

## **2014 REPORT ON THE STATE OF THE ART OF RARE DISEASE ACTIVITIES IN EUROPE**



## **STATE OF THE ART OF RARE DISEASE ACTIVITIES IN GERMANY**

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The European Union Committee of Experts on Rare Diseases (EUCERD) was established in 2009 and its mandate ended in 2013. It is replaced from 2014 by the Commission Expert Group on Rare Diseases. The EUCERD Joint Action continues to support the activities of the new Expert Group until 2015.

More information on the activities of the former European Union Committee of Experts on Rare Diseases and the EUCERD Joint Action can be found at [www.eucerd.eu](http://www.eucerd.eu).

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## ACRONYMS

CAT - Committee for Advanced Therapies at EMA  
CHMP - Committee for Medicinal Products for Human Use at EMA  
COMP - Committee on Orphan Medicinal Products at EMA  
DG - Directorate General  
DG Enterprise - European Commission Directorate General Enterprise and Industry  
DG Research - European Commission Directorate General Research  
DG Sanco - European Commission Directorate General Health and Consumers  
EC - European Commission  
ECRD - European Conference on Rare Diseases  
EEA - European Economic Area  
EMA - European Medicines Agency  
ERN - European reference network  
EU - European Union  
EUCERD - European Union Committee of Experts on Rare Diseases  
EUROCAT - European surveillance of congenital anomalies  
EUROPLAN - European Project for Rare Diseases National Plans Development  
EURORDIS - European Organisation for Rare Diseases  
FDA - US Food and Drug Administration  
HLG - High Level Group for Health Services and Medical Care  
HTA - Health Technology Assessment  
IRDiRC – International Rare Diseases Research Consortium  
JA - Joint Action  
MA - Market Authorisation  
MoH - Ministry of Health  
MS - Member State  
NBS - New born screening  
NCA - National Competent Authorities  
NHS - National Health System  
PDCO - Paediatric Committee at EMA  
RDTF - EC Rare Disease Task Force  
WG - Working Group  
WHO - World Health Organization

## GENERAL INTRODUCTION

This document was produced by the Scientific Secretariat of the European Union Committee of Experts on Rare Diseases (EUCERD), through the EUCERD Joint Action: Working for Rare Diseases (N° 2011 22 01), which covers a three year period (March 2012 – February 2015).

The European Union Committee of Experts on Rare Diseases (EUCERD) was established in 2009 and its mandate ended in 2013. It is replaced from 2014 by the Commission Expert Group on Rare Diseases. The EUCERD Joint Action continues to support the activities of the new Expert Group until 2015.

The present report aims to provide an informative and descriptive overview of rare disease activities at European Union (EU) and Member State (MS) level in the field of rare diseases and orphan medicinal products up to the end of 2013. A range of stakeholders in each Member State/country have been consulted during the elaboration of the report, which has been validated as an accurate representation of activities at national level, to the best of their knowledge, by the Member State/country representatives of the Commission Expert Group on Rare Diseases. The reader, however, should bear in mind that the information provided is not exhaustive and is not an official position of the European Commission, its Agencies or national health authorities.

The report is split into six parts:

Part I: Overview of rare disease activities in Europe

Part II: Key developments in the field of rare diseases in 2013

Part III: European Commission activities in the field of rare diseases

Part IV: European Medicines Agency activities and other European activities in the field of rare diseases

Part V: Activities in EU Member States and other European countries in the field of rare diseases

Part VI: Activities at National level in each EU Member State and other European countries in the field of rare diseases

Parts I – V also include a description of the methodology, sources and validation process of the entire report, and a selected bibliography and list of persons having contributed to the report.

The present document contains the information from Parts II and V of the report concerning Germany. A list of contributors to the report and selected sources are in annex of this document. For more information about the elaboration and validation procedure for the report, please refer to the general introduction of the main report.

Each year, there are around 15 000 downloads of the different sections of the report combined.

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# RARE DISEASE ACTIVITIES IN GERMANY

## Definition of a rare disease

Stakeholders in Germany accept the European Regulation on Orphan Medicinal Products definition of a prevalence of not more than 5 in 10 000 individuals.

## National Plan of Action for People with Rare Diseases

In the German health care system every patient is entitled to complete health care coverage consisting of preventive, diagnostic, therapeutic and rehabilitative measures. The medical care of patients is generally of high quality and the access to medical doctors and specialists is on a high international standard.

In 2009, the German Federal Ministry of Health (BMG) published a research report entitled "Measures to improve health in people with rare diseases." The goal of this study was, first, to analyse the care currently offered 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. The results of this research report pointed clearly to the need to improve the pluralistic health care system in Germany to include the prevention, diagnosis and therapy of rare diseases. In the process, the priority fields of action in the areas of the general care situation, specialised forms of care, diagnosis, therapy, exchange of information and experience as well as research, were identified. The report suggested that improvements would only be possible 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 Seltenern Erkrankungen* (NAMSE)<sup>1</sup>) 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 - a co-ordination and communication platform comprising all key bodies and organisations - responsible for coordinating and publishing the common efforts. The primary goal of NAMSE was to prepare suggestions for establishing a National Plan of Action for People with Rare Diseases by 2013 as well as supporting the establishment of national centres of expertise. All essential partners from the health care system involved with rare diseases (both central and umbrella organizations) were and still are participants in the National Action League: the Federal Ministry of Health, the Federal Ministry of Education and Research, the Federal Ministry of Labour and Social Affairs, the Federal Ministry for Family Affairs, Senior Citizens, Women and Youth, the 16 Federal *Laender* (*federal states*), health insurance funds (sickness funds), associations of panel doctors, hospital associations, the Federal Joint Committee, medical societies, scientific societies, patient representatives, including the National Alliance for Rare Diseases "ACHSE". NAMSE is coordinated in a joint effort by the Ministry of Health, the Ministry of Education and Research and ACHSE. By accepting the common declaration all members of NAMSE 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. NAMSE consists of a Steering Committee. The Steering Committee in turn consists of the representatives from the 28 member partners of NAMSE. This committee sets the goals and defines the methods in accordance with the results of the research report. Thus, for the drafting of the National Plan of Action the four workgroups were founded to implement the four major action fields "information management," "diagnostics," "care/centres/networks" and "research." Members of these workgroups were high-ranking experts from the respective fields.

One established goal is to contribute to implementing the Recommendation of the Council of the European Union. This includes the drafting of a National Action Plan for Rare Diseases and its implementation and monitoring, the coordination of measures for improving the health situation of persons with rare diseases, supporting the establishment of centres of expertise, initiating pilot projects and further action in the field of rare diseases, and assembling initiatives and making all actors involved cooperate in a coordinated and goal-orientated manner to put patients' care first.

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<sup>1</sup> <http://namse.de/>

At the end of a three-year co-ordination process, which required the commitment of all of those involved in the healthcare sector, the German National Plan of Action for People with Rare Diseases<sup>2</sup> was adopted in August 2013. A total of 52 policy proposals have been included in this plan covering 7 action fields. This publication of these policy proposals concludes the first phase of the National Plan of Action for People with Rare Diseases. Now begins the implementation and monitoring phase of the suggested proposals.

### Centres of expertise

The implementation of national centres of expertise in Germany is challenged by the decentralised, federal structure of the German health care system, since the provision of sufficient structural resources for health care is a matter solely concerning the *Laender* (federal states). German legislation provides the basis for the *Ambulante Spezialfachärztliche Versorgung* (highly specialised outpatient care) for a limited number of diseases (see below), some of which are rare. In order to improve further the care of complex diseases – in particular rare diseases – new opportunities were opened by the Act on Care Structures in the Statutory Health Insurance System (*GKV-Versorgungsstrukturgesetz – GKV-VStG*) that entered into force on 1 January 2012. It provides for the gradual establishment of a new specialist care sector aimed to achieve seamless care provision between outpatient and inpatient settings. Specifically, highly specialised outpatient care can now be provided by both hospitals and non-hospital doctors (office-based specialists) on a high level and at the same conditions in terms of quality and remuneration (Social Code V, Section 116b).

Highly specialised out-patient care comprises the diagnosis and management of complex, hard-to-treat diseases that require special qualifications, interdisciplinary co-operation and appropriate equipment. They include rare diseases and conditions with correspondingly low case numbers such as:

- tuberculosis
- cystic fibrosis
- haemophilia
- malformations, congenital skeletal abnormalities and neuromuscular conditions
- serious immunological disorders
- biliary cirrhosis
- primary sclerosing cholangitis
- Wilson's disease
- transsexualism
- caring for children with congenital metabolic disorders
- Marfan's syndrome
- pulmonary hypertension
- short bowel syndrome
- caring for pre- and post-transplant patients and for living organ donors

The sector of highly specialised outpatient care is organised by the Federal Joint Committee (*Gemeinsamer Bundesausschuss, G-BA*) that fleshes out the relevant legal provisions through binding guidelines. This includes, particularly, the specification of diseases, scope of treatment, technical resources and staff required for service provision as well as referral requirements and quality assurance measures. The Federal Joint Committee (*G-BA*) also can extend this list of diseases which has been stipulated by law (Social Code V, Section 116b).

The Federal Joint Committee (*G-BA*) is the supreme decision-making body of the so-called self-governing system of service providers and health insurance funds in Germany<sup>3</sup>. In the field of outpatient care for rare diseases provided by hospitals according to Social Code Book V, Section 116b, the Federal Joint Committee (*G-BA*) has to regulate both the structural and personnel resources needed for outpatient care provided by both hospitals and office-based specialists. Consequently, all of these service providers are subject to the same staffing, equipment and regulatory/contractual requirements as well as special measures for quality assurance. Basically, access is free for service providers that prove compliance with the applicable requirements.

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<sup>2</sup> <http://www.namse.de/images/stories/Dokumente/Aktionsplan/national%20plan%20of%20action.pdf>

<sup>3</sup> Physicians, dentists, hospitals and health insurance funds are represented in the *G-BA*. Since 2004 national groups representing patients were given the right to file applications and to participate in the consultations of the *G-BA*. The *G-BA* issues the directives/binding guidelines that are necessary for safeguarding medical service provisions. The latter aims to ensure that medical services for persons insured under the statutory health insurance in Germany are adequate, appropriate and efficient. The *G-BA* issues directives and thus determines the benefit package of the statutory health insurance (*gesetzliche Krankenversicherung, GKV*) covering about 70 million people. The *G-BA* is responsible for reimbursement decisions in the statutory health insurance (*GKV*).

From now on, the Federal Joint Committee (*G-BA*) will be able to broaden the catalogue of services and diseases in response to an application from one of its member organisations or the organisations on the Federal level that champion the interests of patients, also the self-help organisations of chronically ill and disabled persons. In addition to the so-called 'Section 116b centres', other centres like social-paediatric centres (Social Code V, Section 119) or university clinics for outpatient care (Social Code V, Section 117) may also be involved in the treatment of rare disease patients. This applies also to specialised ambulatory care offered by authorized physicians in hospitals.

Several self-appointed centres for rare diseases already exist in Germany<sup>4</sup>. However, these do not share a nation-wide concept and are not reviewed in respect of any specific quality criteria for rare diseases. NAMSE recommends the establishment of centres 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. Some centres of expertise have a special role to play since, as reference centres, 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.

To facilitate the implementation of the three-tiered model of centres for rare diseases two actions were proposed by NAMSE. First existing funding options are to be used to ensure funding for the three-tiered structure of the centres for rare diseases. Once questions of funding and implementation have been resolved, it is recommended that the care providers implement the three-tiered model of NAMSE. Secondly a working group has been established in NAMSE by the steering committee to prepare the designation process for the three-tiered model of centres for rare diseases, taking into account the commonly agreed upon criteria published in the National Plan of Action. By now, a transparent preliminary procedure to designate the centres is under development by NAMSE.

The self-appointed centres for rare diseases hold regular meetings to improve networking (coordinated by Prof. Wagner). The group decided in 2013 to continue the state-wide cooperation of these centres; to share the experiences of the centres, with particular emphasis on their coordinating functions in both the framework of the medical faculties and the administration of the university hospitals; to share efforts to attain sustainability; to help patients with rare and very rare diseases, and their responsible physicians/experts or clinical departments, to find and use the best expertise available; to coordinate an application for financial support for clinical research; to share information on the participation of National or European institutions for research and clinical care in the field of rare diseases.

## Registries

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.

NAMSE recommends to set up a web-portal of registries concerning rare diseases in Germany. This facilitates access to existing registries, for example, through a webportal – a "telephone book" of such registries as it were. This webportal could represent in the future the national interface to communicate with the European registry platform of the EU-Commission Joint Research Centre in Ispra. Further NAMSE recommends to develop a prototypical registry for a "Disease-Specific Registries of Rare Diseases". This prototype – or individual software modules contained therein – should be adaptable for existing registries. A standardization of all existing registries is desirable.

Further NAMSE recommends 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. The German Federal Ministry of health supports a project to include Orphacodes into the current coding system of the ICD-10 GM to ensure that rare diseases are coded in health information systems.

There is no public central clinical trial registry dedicated solely to rare diseases. However the German Clinical Trials Register (Deutsches Register Klinischer Studien, DRKS) which is funded by the Federal Ministry of Education and Research (BMBF) aims at registering all trials performed in Germany, including those for rare diseases. All federal states are obliged to register cancers, including rare cancers, in existing population based cancer registries. An analysis based on the Orphanet database identifies about 80 registries, most of them belonging to academic institutions. Some of these registries are implicated in international networks or covers the whole European region.

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<sup>4</sup> Listed in <http://www.orpha.net/national/DE-DE/index/zentren-für-se/>

German teams contribute to European registries such as CompERA-XL, CWS-SoTiSaR, DOSAK, CEDATA-GPGE, EUROCAT, TREAT-NMD, EBAR, ENETS, EPICURE, EU-RHAB, EurIPFreg, EUROFA-EFACT, EHDN, EIMD, EurIPFnet, E-IMD, EURIPEDES, European Alport registry, EuroDSD, EUROSCA-R, EUTOS, Kids Lung Register, KINDLERNET, NCL-Registry, PODONET, Register for rare myeloproliferative neoplasms, RetDis Database, and RegiSCAR, and generally to [clinicaltrials.eu](http://clinicaltrials.eu).

### **Genetic testing and Newborn Screening Policy**

The Genetic Diagnosis Act (Gendiagnostikgesetz – GenDG) establishes the prerequisites for genetic testing, and genetic analysis conducted in the framework of genetic testing and stipulates requirements for the use of genetic samples and data. It applies to genetic testing and genetic analysis on born human beings as well as on embryos and fetuses during pregnancy and to the handling of the genetic samples and genetic data obtained in the process for medical purposes, to clarify parentage as well as the insurance sector and working life. It does not, however, apply to genetic testing and analysis and the handling of genetic samples and data *inter alia* for research purposes. The GenDG seeks to prevent discrimination based on genetic characteristics, to protect human dignity and the right to informational self-determination and aims at providing binding standards for good genetic testing practice.

Since 2005 there has been a mandatory legalised screening program covering fourteen conditions: phenylketonuria, biotinidase deficiency, galactosaemia, MCAD deficiency, VLCAD deficiency, LCHAD deficiency, CPT1, CPT2, CAT deficiencies, maple syrup urine disease, glutaric aciduria type 1, isovaleric acidemia, congenital adrenal hyperplasia and congenital hypothyroidism.

Newborn screening is a genetic test as defined in the GenDG. As such, it is subject to the exclusive right of medical professionals to practise medicine as well as the requirements for informed and written consent. The Federal Joint Committee - as the joint self-administration body representing health insurance funds, the medical profession and hospitals - specifies in a binding guideline the conduct of newborn screening and the diseases and conditions the screening for which is eligible for reimbursement by the statutory health insurance system.

Diagnostic tests are registered as available in Germany for 1880 genes and an estimated 2074 diseases in the Orphanet database<sup>5</sup>.

### **National alliances of patient organisations and patient representation**

In Germany, the German National Alliance for Chronic Rare Diseases (ACHSE) is a network of more than 100 patient organisations of people living with a specific rare disease. Through ACHSE, rare disease patient organisations support each other, exchanging know-how so as to strengthen their influence in the political arena and improve the quality and duration of life of people living with a rare disease. ACHSE is an active member of EURORDIS and a member of its Council of National Alliances.

In Germany, health-related self-help groups and organisations are eligible for financial support from the statutory health insurance funds. A legislative reform (1 January 2009) has made access to funding easier and the distribution of the funding ear-marked by the statutory health insurance funds is guaranteed: this meant about €40 million in 2011.

The Ministry of Health currently supports different projects concerning the participation of patients with rare diseases at the Charité Berlin. One of these projects (2009 – 2011) dealt with the “Contribution of self-help groups/ patient organisations to the organisation of interfaces within the health care system”, aimed at improving patient participation and orientation. The Ministry of Health also supports other activities in the field of rare diseases such as conferences, brochures, workshops.

An important role is played in the regulation of the medical services of the German health care system by self-governing bodies such as patient associations: since 2004, national groups representing patients participate in the consultations of the Federal Joint Committee.

### **Sources of information on rare diseases and national help lines**

#### ***Orphanet activities in Germany***

The Orphanet portal on rare diseases is available in German<sup>6</sup> and is widely used as a major information source on rare diseases in Germany. Since 2001 there is a dedicated Orphanet team in Germany, currently hosted by the Human Genetics department of the Hannover Medical School (MHH). This team is in charge of collecting

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<sup>5</sup> Information extracted from the Orphanet database (January 2014): this information is not verified by the German Federal Ministry of Health.

<sup>6</sup> [www.orphanet.de](http://www.orphanet.de)

data on rare disease related services (specialised clinics, medical laboratories, ongoing research, registries, clinical trials and patient organisations) in their country for entry into the Orphanet database. This team was officially designated as the Orphanet national team for Germany by the Federal Ministry of Health in 2010. In 2010, the Orphanet-Germany national website was launched<sup>7</sup>. This German language page is maintained by the Orphanet-Germany team and features information, news and events specific to field of rare diseases in Germany. Users can access the main Orphanet site in any of the five available languages, as usual, from this page.

Further, NAMSE recommends to set up a central and integrated information portal for rare diseases on the Internet with the focus on quality-assured knowledge for patients, their relatives and experts. An interactive map of all care-giving structures (se-atlas) is being developed as one part of the portal. The different care offers should be presented by the map and additional information on contact details of the professionals and institutions for the respective disease. [www.se-atlas.de](http://www.se-atlas.de)

### **Official information centre for rare diseases**

There is no official information centre on rare diseases in Germany.

### **Help line**

There is currently no official help line for rare diseases in Germany. 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. A project (ZIPSE) funded by the Federal Ministry of Health concerning an information portal for rare diseases is going to examine the need for such a service. However, ACHSE offers a privately funded help line for people living with a rare disease since 2006 and answers about 600 to 800 requests per year. The help line is also open for professionals, but not often addressed by them. The help line is financed solely with donations and through charity events.

### **Other sources of information on rare diseases**

All medicinal products, including orphan medicinal products, are included in a database called PharmNet, run by the German Institute of Medical Documentation and Information (DIMDI) ensuring public access to package leaflet, summary of product characteristics (Fachinformation in German) and the assessment report (publicly accessible version).

On the first of January 2011 Section 42b AMG (Arzneimittelgesetz, Medicinal Products Law) came into force stipulating pharmaceutical companies and sponsors of clinical trials to report results of clinical trials to the federal higher authorities for purposes of publication in the public database PharmNet.Bund run by DIMDI<sup>8</sup>.

The ACHSE website<sup>9</sup> provides a platform for information on rare diseases. This platform is a validated and patient-orientated source of information. It encourages patient organisations to improve their information continuously. ACHSE has also established a help line to inform patients and their families in particular those without a diagnosis or an established patient organisation.

The KINDERNETZWERK<sup>10</sup> offers a service line for patients with rare diseases together with patient oriented online diseases descriptions. The KINDERNETZWERK additionally holds a database for registering parents with children suffering of rare diseases. Information on patient groups can also be found at the NAKOS website<sup>11</sup> (The National Clearing House for the Encouragement and Support of Self-Help Groups). Other non-rare disease specific help lines are available to help patients understand the health care system.

Beside the above mentioned internet information sources for rare diseases there exist several informational websites for rare diseases run by e.g. patient organisations, learned societies and university institutions. Some (genetic) diagnostic labs also offer information about tested diseases in detail. Several other internet databases are offering information on common diseases which imply also information on rare diseases: DermIS ([www.dermis.net](http://www.dermis.net)) an internet based information system for dermatology (recently public funded by the Federal Ministry of Education and Research, now private funding by Bayer Health Care),

<sup>7</sup> <http://www.orpha.net/national/DE-DE/index/startseite/>

<sup>8</sup> protocol related data from clinical trials (<http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm>), result related in the near future (<http://www.pharmnet-bund.de/dynamic/de/ergebnisberichte/index.htm>).

<sup>9</sup> [www.achse.info](http://www.achse.info)

<sup>10</sup> [www.Kindernetzwerk.de](http://www.Kindernetzwerk.de)

<sup>11</sup> [www.nakos.de](http://www.nakos.de)

ONKODIN ([www.onkodin.de](http://www.onkodin.de)) with focus on hematological diseases, public funding, [www.patienten-information.de](http://www.patienten-information.de) ([www.patienten-informationen.de](http://www.patienten-informationen.de)) of the ÄZQ (Agency for Quality in Medicine) – an initiative of the Bundesärztekammer (German Medical Association) and the Kassenärztliche Bundesvereinigung (National Association of Statutory Health Insurance Physicians) and others. The University Rostock, Albrecht-Kossel-Institut for Neurodegeneration is hosting the data-base [www.selteneerkrankungen.de](http://www.selteneerkrankungen.de), mainly focusing on rare neurodegenerative diseases and the laboratories that are apparently qualified for diagnosis (Funding is unclear). There is also the Rare Metabolic Diseases Database which receives public funding from the German Federal Ministry of Education and Research, and is hosted by the Bielefeld University, Bioinformatics Department. It also represents a patient registry for rare metabolic diseases.

### Guidelines

For some rare diseases there exist practice clinical guidelines (i.e. cystic fibrosis, diagnostic of myopathy, congenital adrenal hyperplasia) from the AWMF (Association of the Scientific Medical Societies, *Arbeitsgemeinschaft Wissenschaftlicher Medizinischer Fachgesellschaften*). In 2011 the Institute for Quality and Efficiency in Health Care (IQWiG) published a rapid report (V 10-01) concerning the question “What type of evidence is currently being considered in the development of clinical practice guidelines for rare diseases?”<sup>12</sup>.

### Training and education initiatives

Germany is elaborating a national catalogue of learning objectives for medicine for medical students. In this process criteria are being developed to integrate rare diseases in this catalogue to better incorporate them in basic medical training.

The Centre for Rare Diseases Tuebingen (University Hospital Tuebingen) provides continued education for physicians since April 2011. The program is called the German Academy for Further Medical Training on Rare Diseases (FAKSE). The goals of the academy were: to educate practice-based physicians and clinicians on the matter of rare diseases in an interdisciplinary and illustrative fashion; to raise awareness for these disorders and provide physicians with methodologies and “Red Flags” for better recognition of RD; and to bring physicians in contact with relevant experts and patient organisations. Throughout its first year, FAKSE organised four training courses and has already trained 250 physicians. Before and beside this programme there exist also other possibilities for continued education for physicians concerning rare diseases.

### National rare disease events in 2013

The German Society of Human Genetics (GfH) holds an annual conference in association with the Swiss and Austrian Societies of Human Genetics, where topics concerning rare diseases are given a spotlight. Several paediatric subspecialties have a tradition of focussing on rare diseases, especially the *Arbeitsgemeinschaft Pädiatrische Stoffwechselerkrankungen* (Paediatric Metabolic Medicine), Paediatric nephrology, Deutsche Gesellschaft für Kinderendokrinologie und –diabetologie (DGKED) e.V. (Paediatric endocrinology) and Paediatric rheumatology, all holding yearly meetings often including patient organisations. ACHSE organises meetings for patient organisations twice a year.

To mark Rare Disease Day 2013 a number of events were held across Germany to raise awareness of rare diseases in Berlin, Bielefeld, Dessau, Essen, Flensburg, Hamburg, Cologne, Münster, Nuremberg and Würzburg. The events included information stands and fairs, press conferences and balloon campaigns. Hospitals, medical professionals, health insurers and celebrities joined the cause to raise public awareness of rare diseases. In addition, the annual Eva Luise Köhler Research Prize for Rare Diseases was awarded in Berlin.

The ACHSE-Central Prize for Patient-Centered Care (ACHSE-Central Versorgungspreis) was awarded in Düsseldorf on 26 June 2013.

The Innovation-Congress “Rare heroes – Orphan Drugs and Rare Diseases in Germany” (Innovationskongress “Seltene Helden – Orphan Drugs und Seltene Erkrankungen in Deutschland) was held on 13 October 2013 by the Institute for Health and Social Research - IGES, Berlin

The Workshop “Registries for patients with undiagnosed Rare Diseases” was held on 21 November 2013 by Reseach for Rare (Research Networks sponsored by BMBF), TMF e.V. and ACHSE e.V.

### Hosted rare disease events in 2013

Amongst the events hosted in Germany and announced in *OrphaNews Europe* was the LeukoTreat Final Public Conference (3-6 July 2013, Berlin).

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<sup>12</sup> [https://www.iqwig.de/download/V10-01\\_Executive\\_Summary\\_Evidence\\_for\\_guidelines\\_on\\_rare\\_diseases.pdf](https://www.iqwig.de/download/V10-01_Executive_Summary_Evidence_for_guidelines_on_rare_diseases.pdf)

## **Research activities and E-Rare partnership**

### ***National research activities***

In 2003, the Federal Ministry for Education and Research (*Bundesministerium für Bildung und Forschung, BMBF*) funded ten networks of national academic groups, clinical centres, specialised laboratories and patients organisations for basic and clinical research for an initial three years. After a successful interim evaluation, nine of the networks for rare diseases were funded for another two years. The budget of this rare disease research programme was €31 million.

In 2007, the BMBF opened a new funding programme on rare diseases research with a substantial increase in budget to €24 million for the first 3 year period and a possible extension of the maximum funding duration of 3 times renewable 3 year periods for new networks. Starting in October 2008, 16 networks were funded for 3 years. In 2010, the networks have been granted €6 million additional funds for investments in shared research equipment, most notably next generation sequencing. In September 2010, a new call for proposals for the possible extension of previously funded networks and the creation of new networks was published. After the evaluation of 39 proposals by a review board of international rare disease experts, the BMBF is currently funding 12 research consortia since 2012 with more than €23million for three years.

Additional funding of rare disease research is ongoing in other funding initiatives of the BMBF such as the National Genome Research Network (NGFN), Innovative Therapies, Regenerative Medicine, Molecular Diagnostics, Clinical Trials and others with about €20 million in 2013. All these activities are funded within the framework programme "Health research". In co-operation with the Federal Ministry of Health, the BMBF assumes responsibility for the programme which is financed with funds from the BMBF. The support of RD research continues to be an important topic within this framework programme.

In 2013, the BMBF has commissioned a survey to collect information on funded research projects in Germany. The results are expected for summer 2014 and will be taken into account for the strategic development of future RD research funding.

The *Eva Luise und Horst Köhler Stiftung für Menschen mit Seltenen Erkrankungen*, a foundation of the former First Lady and the former president of the Federal Republic of Germany, is dedicated to patients with rare diseases and supports research projects into rare diseases annually since 2006.

Regional sources of funding are also available.

### ***Participation in European research projects***

Teams in Germany participate/have participated in 182 projects related to rare diseases and coordinated 57 projects.

### ***E-Rare***

Germany is a partner of the E-Rare project, represented by the BMBF and the Project Management Agency of the German Aerospace Centre (*PT-DLR*). Germany participated in the E-Rare joint transnational calls in 2007, 2009, 2011 and 2012 and funds the participating German research groups of 45 transnational research projects with a total of about €13 million. Germany participated in the 5<sup>th</sup> Joint Transnational Call in 2013 with German research groups participating in 8 of the 12 projects selected for funding with about € 2.8 million.

### ***IRDiRC***

The Federal Ministry of Education and Research (BMBF) is a committed member of IRDiRC.

### ***Orphan medicinal products***

#### ***Orphan medicinal product committee***

No specific information reported.

#### ***Orphan medicinal product market availability situation***

No specific information reported.

#### ***Orphan medicinal product pricing policy***

All orphan medicinal products are reimbursed directly after market authorisation. As the German maximum reimbursement prices scheme (Festbeträge) normally does not cover orphan medicinal products. Only generic products and those considered to belong to the same pharmacological or therapeutic group can be subject to maximum reimbursement prices that eventually set the retail-price of the manufacturer. Effective 1 January 2011, for every new drug with a new active substance a binding ex-factory price based on the added value of the drug has to be negotiated on Federal Level. This is carried out by the Federal Association of Sickness Funds

and the manufacturer. If no agreement can be achieved, the price is set by arbitrage committee, in which both contract parties are represented. For the first 12 months following marketing authorisation each new drug is still reimbursed at the full price set by the manufacturer. Mandatory Price Negotiations have been introduced by the Act for the New Order for the Drug Market in Social Health Insurance (AMNOG). According to this law, previous to price negotiations the value of the drug is evaluated. The manufacturer issues a Dossier when they enter the market. It is assessed by the German Institute for Quality and Efficiency in Health Care (IQWiG). The Federal Joint Committee (G-BA) appraises and decides on the added value of the drug compared to standard therapy. Orphan medicinal products authorised by EMA under EU-regulation 141/2000 with an annual turnover below €50 million are exempted from the benefit assessment, because the benefit is taken as granted. Still, price negotiations are mandatory also for these drugs.

#### **Orphan medicinal product reimbursement policy**

Once authorised at European level, all orphan medicinal products are fully reimbursed by the statutory health insurance (GKV). Until 31 December 2010, all newly authorised drugs could be put on the marketplace without any restrictions on reimbursed prices. Only generic products and those considered to belong to the same pharmacological or therapeutic group could be subject to maximum reimbursement prices that eventually set the retail-price of the manufacturer. Effective 1 January 2011, the act on new regulations for the drug-market (AMNOG) is mandating that all drugs with patented substances are subject to a cost/benefit analysis followed by a price negotiation. However, while this procedure that is limited to 12 months following marketing authorisation, is running, the product is still reimbursed at the price set by the manufacturer.

#### **Other initiatives to improve access to orphan medicinal products**

Irrespective of the prevalence of the disease, the off-label use of drugs is reimbursed by the statutory health insurance (GKV) on the following conditions: the drug will be used to treat a life-threatening or fatal disease; there is an absence of pharmaceutical therapy with a marketing authorisation in Germany; and there is scientific evidence of positive therapeutic effects<sup>13</sup>.

In Germany, as in many other European countries, it has been basically possible to administer promising medicinal products for severely ill patients before authorisation in case no alternatives exist. In 2005, on the basis of Art. 83 of the Regulation (EC) No 726/2004 the German government implemented general rules providing such medicinal products in form of so-called Compassionate Use Programmes in Section 21 subsection 2 no. 6 of the German Medicinal Products Act. In 2009 it was added that the provision of a medicinal product in such cases has to be free of charge. An ordinance, coming into force 2010, contains special regulations for the proper procedure of Compassionate Use Programmes. An overview on Compassionate Use Programmes confirmed by the Federal Institute for Drugs and Medical Devices (BfArM) is available on the website<sup>14</sup>. Once authorised, all orphan medicinal products are fully reimbursed by statutory health insurance.

#### **Other therapies for rare diseases**

No specific information reported.

#### **Orphan devices**

No specific information reported.

#### **Specialised social services**

No specific activity reported.

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<sup>13</sup> Orphan Drugs in Europe : Pricing, Reimbursement, Funding and Market Access Issues, Donald Macarthur (2011)

<sup>14</sup> [www.bfarm.de](http://www.bfarm.de)

# DEVELOPMENT OF RARE DISEASE ACTIVITIES IN 2013 IN GERMANY

## **National Plan of Action for People with Rare Diseases**

At the end of a three-year co-ordination process, which required the commitment of all of those involved in the healthcare sector, the German National Plan of Action for People with Rare Diseases<sup>15</sup> was adopted in August 2013. A total of 52 policy proposals have been included in this plan covering 7 action fields. This publication of these policy proposals concludes the first phase of the National Plan of Action for People with Rare Diseases. Now begins the implementation and monitoring phase of the suggested proposals.

## **Centres of expertise**

To facilitate the implementation of the three-tiered model of centres for rare diseases two actions were proposed by NAMSE. First existing funding options are to be used to ensure funding for the three-tiered structure of the centres for rare diseases. Once questions of funding and implementation have been resolved, it is recommended that the care providers implement the three-tiered model of NAMSE. Secondly a working group has been established in NAMSE by the steering committee to prepare the designation process for the three-tiered model of centres for rare diseases, taking into account the commonly agreed upon criteria published in the National Plan of Action. By now, a transparent preliminary procedure to designate the centres is under development by NAMSE.

The self-appointed centres for rare diseases hold regular meetings to improve networking (coordinated by Prof. Wagner). The group decided in 2013 to continue the state-wide cooperation of these centres; to share the experiences of the centres, with particular emphasis on their coordinating functions in both the framework of the medical faculties and the administration of the university hospitals; to share efforts to attain sustainability; to help patients with rare and very rare diseases, and their responsible physicians/experts or clinical departments, to find and use the best expertise available; to coordinate an application for financial support for clinical research; to share information on the participation of National or European institutions for research and clinical care in the field of rare diseases.

## **Registries**

NAMSE recommends to set up a web-portal of registries concerning rare diseases in Germany. This facilitates access to existing registries, for example, through a webportal – a “telephone book” of such registries as it were. This webportal could represent in the future the national interface to communicate with the European registry platform of the EU-Commission Joint Research Centre in Ispra. Further NAMSE recommends to develop a prototypical registry for a “Disease-Specific Registries of Rare Diseases”. This prototype – or individual software modules contained therein – should be adaptable for existing registries. A standardization of all existing registries is desirable.

Further NAMSE recommends 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. The German Federal Ministry of health supports a project to include Orphacodes into the current coding system of the ICD-10 GM to ensure that rare diseases are coded in health information systems.

## **Sources of information on rare diseases and national help lines**

### ***Orphanet activities in Germany***

NAMSE recommends to set up a central and integrated information portal for rare diseases on the Internet with the focus on quality-assured knowledge for patients, their relatives and experts. An interactive map of all care-giving structures (se-atlas) is being developed as one part of the portal. The different care offers should be presented by the map and additional information on contact details of the professionals and institutions for the respective disease. [www.se-atlas.de](http://www.se-atlas.de)

### ***Help line***

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

<sup>15</sup> <http://www.namse.de/images/stories/Dokumente/Aktionsplan/national%20plan%20of%20action.pdf>

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. A project (ZIPSE) funded by the Federal Ministry of Health concerning an information portal for rare diseases is going to examine the need for such a service.

### **Training and education initiatives**

Germany is elaborating a national catalogue of learning objectives for medicine for medical students. In this process criteria are being developed to integrate rare diseases in this catalogue to better incorporate them in basic medical training.

### **National rare disease events in 2013**

The German Society of Human Genetics (GfH) holds an annual conference in association with the Swiss and Austrian Societies of Human Genetics, where topics concerning rare diseases are given a spotlight. Several paediatric subspecialties have a tradition of focussing on rare diseases, especially the Arbeitsgemeinschaft Pädiatrische Stoffwechselerkrankungen (Paediatric Metabolic Medicine), Paediatric nephrology, Deutsche Gesellschaft für Kinderendokrinologie und –diabetologie (DGKED) e.V. (Paediatric endocrinology) and Paediatric rheumatology, all holding yearly meetings often including patient organisations. ACHSE organises meetings for patient organisations twice a year.

To mark Rare Disease Day 2013 a number of events were held across Germany to raise awareness of rare diseases in Berlin, Bielefeld, Dessau, Essen, Flensburg, Hamburg, Cologne, Münster, Nuremberg and Würzburg. The events included information stands and fairs, press conferences and balloon campaigns. Hospitals, medical professionals, health insurers and celebrities joined the cause to raise public awareness of rare diseases. In addition, the annual Eva Luise Köhler Research Prize for Rare Diseases was awarded in Berlin.

The ACHSE-Central Prize for Patient-Centered Care (ACHSE-Central Versorgungspreis) was awarded in Düsseldorf on 26 June 2013.

The Innovation-Congress “Rare heroes – Orphan Drugs and Rare Diseases in Germany” (Innovationskongress “Seltene Helden – Orphan Drugs und Seltene Erkrankungen in Deutschland) was held on 13 October 2013 by the Institute for Health and Social Research - IGES, Berlin

The Workshop “Registries for patients with undiagnosed Rare Diseases” was held on 21 November 2013 by Reseach for Rare (Research Networks sponsored by BMBF), TMF e.V. and ACHSE e.V.

### **Hosted rare disease events in 2013**

Amongst the events hosted in Germany and announced in *OrphaNews Europe* was the LeukoTreat Final Public Conference (3-6 July 2013, Berlin).

### **Research activities and E-Rare partnership**

#### ***National research activities***

Additional funding of rare disease research is ongoing in other funding initiatives of the Federal Ministry for Education and Research (*Bundesministerium für Bildung und Forschung, BMBF*) such as the National Genome Research Network (NGFN), Innovative Therapies, Regenerative Medicine, Molecular Diagnostics, Clinical Trials and others with about €20 million in 2013. All these activities are funded within the framework programme “Health research”. In co-operation with the Federal Ministry of Health, the *BMBF* assumes responsibility for the programme which is financed with funds from the *BMBF*. The support of RD research continues to be an important topic within this framework programme.

In 2013, the BMBF has commissioned a survey to collect information on funded research projects in Germany. The results are expected for summer 2014 and will be taken into account for the strategic development of future RD research funding.

#### ***E-Rare***

Germany participated in the 5<sup>th</sup> Joint Transnational Call in 2013 with German research groups participating in 8 of the 12 projects selected for funding with about € 2.8 million.

## LIST OF CONTRIBUTIONS<sup>16</sup>

### Contributions in 2010

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Georg F. Hoffmann (*Department of Pediatrics, University of Heidelberg*)

Gabriele Dreier

Daniela Eidt-Koch (*First author of the study "Strategies for improving the health care situation of patients with rare disease in Germany"*)

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### Contributions in 2011

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- *Maßnahmen zur Verbesserung der gesundheitlichen Situation von Menschen mit Seltene n Erkrankungen in Deutschland* (Strategies for improving the health care situation of patients with rare disease in Germany)  
[http://www.bmg.bund.de/fileadmin/dateien/Downloads/Forschungsberichte/110516\\_Forschungsbericht\\_Seltene\\_Krankheiten.pdf](http://www.bmg.bund.de/fileadmin/dateien/Downloads/Forschungsberichte/110516_Forschungsbericht_Seltene_Krankheiten.pdf)

<sup>16</sup> The contributors and validators of the report have contributed information which is accurate to the best of their knowledge. However, readers should take note that the contents of this report are illustrative and not exhaustive.

<sup>17</sup> All websites and documents were last accessed in May 2014.

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