2013 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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More information on the European Union Committee of Experts on Rare Diseases can be found at 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 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 2012. 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 European Union Committee of Experts 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 2012
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

Each part contains the following description of the methodology, sources and validation process of the entire report, and concludes with 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.

The German Federal Ministry of Health can only verify the information and data which concern federal responsibilities. The information provided here is illustrative and not exhaustive, and that it is validated by the EUCERD Member State representative to the best of their knowledge.
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 for rare diseases and related actions
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. There is no national plan for rare diseases in Germany at the moment, and there are no specific funds allocated to rare diseases in the health care system, although ad hoc funding for rare disease projects does exist.

However, the first steps are being made to establish a national plan for rare diseases. An in-depth evaluation of the situation of patients affected by rare diseases in Germany was published by the Federal Ministry of Health in August 2009. The study is entitled “Maßnahmen zur Verbesserung der gesundheitlichen Situation von Menschen mit Seltenen Erkrankungen in Deutschland” (‘Strategies for improving the health care situation of patients with rare disease in Germany’). The study analyses the current situation of care for persons with rare diseases in Germany from the perspective of various actors in the health care system by evaluating the perspective of public organisations, service providers and patient organisations on the basis of quantitative and qualitative surveys in the form of questionnaires, individual interviews and group discussions. In the process, the priority spheres for action in the areas of the general care situation, specialised forms of care, diagnosis, therapy, exchange of information and experience as well as research, are identified. This provides the basis for discussions regarding the first implications of implementing a national action forum as well as a national action plan for rare diseases in Germany. Subsequently, possible solutions for individual areas will finally be developed in co-ordination with existing and planned activities at EU level.

The Federal Ministry of Health in Germany initiated a national action league for people with rare diseases - Nationales Aktionsbündnis für Menschen mit Seltenen Erkrankungen (NAMSE) – in Berlin on 8 March 2010. NAMSE is a co-ordination and communication platform comprising all key bodies and organisations. The following stakeholders are part of this platform and the steering committee: 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 Länder (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.

This platform provides the basis for further concerted action, including the implementation of a National Action Plan on Rare Diseases. All partners, the major institutions and stakeholders of the German health care system, adopted a common declaration to improve the health situation for people with rare diseases in Germany. By this declaration all partners of the action league declare their willingness to contribute towards the implementation of the established goals through their active participation in the action league. 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 as recommenced in the EU Council Recommendation on an action in the field of rare diseases, 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. The process is organised in a steering committee and four working groups. Amongst others they try to identify ways how to improve the information on rare diseases, how to speed up the diagnosis of a rare disease, how centres of rare diseases could be structured, how to reach the experts and how research can more easily benefit the patients. At the end of this process the national action league for

1 http://namse.de/
people with rare diseases will recommend different actions for the German National Action Plan for Rare diseases.

By the end of 2012, around 60-70 proposed measures had been discussed in a workshop with all members of the NAMSE working groups. In the context of the elaboration of the national plan, the objective is to adopt the proposed measures in 2013 by NAMSE and then to hand them over to the federal government which will adopt the plan.

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 outpatient 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 (Gemeinsamer Bundesausschuss, 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 Germany2. In the field of outpatient care for rare diseases provided by hospitals according to Social Code Book V, Section 116b, the 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

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2 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 ensured 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).
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.

From now on, the Joint Committee 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.

There are already several self-appointed centres for rare diseases in Germany\(^1\). However, these do not share a nation-wide concept and are not reviewed in respect of any specific quality criteria for rare diseases. Therefore, it falls to the NAMSE process to define and develop national framework conditions for centres and networks dedicated to rare diseases. This process is underway, with a number of meetings organised to discuss criteria and indicators for such centres. This also includes topics such as the setting up of registries and biobanks as it does the drafting of criteria and eligibility procedures for the certification of future centres. The self-appointed centres for rare diseases hold regular meetings to improve networking (coordinated by Prof. Wagner, EUCERD member). The group decided in 2012 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**
There are some registries for rare diseases in Germany, although there is no centralised accreditation or designation of these registries. The future rare disease action plan will consider the area of registries and a possible minimal data set to be applied. 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.

German teams contribute to European registries such as CompERA-XL, CWS-SoTiSaR, DOSAK, CEDATA-GPGE, EUROCAT, TREAT-NMD, EBAR, ENETS, EPICURE, EU-RHAB, EurIPFreg, 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.

**Genetic testing and Newborn Screening Policy**
On 1 February 2010, a law passed by the German Bundestag regulating genetic testing in humans officially entered into force. The Genetic Diagnostics Act (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 foetuses 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 Genetic Diagnostics Act 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 acidaemia, congenital adrenal hyperplasia and congenital hypothyroidism.

\(^1\) Listed in [http://www.orpha.net/national/DE-DE/index/zentren-für-se/](http://www.orpha.net/national/DE-DE/index/zentren-für-se/)
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 Joint Federal 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 1754 genes and an estimated 1922 diseases in the Orphanet database.4

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 live 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 earmarked 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 German5 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 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 launched6. 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.

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. 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

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4 Information extracted from the Orphanet database (December 2012): this information is not verified by the German Federal Ministry of Health.
5 www.orphanet.de
6 http://www.orpha.net/national/DE-DE/index/startseite/
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. The ACHSE website 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 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 (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) 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), ONKODIN (www.onkoden.de) with focus on hematological diseases, public funding, www.patienten-information.de (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.selteneeinkrankungen.de, mainly focusing on rare neurogenerative 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.

**Good practice 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?”

**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. In 2012, two more courses on rare auto inflammatory diseases and rare tumours were held. Further courses for 2013 are already being planned. Before and beside this programme there exist also other possibilities for continued education for physicians concerning rare diseases.

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8 www.achse.info

9 www.Kindernetzwerk.de

10 www.nakos.de

11 https://www.iqwig.de/download/V10-01_Executive_Summary_Evidence_for_guidelines_on_rare_diseases.pdf
National rare disease events in 2012
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 pediatric subspecialities have a tradition of focussing on rare diseases, especially the Arbeitsgemeinschaft Pädiatrische Stoffwechselkrankungen (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.

In Germany several events were organised to mark Rare Disease Day 2012, coordinated by ACHSE. These events took place in Bielefeld, Dessau, Essen, Flensburg, Halle, Hamburg, Köln, München, Nürnberg and Würzburg. On 28 February 2012, the Eva Luise Köhler prize for research on rare diseases was awarded12. On 29 February 2012 a political symposium on the theme “rare but strong together – finding better ways for people with rare diseases” was organised by ACHSE and attended by the German Minister of Health, Daniel Bahr, and the President of the German Medical Association. Expert panel discussions provided the opportunity for in depth discussion on a number of themes. On 29 February 2012, the 3rd Rare Disease Day Symposium organised by Orphanet Germany was held at the Hannover Medical School. More than 30 different support groups attended the event and manned the stands at the event, providing an opportunity to meet the 350 visitors about. Some patient organisations gave talks together with the professionals from the newly created centre of rare diseases of the Hannover Medical School. This year was also the first time that professionals from the pharma industry presented their activities in the field of orphan medicinal products.

Hosted rare disease events in 2012
Amongst the events hosted in Germany and announced in OrphaNews Europe were: 4th International Tuebingen-Symposium on Pediatric Solid Tumors (Tuebingen, 16-18 February 2012), International Meeting on Rare Diseases: Mechanisms and New Therapeutic Approaches (Freiburg, 22-24 February 2012), 5th International Conference on Ectodermal Dysplasia (ED2012) (Erlanger, 1-3 June 2012), 10th International primary hyperoxaluria workshop (Bonn, 22-23 June 2012), European Human Genetics Conference 2012 (Nurnberg, 23-26 June 2012), Retina International World Congress (Hamburg, 14-15 July 2012).

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 are currently being funded. Six of these are extensions of previously funded networks, while the other 10 networks are new. 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 the 10 networks which started in 2008 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 has selected 12 networks for funding starting in 2012 with more than €21 million 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 2011. 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 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.

12 http://www.achse-online.de/cms/was_tut_achse/forschung_vorantreiben/koehler_forschungspreis.php
Participation in European research projects

German teams, or have participated, in European research projects for rare diseases including: ALS-degeneration, ACADEMIC GMP, AIPEGEM, ALPAMAN, AUTOROME, ANTEPRION, BIOMALPAR, BNE, CAV-4-MPS, CRANIRARE, CURE-FXS, CHD PLATFORM, CILMALVAC, CUREHLH, CURE-FXTAS, DSD-LIFE, DRUGSFORD, DEMCHILD, DARTRIX, EDEN, EMVDA, EMINA-2, ENRAH, ENCE-PLAN, EURADRENAL, ENS@T, EUCILIA, EUNEFRON, EURIFNET, EUROBOMET, ESPOIR, EURENOMICS, EUROBFNS, EUROCDG, EUROLAMINOPATHIES, EUROPEAN LEUKEMIA NET, EUROSCA, EURO-SCAR, EUROTAPS, EURORETT, EUROMOTOR, EUR-USH, EuroDBA, EUROSPA, ERMION, EuPAPNet, EUBNFS, EURO-CDG, ELA2-CN, EMINA, EPINOSTICS, EUREGENE, EUROPEAN LEUKEMIA NET, EMISA-SG, ESDN, FNAIT, FASTEST-TB, GAPVAC, GETHERHAL, GENEGRRAFT, GENOMIT, HEART-DM, HMA-IRON, HAE III, HDLIMICS, HUE-MAN, HMACASP, IPF-AE, IMPACTT, INNOVALY, INTEREAL, IMMOMEC, INOTHER, KINDLERNET, LEISHDRUG, NEUROMICS, MANASP, MITOTARGET, MTMpathies2, MYORES, MIMOVAX, MOLDIAG-PACA, NEUROSIS,NSEuroNet, NEUROTEN, NEMMYOP, NEWTBDURUGS, PULMOTENSION, OVCAD, OPTIPS, OVER-MyR, OPTATIO, OSTEOPETR, PPPT-MJB, PYRAMID, PADDINGTON, PONDNET, PEMPHIGUS, RD-Connect, RD PLATFORM, RevertantEB, RAREBESTPRACTICES, RHORCOD, RATSTREAM, RARE-G, RISCA, Splice-EB, STRONG, SKIN-DEV, TIRCON, TAIN, TARGET-CdLS, TRANSPOMART, WHIM-Thernet, WHIPPLE’S DISEASE and TB-VIR.

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 and 2011 and funds the participating German research groups of 35 transnational research projects with a total of about €10 million. Germany participated in the 4th Joint Transnational Call in 2012 with German research groups participating in 10 of the 11 projects selected for funding of about €3.4 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 incentives

Orphan medicinal products are also exempted from the mandatory rebate to the statutory and private health insurance funds on sales of products outside the German maximum reimbursement prices (Festbeträge) system, though evidence for the need of this exemption must be provided by the company13. See further under section “Orphan medicinal product reimbursement policy”.

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, they were excluded from any on reimbursed prices. 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 patented or non-generic substances a binding ex-factory price based on the value of the drug have 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.

13 Orphan Drugs in Europe : Pricing, Reimbursement, Funding and Market Access Issues, Donald Macarthur (2011)
**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. 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.

**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.

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.

**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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**DEVELOPMENT OF RARE DISEASE ACTIVITIES IN 2012 IN GERMANY**

**National plan for rare diseases and related actions**

By the end of 2012, around 60-70 proposed measures had been discussed in a workshop with all members of the Nationales Aktionsbündnis für Menschen mit Seltenen Erkrankungen (NAMSE) working groups. In the context of the elaboration of the national plan, the objective is to adopt the proposed measures in 2013 by NAMSE and then to hand them over to the federal government which will adopt the plan.

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14 Orphan Drugs in Europe: Pricing, Reimbursement, Funding and Market Access Issues, Donald Macarthur (2011)
15 [www.bfarm.de](http://www.bfarm.de)
16 [http://namse.de/](http://namse.de/)
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).

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 (Gemeinsamer Bundesausschuss, 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. In the field of outpatient care for rare diseases provided by hospitals according to Social Code Book V, Section 116b, the 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.

From now on, the Joint Committee 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.

There are already several self-appointed centres for rare diseases in Germany. However, these do not share a nation-wide concept and are not reviewed in respect of any specific quality criteria for rare diseases. Therefore, it falls to the NAMSE process to define and develop national framework conditions for centres and networks dedicated to rare diseases. This process is underway, with a number of meetings organised to discuss criteria and indicators for such centres. This also includes topics such as the setting up of

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17 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 ensured 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).

18 Listed in http://www.orpha.net/national/DE-DE/index/zentren-für-se/
registries and biobanks as it does the drafting of criteria and eligibility procedures for the certification of future centres. The self-appointed centres for rare diseases hold regular meetings to improve networking (coordinated by Prof. Wagner, EUCERD member). The group decided in 2012 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.

Training and education initiatives
The Centre for Rare Diseases Tuebingen (University Hospital Tuebingen) provides continued education for physicians since April 2011 entitled the German Academy for Further Medical Training on Rare Diseases (FAKSE) in April 2011. In 2012, two more courses on rare auto inflammatory diseases and rare tumours were held. Further courses for 2013 are already being planned.

National rare disease events in 2012
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 subspecialities have a tradition of focussing on rare diseases, especially the Arbeitsgemeinschaft Pädiatrische Stoffwechselkrankungen (Paediatric Metabolic Medicine), Paediatric nephrology, Deutsche Gesellschaft für Kinderendokrinologie und –diabetologie (DGGED) e.V. (Paediatric endocrinology) and Paediatric rheumatology, all holding yearly meetings often including patient organisations. ACHSE organises meetings for patient organisations twice a year.

In Germany several events were organised to mark Rare Disease Day 2012, coordinated by ACHSE. These events took place in Bielefeld, Dessau, Essen, Flensburg, Halle, Hamburg, Köln, München, Nürnberg and Würzburg. On 28 February 2012, the Eva Luise Köhler prize for research on rare diseases was awarded\(^\text{27}\). On 29 February 2012 a political symposium on the theme “rare but strong together – finding better ways for people with rare diseases” was organised by ACHSE and attended by the German Minister of Health, Daniel Bahr, and the President of the German Medical Association. Expert panel discussions provided the opportunity for in depth discussion on a number of themes. On 29 February 2012, the 3rd Rare Disease Day Symposium organised by Orphanet Germany was held at the Hannover Medical School. More than 30 different support groups attended the event and manned the stands at the event, providing an opportunity to meet the 350 visitors about. Some patient organisations gave talks together with the professionals from the newly created centre of rare diseases of the Hannover Medical School. This year was also the first time that professionals from the pharma industry presented their activities in the field of orphan medicinal products.

Hosted rare disease events in 2012
Amongst the events hosted in Germany and announced in OrphaNews Europe were: 4th International Tuebingen-Symposium on Pediatric Solid Tumors (Tuebingen, 16-18 February 2012), International Meeting on Rare Diseases: Mechanisms and New Therapeutic Approaches (Freiburg, 22-24 February 2012), 5th International Conference on Ectodermal Dysplasia (ED2012) (Erlanger, 1-3 June 2012), 10th International primary hyperoxaluria workshop (Bonn, 22-23 June 2012), European Human Genetics Conference 2012 (Nurnberg, 23-26 June 2012), Retina International World Congress (Hamburg, 14-15 July 2012).

Research activities and E-Rare partnership
National research activities
The Federal Ministry for Education and Research (Bundesministerium für Bildung und Forschung, BMBF) funded 12 networks national academic groups, clinical centres, specialised laboratories and patient organisations for basic and clinical research starting in 2012 with more than €21million for three years.

E-Rare
Germany participated in the 4\(^{th}\) Joint Transnational Call in 2012 with German research groups participating in 10 of the 11 projects selected for funding of about €3.4 million.

\(^{27}\) [http://www.achse-online.de/cms/was_tut_achse/forschung_vorantreiben/koehler_forschungspreis.php](http://www.achse-online.de/cms/was_tut_achse/forschung_vorantreiben/koehler_forschungspreis.php)
LIST OF CONTRIBUTIONS

Contributions in 2010
Manfred Stuhrmann-Spangenberg and Kathrin Rommel (Orphanet Germany, Medizinische Hochschule Hannover)
Ralph Schuster (PT-DLR)
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”)
Birgit Schnieders (Federal Ministry of Health)
Andreas Reimann (ACHSE)

Contributions in 2011
Manfred Stuhrmann-Spangenberg (Orphanet Germany, Medizinische Hochschule Hannover)
Ralph Schuster (PT-DLR)
Georg F. Hoffmann (Department of Pediatrics, University of Heidelberg)
Olaf Hiort (Universitätsklinikum Schleswig-Holstein)
Birgit Schnieders and Véronique Héon-Klin (Federal Ministry of Health)

Contributions in 2012
Birgit Schnieders and Véronique Héon-Klin (Federal Ministry of Health)
Georg F. Hoffmann (Department of Pediatrics, University of Heidelberg)
Olaf Hiort (Universitätsklinikum Schleswig-Holstein)
Ute Rehwald (Federal Ministry Of Research And Education)
Manfred Stuhrmann-Spangenberg (Orphanet Germany, Medizinische Hochschule Hannover)
Miriam Mann (ACHSE)
Thomas Wagner (Klinikum der Johann Wolfgang Goethe-Universität)

Contributions in 2013
NAMSE Coordinating Group (Federal Ministry of Health (BMG), Federal Ministry of Education and Research (BMBF), Allianz Chronischer Seltenener Erkrankungen (ACHSE e.V.)

Validated by all the contributors 2013, see above
For the Federal Ministry of Health: Birgit Schnieders and Véronique Héon-Klin (EUCERD Representative and EUCERD Alternate Representative Germany, Federal Ministry of Health)
For the Federal Ministry of Education and Research: Ralph Schuster (PT-DLR)
For the patient alliance, Allianz Chronischer Seltener Erkrankungen (ACHSE e.V.): Miriam Mann (ACHSE)

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- BMG - German Federal Ministry of Health

20 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.
21 All websites and documents were last accessed in May 2013.
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