and beyond standard care Criterion: Access to high throughput methods incl. interpretation and qualified patient information (perhaps in cooperation with patient organizations) Task: Nationwide guidance of patients towards specialized care opportunities Criterion: Availability of a patient "guide" Task: Mandatory participation in the mapping of available care provision facilities Criterion: Participation in corresponding measures (e.g., regular enquiries regarding care structures) Task: Structured cooperation with non-disease specific and specialist patient organizations (where available), e.g., participation in continuing education, information events, preparation of patient information Criterion: SOPs for cooperation with patient organizations Task: Participation in the development of	documented team meetings 7. Concept for psychosocial care 8. Transitional concept Task: Structured cooperation with relevant specialist patient organization (where available), e.g., participation in further education, information events, preparation of patient information Criterion: SOPs for cooperation with patient organizations Task: Participation in disease-specific networking of all type B centers Criterion: SOPs for joint case reviews, quality circles, etc. Task: Disease-specific networking with type C centers (or primary care providers and other non-medical providers) Criterion: SOPs for joint case reviews, SOPs for outpatient consultation/clinics, availability of necessary IT incl. provisions for telemedicine Task: Implementation of special diagnostics Criterion: Access to special diagnostic methods required for the specific rare disease or disease group in acc. with guidelines or consensus papers Task: Participation in the development of information services Criterion: SOPs for participation in the	lines or consensus papers, where necessary in cooperation 5. Concept for psychosocial care 6. Proof of the composition of the team, SOPs for case reviews within the team; regular, documented team meetings Task: Structured cooperation with the relevant patient organization (where available) Criterion: SOPs for cooperation with the patient organization (where available), e.g., participation in further education, information events, preparation of patient information Task: Mandatory cooperation with the correspondingly specialized type B and, if necessary, type A centers Criterion: Cooperation schemes have been agreed upon, reporting channels, the obligations regarding the transmission of documentation and participation in registries are clearly delineated therein Task: Integration via the individual type A center in research projects and clinical studies Criterion: SOPs for clear, documented cooperation Task: Regular participation of physicians, care providers and nonmedical personnel in continuing education on the

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		Type A (reference centers for rare diseases, with centers of expertise for xyz)	Type B (centers of expertise for a specific rare disease or disease group x)	Type C (cooperating centers for a specific rare disease or disease group x)
		common diagnostic and therapy standards Criterion: Collaboration/initiation of guidelines and consensus papers, international networking Task: Support for type B and type C centers in planning therapy based on specific standards Criterion: Specific SOPs for specialized outpatient clinics, availability of necessary IT incl. provisions for telemedicine Task: Support for type B and type C centers based on specific standards for special diagnosis and diagnosis confirmation Criterion: Specific SOPs for specialized outpatient clinics, availability of necessary IT incl. provisions for telemedicine Task: Establishment, coordination, participation in national and international registries Criterion: Availability of corresponding infrastructure, SOPs for networking, compliance with accepted standards	development of information services Task: Mandatory participation in the mapping of available care provision facilities Criterion: Participation in corresponding measures (e.g., regular enquiries regarding care structures)	specific rare diseases Criterion: Rules of documentation to prove participation in continuing education, concept for team training Task: Participation in health services research Criterion: Availability of IT structure for participation in registries
	Teaching	Task: Regular opportunities for continued education (training/advanced training incl. rotation programs) in cooperation with patient organizations Criterion: Concept for the participation in and the realization of such programs, concept for the academic supervision of young scientists with respect to the rare disease in question Task: Organization and realization of (interdisciplinary) continued	Task: Regular opportunities for continued education (advanced training) for physicians/nonmedical personnel (where necessary training) Criterion: Concept for continued education programs (advanced training) for medical and nonmedical team members Task: Organization and implementation of (interdisciplinary) continued education measures Criterion: Concept for regular	Task: Regular participation in continued education on the individual rare diseases for physicians, care providers and nonmedical personnel Criteria: Rules of documentation to prove participation in continued education, continued education concepts for team training

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It must be updated and further developed as necessary.

		Type A (reference centers for rare diseases, with centers of expertise for xyz)	Type B (centers of expertise for a specific rare disease or disease group x)	Type C (cooperating centers for a specific rare disease or disease group x)
		training Criterion: Concept for regular courses of continued training	continued education courses	
	Research	Task: Scientific research on the individual rare diseases, i.e., research orientation incl. centers for clinical studies, to include the following items: Basic research (1. Genetics and etiology, 2. Pathophysiology, mechanisms of disease, 3. Development of medicinal products, preclinical research) Clinical research (1. cohort studies, networks, registries, methodical development and creation of registries and biobanks, 2. Diagnostic research, biomarkers, 3. Therapeutic studies, health services research, implementation of clinical studies Criteria: The institution needs a research concept that covers basic research, clinical research and health services research. When setting up a type A center, the following prerequisites, which go beyond the criteria for type B and type C centers, are necessary: 1. Coordination and management of the data of networked registries, if applicable also with biobanks, crosslinked with other databases 2. Qualified (institutionalized) cooperation with patient organizations 3. Integration in the research network of the type A centers 4. National/international links to other research institutions and EU-networks 5. Availability of a study infrastructure for initiating, carrying out and heading clinical studies (incl. the	Task: Participation in research projects, clinical studies, health services research, registries Criterion: Availability of necessary IT structure, documentation of patients in the registries, availability of an infrastructure for clinical studies (incl. availability of qualified personnel) for implementing and, if necessary, heading clinical studies; SOPs for procedures and contents of cooperation with type A/ type C centers; cooperation agreements with other centers or partners, compliance with (as yet undefined) criteria of research quality	Task: Informing patients under care regarding participation in research projects (registries, health services research, if necessary basic research) and clinical studies in collaboration with the specific type A/type B center Criterion: SOPs for the procedures regarding participation of patients in research projects at type A/type B centers incl. consideration of ethical aspects; SOPs on contents and procedures regarding cooperation with type A/type B centers; cooperation agreement with type A/type B centers Task: Participation in registries/biobanks Criterion: Availability of IT structure for participation in registries/biobanks, SOPs on contents and procedures regarding cooperation; cooperation agreements Task: Participation in health services research projects Criterion: Availability of an IT-structure for participation in registries

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		Type A (reference centers for rare diseases, with centers of expertise for xyz)	Type B (centers of expertise for a specific rare disease or disease group x)	Type C (cooperating centers for a specific rare disease or disease group x)
		availability of qualified personnel) 6. Availability of necessary infrastructure for carrying out basic research (laboratories, equipment, IT systems, etc.) 7. Concept for quality control of registries, clinical studies, etc. 8. Cooperation agreements with partners 9. SOPs on content and procedures of cooperation 10. Compliance with criteria of research quality (to be defined)		
non-disease specific		Task: Diagnostics of patients with an unclear diagnosis Criteria: • SOPs for interdisciplinary diagnosis of patients with an unclear diagnosis (interdisciplinary consultation for unestablished diagnoses) • Access to high throughput methods • Access to special innovative diagnosis methods • Participation in remote diagnostic procedures using telemedicine Task: Structural prerequisites for dealing with absent or unclear diagnoses Criteria: • Availability of a patient guide/coordinator • SOPs for patients with an unclear diagnosis • SOPs for multiprofessional and interdisciplinary cooperation • Availability of telemedicine opportunities • Coordination partner for EU reference networks for multiple rare diseases		

Notation: The catalogue of criteria is preliminary and serves as a guide only.
It must be updated and further developed as necessary.

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