

National Plan for Rare Diseases

Nationaal Plan Zeldzame Ziekten



National Plan for Rare Diseases

NPZZ

10 October 2013

Colophon

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Summary

This summary contains the most important points of the National Plan for Rare Diseases (Dutch: Nationaal Plan Zeldzame Ziekten – NPZZ for short).

Goal of the Plan

With this National Plan for Rare Diseases, ZonMw proposes activities that are needed to improve the situation of people in the Netherlands suffering from a rare disease.

The plan was put forward to the minister of Health, Welfare and Sport (VWS).

During the Council of Health Ministers of the EC (Luxembourg 2009), the Netherlands endorsed the Recommendation of the Council¹. Like all other Member States, the Netherlands pledged to create a strategy plan in 2013 at the latest, to function as guidelines and provide structure to all relevant measures in the area of rare diseases, with regard to their health and social system. In line with this Recommendation, the Minister of VWS informed the House of Representatives (Netherlands) in writing on February 2012 of the Dutch strategy with regard to rare diseases². The present NPZZ is another supplement to and elaboration of this strategy.

Creation of the NPZZ

The Stuurgroep Weesgeneesmiddelen (up to 31.12.2011) and then the ZonMw Klankbordgroep NPZZ (NPZZ) have guided the creation of the plan. A website (www.npzz.nl) has been created providing information about several activities with regard to rare diseases. Earlier versions have been submitted for consultation on this website.

Besides this, several workgroups and practicing parties have contributed and commented on the concept versions.

See also appendix I.

Key problems concerning rare diseases

Patients suffering from rare diseases experience problems that differ in nature. The key problem which causes most of the other problems and difficulties, is the rarity of the illness.

Knowledge and experience of rare diseases are limited³. It is estimated that there are 5,000-8,000 different rare diseases, which probably affect 6-8% of the population.

Although there is a serious lack of reliable epidemiological information about preventing rare diseases in the Netherlands, it is certain that a significant percentage of the Dutch population is affected by a rare disease, which is often hereditary, chronic and incapacitating.

¹ RECOMMENDATION OF THE COUNCIL of 8 June 2009 concerning actions in the area of rare diseases (2009/C 151/02)

² Dutch Strategy concerning rare diseases, 29 February 2012 GMT/IB/3096637 (summary in the appendices)

³ Kole, A et al. Rare diseases social epidemiology; Analysis of inequalities, Advances in Experimental Medicine and Biology, 2010 & VSOP Information for people with a rare condition, research of the available information, problems and solutions, February 2002

The problems described in the NPZZ are the following:

- Lack of awareness, providing information, knowledge and education (see chapters 2 and 3)

There is still too much unknown to the different actors involved (patients, care providers, researchers, insurers, government) concerning rare diseases.

The cause of this is the rare nature of them. This means that relatively little research has been carried out and that the alertness to and knowledge of rare diseases of the aforementioned actors, as well as the media and the general public, has remained limited.

This unfamiliarity concerns epidemiology, genetics, pathology and medical treatment, and causes a delay when diagnosing the patient.

Among other things, recent information, or summary information (databases of experts, registers of patients) is lacking. At this moment, information technology (ICT) is not used sufficiently to improve the provision of information, and e-learning is not used sufficiently to improve our knowledge of rare diseases.

During the education and further training of physicians, the phenomenon of rare diseases is rarely mentioned explicitly. It is expected that 80% of rare diseases are genetic, usually monogenetic⁴.

The new possibilities for screening, genetic diagnostics and preconceptional care are still insufficiently known by professional groups, patients, parents and family members.

- Organisation of care and availability of therapy (see chapter 4)

There is a need for customised care and more general awareness of rare diseases among care professionals and healthcare experts. The problems indicated above cause delays to correct diagnoses, with patients often not referred to the right places for care and treatment.

However, it is presently not possible for a large percentage of people with a rare disease to receive a precise diagnosis⁵.

Furthermore, there is insufficient collaboration and alignment between different care providers who are involved with care in the hospital and close to home. ICT tools in the area of e-health are currently insufficient⁶. For most rare diseases, there is no chain of care or care path system in place indicating measures for prevention or treatment of complications. For adequate care and treatment of rare diseases, expert centres are of great value. However, it is presently not clear in the Netherlands where expertise for rare diseases can be found and which criteria these centres meet or should meet. Another important issue is how therapies for rare diseases can remain available through expertise centres in the long term.

- Scientific research in the area of rare diseases (see chapter 5)

There is a demand for more medical scientific research concerning the causes, symptoms, natural course and treatment of rare diseases. This also applies to the need to develop innovative medicines. There is also a demand for social science research into aspects regarding the quality of life and into valid tools to measure the gains of a new therapy in comparison with the natural course and / or standard treatment. It has become clear that patient registration and databases are still an insufficient part of research and care.

- The function of patient organisations (see chapter 6)

Patient organisations for rare diseases are not sufficiently collaborating in an effective manner to become familiar with the problems affecting people with rare diseases in terms of policies, research and care. They are currently too scattered, leading to an incoherent policy with regard to solving the different problems that affect patients with rare diseases. The collaboration of patient organisations could improve the treatment of different problems. For example, by systematically collecting information about experienced care issues, early symptoms or information regarding the natural course. Because of this, creating a chain of care or care path system is also promoted.

- demand for direction and coordination (see chapter 7)

⁴ <http://www.nationaalkompas.nl/gezondheidsdeterminanten/persoonsgebonden/genetische-factoren/hoer-zijn-genetische-factoren-geassocieerd-met-ziekten-en-aandoeningen/>

⁵ There are different reasons for this. It is possible that different symptoms are not recognised as a specific disease, the disease is very rare and/or it is not (yet) possible to diagnose the disease in the clinic or laboratory. It is often known which group of conditions the disease probably belongs to (muscle disease, metabolic disorder, chromosomal abnormality, etc.).

⁶ E-health is the use of information and communication technology (ICT) to support the improvement of health and healthcare. For example, tele-consultation by physician and tele-monitoring of patients with chronic diseases

In 2012-2013 a number of new projects were financed and started up in the area of rare diseases and orphan drugs. However, coordination and alignment of activities are lacking, especially with regard to collective aspects. A thematic working method does not contribute to a lasting improvement of the condition of people with rare diseases. Direction and coordination of the activities described in the NPZZ are needed.

Solutions / Recommendations in the NPZZ

To solve the aforementioned issues, the NPZZ offers recommendations in the following areas:

- Education of care professionals

Paying constant attention to rare diseases during the education of care providers to increase the sensitivity and awareness of specific symptoms of rare diseases, and increase early identification and diagnostics in that manner, as well as referral to experts/professional colleagues. Also, to foster the further training of care providers with regard to rare diseases within their own professional area and expertise.

- Management and availability of knowledge concerning rare diseases

Combining information and knowledge about rare diseases and making this information and knowledge about rare diseases widely available to several target groups.

- Organisation of care and availability of therapy

Formally appointing expertise centres and adding these to a database in order to make it known where to find the expertise, and the criteria they meet. This also requires the central collection of patient information, treatment using (orphan) drugs, creating a multidisciplinary care chain and care path systems for rare diseases, for which an expertise centre is in charge.

- Scientific research

More financial means should be made available for research into: causes, pathogenesis, genetics and innovative therapeutic options for rare diseases, especially those diseases that have not been paid a lot of attention up to now, such as diseases for which only symptomatic treatments are presently available. Furthermore, there is a demand for research into care, aspects relating to the quality of life and new methods to diagnose rare diseases and to measure findings and the cost effectiveness of the treatment of rare diseases.

- Consistency, coordination and evaluation of policy recommendation

Appointing a director/coordinator in relation to the aforementioned recommendations will aid consistency and help avoid fragmentation and unnecessary duplications. For each separate recommendation, a party that has initial responsibility is basically appointed. The plan of action will attempt to promote the sense of responsibility of these parties through the recommendation when they take actions. For most recommendations, suggestions are also given for organisations with which collaboration might take place with regard to the point of action/recommendation⁷.

Priorities

Priorities have been drawn up based on actual discussions and consultations.

A few areas and corresponding recommendations can be designated as urgent, pressing, and/or necessary. Other recommendations are more applicable to the medium and long term, or are recommendations that require continuous attention.

Urgent/short term (preferable start next year: 2014):

- Appointing a director for the entire plan.
- Certainty with regard to the policy for expertise centres and European Reference Centres, mostly concerning cross-border care legislation.
- Consistent policy with regard to entitlement and price of orphan drugs.
- Promoting timely and adequate diagnostics and promoting awareness and knowledge of rare diseases among physicians and other care professionals.

⁷ Wherever the Ministry of VWS is mentioned, VWS could also appoint an organisation.

Medium-long term (starting in 2 to 3 years)

- Appointing centres based on uniform criteria, presence of multidisciplinary care chain and care path systems.
- Coordination and alignment of care and information (shared care and chain care).
- Adequate financing of healthcare (chain DBC).
- Continuous financing for running research programmes in the sphere of rare diseases and orphan drugs.

Long term (3 years or more)

- Financing new research/new programmes with regard to rare diseases (medical science, social science).
- Adequate and uniform codification and national registration of rare diseases.
- Long term research into the course of the disease, possible early treatment and measures to prevent and treat complications.
- Development of a new therapy by Dutch researchers and companies.
- Evaluations of activities and results of the plan (NPZZ).

Continuous attention

- Input by patients (or their organisations) for creating policies, deciding priorities, and in general for strong representation of interests regarding rare diseases.
- Adequate education and training of care givers and social workers with regard to rare diseases
- Knowledge and education, early detection and awareness of rare diseases
- Infrastructure for collecting knowledge about rare diseases and maintaining databases.
- Entitlement to and financing of adequate treatment of rare diseases.

1. General introduction

In June 2009 the Recommendation concerning actions in the sphere of rare diseases was signed to improve relative actions in the field of rare diseases⁸. The goal of the Recommendation is to improve the diagnostics and treatment of patients with rare diseases within the Member States of the European Community (EC)⁹. In the Recommendation of the Council it was recognised that this group of patients is vulnerable, and therefore deserves specific attention. The EC considers care for patients as an area for which each Member State is primarily responsible, but recognises that some aspects of this care, due to up scaling, can be organised more efficiently on a European level¹⁰.

The Recommendation that each Member State should preferably have a national plan or strategy by the end of 2013 is on the one hand a collaborative aim for Europe, but on the other each Member State bears primary responsibility for the content of the Plan. The Minister of Health, Welfare and Sport (VWS) bears primary responsibility for the Plan, having signed the Recommendation. The current minister stated the strategy concerning rare diseases in a letter to the House of Representatives (Netherlands) dated 29 February 2012¹¹. This strategy contains elements for which the Government is responsible, such as prevention and early detection (screening) of diseases of newborns, and financing orphan drugs. The principle of the Ministry of VWS is that a National Plan will be drawn up in combination with the strategy. At the request of the Ministry of VWS, the Stuurgroep Weesgeneesmiddelen started preparations for a National Plan in 2011. Several consultations have taken place, and a website has been created for the Rare Diseases National Plan: www.npzz.nl. Input can also be submitted through this website for the NPZZ. At the end of 2011, the Stuurgroep Weesgeneesmiddelen was cancelled. As a result of this, ZonMw (www.zonmw.nl) was allotted a number of tasks by VWS. The most important tasks are: coordination of the creation of the Rare Diseases National Plan (NPZZ) (2012-2013), promoting the transfer of tasks of the previous Stuurgroep Weesgeneesmiddelen to relevant organisations, and supplying those interested with information about rare diseases. ZonMw has appointed a consultation group to support these tasks.

The general goal of the NPZZ is to make recommendations for activities that could improve the position of people with a rare disease in a broad sense, in terms of diagnostics, treatment, care, research and providing information. The NPZZ plans to appoint different actors as heads of such activities.

This plan also has a few limitations.

- Financial aspects: The Ministry of VWS has not allocated a budget for the recommended measures and activities of this plan. Obviously, there will also be recommendations that do not require extra financing. These recommendations apply to different actions that need to be performed within the existing structures/organisations.
- Specificity: No actions for individual situations or for specific rare diseases are described within the NPZZ.
- Continuity: Experience from the Stuurgroep Weesgeneesmiddelen (2001-2011) shows us that healthcare legislation and regulations are constantly subject to change, and that this influences the situation of people suffering from a rare disease. Therefore, a few recommendations are made in this plan that concern the aspects and areas that require continuous attention.

This plan is applicable to rare diseases (see appendix for definitions). It is estimated that 6 to 8% of EU citizens suffer from one of the 5,000 to 8,000 diseases¹². In the Netherlands (as well as in most other Countries) there is no uniform registration of people who suffer from rare diseases, which is why it is difficult to say how many patients are affected¹³. Not much is known either about the impact of rare diseases on the daily life of these patients.

⁸ Publicatieblad EU Aanbeveling van de Raad, 8 June 2009 (2009/C151/02)

⁹ Citation from Strategy of the Netherlands in the field of rare diseases, 29 February 2012 GMT/IB/3096637

¹⁰ Some examples of these are the development of orphan drugs, creating networks for experts and expertise centres, and financial means for research.

¹¹ www.rijksoverheid.nl/documenten-en-publicaties/notas/2012/03/01/de-nederlandse-strategie-met-betrekkingtot-de-zeldzame-ziekten.html

¹² In the Orphanet database 5,954 rare diseases are described (www.orpha.net).

¹³ Italy is mentioned as 'best practice'. National data of patients with rare diseases are gathered there through regional centres.

1.1 National developments

The role of the FBG

General aspects in the sphere of rare diseases will be focused on by the Dutch Forum for Biotechnology and Genetics (FBG)¹⁴. The Ministry of VWS has assigned the role of Steering Committee (plenary sessions among relevant parties) to the FBG. The main point of focus is to discuss subjects in the area of rare diseases together, and to advise the government¹⁵. In 2013, the FBG created a workgroup in which different aspects of the NPZZ will be discussed.

Centres of Expertise for Rare Diseases

With regard to Centres of Expertise for Rare Diseases, several developments are important.

The NFU (UMCs) and STZ (Dutch Specialised Clinical Hospitals) have started an inventory, for which they make use of the criteria for Centres of Expertise that were developed by the Stuurgroep Weesgeneesmiddelen (2011). The EUCERD established criteria in October 2011 that are similar to these. In the Netherlands it has not yet been decided that centres be formally (and centrally) appointed as Centres of Expertise based on criteria. A letter from the VWS about the Dutch Strategy stated: "appointing one or several reference centres for treating specific diseases or a group of related diseases by the government will not take place for the time being".

However, in the Recommendation of the Council, it is recommended that Member States make an inventory of suitable Centres of Expertise in their national territory and consider the creation of Centres of Expertise by the end of 2013 at the latest. Orphanet Nederland and the NFU are comparing the data available to them about experts on rare diseases in Dutch hospitals (August 2013).

This inventory is also relevant with regard to the guidelines for cross-border care (mainly article 12 and 13 for rare diseases). EU Countries should adapt their legislation to the guidelines by 25 October 2013¹⁶.

Effectiveness of research into expensive medication

There are a few developments awaiting further political decisions, or for which it is unclear at this moment what the long-term effect of the measure will be. For example, the decision of the VWS about the efficiency of research into expensive medication (fall of 2013), package management specialist pharmaceuticals (fall of 2013), and plans for transferring orphan drugs from the Dutch Drug Reimbursement System (Geneesmiddelen Vergoedingssysteem - GVS) to the hospital budget (2016).

New projects

During the creation of the NPZZ (2012-2013), a number of new projects were begun. These often relate to described loopholes and obstacles, and may offer solutions. An overview of these projects was added to the appendices.

1.2 European developments

Due to the rarity and the lack of knowledge about these diseases, people with a certain disease experience similar problems within Europe. This is why the European Commission has made several proposals to improve the position of people with rare diseases, the first one being in the Community action programme 1999-2003. In 2006 it was established that, based on principles of solidarity, a patient with a rare disease is entitled to care of the same quality as the quality of care for a patient with a more common disease¹⁷.

The European Recommendation of the Council of Ministers of the European Union (8 June 2009) includes the following: creation of plans and strategies, classification and inventory of rare diseases, research on rare diseases, Centres of Expertise and European Reference Networks for rare diseases, combining expertise in

¹⁴ www.forumbg.nl

¹⁵ See the appendix with the letter to the House of Representatives concerning the Dutch Strategy with regard to rare diseases (GMT/IB/3096637), 29 February 2012

¹⁶ http://ec.europa.eu/health/cross_border_care/legislative_framework/index_en.htm

¹⁷ Council Conclusions on Common values and principles in European Union Health Systems (2006/C 146/01).

Europe, influence of patient organisations and continuity. The EUROPLAN project (European Project for Rare Diseases National Plans Development) is a European project financed by the European Committee (DG-SANCO)¹⁸. The EUROPLAN project aims to promote the development and implementation of national plans, sharing relevant experiences and linking national efforts to a general strategy on a European level. Presently (2013), thirteen Member States including the Netherlands have taken action to create plans or strategies for rare diseases. An overview can be found on the EUROPLAN website¹⁸.

The European Commission has appointed a Committee of Experts responsible for monitoring, evaluating and disseminating the results of measures and activities taken in the area of rare diseases in the different Member States. This Committee, the European Union Committee of Experts on Rare Diseases – EUCERD www.eucerd.eu, consists of representatives from each Member State, representatives of patient organisations, of the pharmaceuticals industry, and representatives of researchers who have conducted projects in the area of rare diseases. The EUCERD issues annual reports about the progress in different Member States. The term of the EUCERD membership for present members ended on 27 July 2013. The European Commission issued a new decision in the summer of 2013, and issued a call for new members for the EUCERD in September¹⁹.

2. Unfamiliarity with rare diseases

Overview of the theme

The problems that occur for people with rare diseases can partially be explained by the lack of familiarity of care professionals for a large number of rare diseases. It is this rarity that leads to unfamiliarity, a late diagnosis and – even after the right diagnosis has been made – little practical experience with the care and treatment of patients with the disease. In foreign (English) documents, unfamiliarity with rare diseases is often described as a lack of awareness. This term is also used more and more in Dutch, but the term 'alertness' over the possibility of a rare disease in a specific patient describes this problem more precisely. A lack of awareness or alertness is linked to the lack of knowledge, experience, and the urgency to do more research or refer the patient to an expert. This will have negative effects on a timely diagnosis, care and treatment.

2.1 What already exists?

The Stuurgroep Weesgeneesmiddelen (2001-2011) has worked to make the terms rare disease and orphan drugs known to the general public, to relevant actors and to politicians and the government. Although the attention paid to patients with rare diseases has increased, many efforts still need to be made to keep a permanent focus on rare diseases. Since 2008 the Dutch Rare Diseases Day is organised annually²⁰. This event contributes to greater awareness of the term rare disease. Family, patients and parents have, through the media, successfully contributed to raising the awareness of rare diseases. Besides this, those directly involved contribute to the awareness of the disease, for example by creating flyers about the condition. They also collect information from their supporters about the symptoms of the disease for diagnostic purposes. The latter is happening more and more, and in a more systematic manner²¹.

2.2 What is missing?

Many rare diseases manifest with 'vague' complaints and symptoms that are difficult to classify. Due to the large diversity of rare diseases, it is not realistic to expect physicians to be able to directly link these symptoms to a specific diagnosis. However, the majority of rare diseases are genetic, and the increased possibilities for genetic diagnostics are insufficiently applied in practice. A large number of rare diseases have not

¹⁸ www.europlanproject.eu

¹⁹ http://ec.europa.eu/health/rare_diseases/expert_group/call_en.htm

²⁰ Organisers are: VSOP, the Zeldzame Ziekten Fonds (ZZF), the KNMP and Stuurgroep weesgeneesmiddelen (up to 2012) and several sponsors such as Genzyme with their GIVE program.

²¹ For example: http://marijke-foundation.eu/Website-AT-PMR-Nederland/Vroegdiagnose_Symptomatrix/symptomatrix.htm

been researched, or only to a limited extent, this means that many aspects regarding the diseases are unknown or hardly known. The impact of having a rare disease on daily life appears not to be researched at all in many cases.

The attention paid to rare conditions should therefore be raised considerably in the areas of public healthcare, healthcare policies (government), work, school and housing, especially now that a number of care elements have been transferred from the AWBZ to the municipalities (WMO).

2.3 Table of Recommendations for Unfamiliarity with rare diseases

	Recommendations for Unfamiliarity with rare diseases	1 st point of contact/other party/parties
2.3.1	Promote an increased general awareness of the 'phenomenon' of rare diseases with health and care professionals, health insurers, (umbrella) patient organisations, policy creators for the government and municipalities, and with the general public.	VSOP in collaboration with CG Council and NPCF Zeldzame Ziekten Fonds
2.3.2	Increase the alertness of rare diseases with family doctors, physicians in specialist training and further training of medical specialists. Provide education about rare diseases in the medical curriculum (Framework), for specialists in training and the further training of specialists.	Education Framework physicians (NFU) in collaboration with scientific organisations.

3. Information and communication

Overview of the theme

Due to unfamiliarity with rare diseases, patients and their families, as well as care professionals, encounter problems. These concern several aspects, such as: unfamiliarity with the symptoms, aetiology, pathophysiology, genetics, the variable course of many rare diseases, and unfamiliarity with treatment. Accessible information and an improvement of knowledge in several areas is needed, including: education, training, transfer of knowledge (also see the previous chapter) and use of e-learning and e-health. Help with finding the right information can be valuable. Different groups that are looking for information can be differentiated. People with symptoms or relatives looking for an explanation of the symptoms, and a diagnosis of a possible rare disease.

In addition, there are people who have a diagnosis, but are looking for additional information or fellow sufferers. People with very rare diseases, for whom there is often no patient organisation, run into problems more often and are often in need of help with finding information. Another group that is looking for information is that of care professionals, researchers and pharmaceutical companies. They are looking for information about the disease in general, treatment possibilities, expert centres, or financial means to conduct (pharmaceutical) research.

3.1 What already exists?

The Internet has made information about rare diseases more accessible to a wider audience. New social media and new digital ICT technologies are being developed to combine knowledge of rare diseases or to create networks in the area of rare diseases²². Especially for diseases that occur rarely, the worldwide web is an important tool to find other sufferers and exchange information.

Patient organisations have usually collected considerable information and collaborate with physicians to improve the information with regard to the care and treatment of rare diseases. The GP brochures about rare diseases²³ and the development of care standards for rare diseases²⁴ are examples of this. In the Netherlands there are several websites with information about several rare diseases and corresponding organisations, such as the public information centre Erfocentrum²⁵. The Erfocentrum also functions as a helpdesk for questions, by email or phone. The website offers information about genetic conditions and genetic research. Furthermore, the more scientifically oriented Orphanet offers information about rare diseases²⁶, also in Dutch, since June 2013.

There are several websites that offer information about pharmaceuticals for rare diseases (orphan drugs). For example, the European Medicines Agency (EMA)²⁷, College ter Beoordeling van Geneesmiddelen (CBG)²⁸ and the professional association of pharmacists (KNMP)²⁹. Since October 2013 the orphan drugs information portal is online. This website offers information aimed at researchers and companies about the development, regulations, financing and price of orphan drugs³⁰. Information on the previous stuurgroep weesgeneesmiddelen³¹ website is transferred to stakeholders as much as possible, allowing them to take over the tasks in this area. Policy information about rare diseases and orphan drugs can be found through the government website³².

3.2 What is missing?

As the above makes clear, a lot of information is available. Not all information about rare diseases has good quality content or is available in Dutch. Sometimes the information is not up to date, or very limited. Furthermore, the information is fragmented between different websites and their organisations. There is a need for a central database or the interlinking of internet portals, to which people can be referred. Different initiatives should work more closely. It makes sense that patient organisations, together with existing information centres and hospitals, can play a central role in this area. It is also important that people have somewhere to go to report problems within the healthcare system, or for example the price of treatment. In this sense, a helpdesk would also have a monitoring function. Such a function is primarily related to patient organisations.

Knowledge about certain rare diseases is in many cases limited to a single physician or a small group of physicians and researchers in a hospital. An important problem with this is that it is not clear at the moment where the expertise can be found, and which criteria are met. Regional hospitals, children's healthcare or GPs often lack general knowledge about and awareness of rare diseases. The sharing of information between experts and other care professionals – making use of each other's expertise – does not happen enough yet. ICT (such as e-health and e-learning) could contribute to the exchange of knowledge. For more and more groups of diseases, applications are being developed that could also be valuable for exchanging knowledge about rare diseases.

²² www.linkedin.com/groups/Zeldzame-Ziekten-3909302; www.dutchorphandrugnetwork.nl; www.nhcp.nl/home

²³ www.vsop.nl/nl/publicaties/downloads/huisartsenbrochures

²⁴ www.zorgstandaarden.net

²⁵ www.erfocentrum.nl

²⁶ www.orpha.net

²⁷ www.ema.europa.eu

²⁸ www.cbg_meb.nl

²⁹ <http://farmanco.knmp.nl/tekortweesgeneesmiddel>

³⁰ The site was initiated by BioFarmind and founded with a start-up subsidy by ZonMw (www.weesgeneesmiddelen.info)

³¹ www.weesgeneesmiddelen.nl

³² www.rijksoverheid.nl

3.3 Table of recommendations for Information and Communication

	Recommendations for Information and Communication	1 st point of contact / other party/parties
3.3.1	Improvement of differential diagnostics of rare diseases by: a) implementing ICT: e-learning and other ICT applications; b) Implementing e-mail and video consultations from the expertise centre; c) Improving the visibility of rare diseases (general) and information about centres of expertise.	NFU/STZ Patient organisations Health insurers
3.3.2	Knowledge about the symptoms of rare diseases and the tools needed to diagnose rare diseases need to be improved in primary and secondary healthcare.	NHG and AJN (and NCJ) in collaboration with other scientific organisations.
3.3.3	Portal website and helpdesk and referring function for: - People looking for a diagnosis; - Patients and/or parents/family looking for information about the disease, (genetic) research, fellow sufferers, a patient organisation or expertise centre. - Care givers, students or teachers looking for general information about (guidance of people with) rare diseases - The systematic collection of information from the group of patients with rare diseases (and their parents)	Erfocentrum In collaboration with Orphanet and VSOP
3.3.4	Improving general access to information concerning rare diseases in intelligible language for patients, family and referring physicians.	Erfocentrum and Orphanet in collaboration with NFU (TRF portal)
3.3.5	Helpdesk or hotline for people who have problems with care or prices for treatment (monitoring function for representation of interests).	VSOP in collaboration with CG Council and NPCF
3.3.6	Creating an overview of all organisations in the Netherlands of patients and relatives involved with	PGO support in collaboration with VSOP CG Council and NPCF

	rare diseases.	
3.3.7	Scientific organisations, professional groups patient organisations regularly organise symposia or further training concerning several aspects of rare diseases.	KNMG, KNMP, NHG, VenVN, patient organisations, FBG. On a European level EURORDIS or EPPOSI

4. Care and availability of treatment

Overview of the theme

The number of rare diseases is high³³, and although the diseases can be divided into groups³⁴, the diversity of the pathology is often wide within a group. The natural course of rare diseases is variable, and the treatment is mostly symptomatic. The coordination of and knowledge about symptomatic or palliative care or new treatment methods is often lacking, and there is no multidisciplinary treatment team. Due to the genetic component of many rare diseases, clinical genetics is an important discipline, but often an unrepresented one in a multidisciplinary team.

Care includes many aspects, from stating a diagnosis to daily and specialised high quality care, at home, in the hospital, or different care organisations. Care also includes psychosocial and social care. In past years there was more focus on increasing the expertise within hospitals. The challenge for coming years is to define centres and to make a connection between these experts in hospitals and care close to home. When improving care for people with rare diseases, one should also explicitly gather and share new knowledge, through research and education (see chapter 2 and 5).

4.1 What already exists?

Diagnostics - what already exists?

For population studies of newborns, the heel prick test is available in the Netherlands. With this, 18 diseases (all rare) can be detected³⁵. For two conditions in the heel prick test (alagille syndrome and sickle-cell disease) a follow-up database has been developed (NEORAH). The number of conditions that can be detected in other Member States of the EU varies between one (1) and thirty³⁶. The Health Council has received a new request for advice from the VWS ministry in 2012 to advise about the increase in the number of diseases that can be detected through the heel prick test³⁷.

Rare diseases are caused by a genetic change in a gene for 80% of patients. Many genetic variants can be found through exome or genome sequencing³⁸. It is however still difficult to identify variants that cause rare diseases. The possibilities for screening the genetic material are increasing, and are expected to be used for more diseases at lower costs in the future. Genetic tests are in principle covered by standard health insurance. National screening takes place under the responsibility of the Dutch government (RIVM). The principle of government policy is that screening the population for diseases is only valuable if a health gain can be achieved by early detection. Screening for conditions is also a task for child healthcare (known as Dutch child healthcare centres). Furthermore, a number of integrated early intervention teams (VTO Teams)³⁹ are located through the country, including experts in the area of detection, diagnostics and guidance for developmental delays.

³³ In the Orphanet database, 5.954 rare diseases are described.

³⁴ For example muscular diseases, metabolic or chromosomal disorders.

³⁵ www.rivm.nl/Onderwerpen/Onderwerpen/H/Hielprik/De_ziektes_die_de_hielprik_opspoor

³⁶ www.iss.it/cnmr/prog/cont.php?id=1621&lang=1&tipo=64

³⁷ www.gezondheidsraad.nl/sites/default/files/Werkprogramma2013_A03.pdf

³⁸ http://en.wikipedia.org/wiki/Whole_genome_sequencing of http://en.wikipedia.org/wiki/Exome_sequencing

³⁹ www.integralevroeghulp.nl

There are also possibilities for diagnosing deviations before and during pregnancy, which could be a sign of rare diseases. The Dutch Forum for Biotechnology (FBG) offered an advisory report to the minister in 2013 in the area of preconceptional genetic research⁴⁰.

Organisation of Care & Centres of Expertise – what already exists?

Concentration of care is becoming more and more important within the organisation of healthcare⁴¹. This concentration of care (knowledge and expertise) is necessary to improve quality. With regard to legislation on cross-border healthcare, the EUCERD has established criteria for Centres of Expertise and for Reference Networks of Centres of Expertise in Europe (www.eucerd.eu). A number of primary terms of criteria for expertise centres for rare diseases are: experience with care and treatment of children and adults with rare diseases, experience with research, multidisciplinary treatment, being part of a network, and gathering and sharing knowledge⁴².

To develop new ICD codes (ICD 11) for rare diseases, a European project was initiated that is coordinated by EUCERD. From the Orphanet, the *Orpha code* was developed. This code can be used with the ICD⁴³. For monitoring data on children in the Netherlands, the digital child form is available. Within this form, the data about pregnancy, family history, birth, birth defects, growth and development as well as vaccinations are recorded. For more than 30 rare diseases, care standards are developed (by the VSOP), in which the necessary care and treatment is described by patients and physicians⁴⁴. Most rare diseases (80%) are hereditary or genetic in nature. A website that offers information for general practitioners is available at www.huisartsengenetica.nl.

Availability of treatment – What already exists?

Since the implementation of European regulations with regard to orphan drugs (in 2000), 70 new pharmaceuticals for 55 different rare diseases have been brought onto the market. The price of these pharmaceuticals is arranged per country. The Netherlands has, after France, the widest availability of these European registered orphan drugs⁴⁵. Intramural via *add-ons* linked to Dutch Diagnose Treatment Combinations (DBC's) (e.g. if costs are more than €10,000)⁴⁶, extramural through the Dutch Pharmaceuticals Reimbursement system (GVS). Since 2006 a number of expensive orphan drugs have been offered to patients through the budget of teaching hospitals. The hospitals concerned were reimbursed the costs of these pharmaceuticals (up to 2013) by policy regulations on orphan drugs. The condition for this was that the data concerning therapeutic value, overheads and efficiency would be collected.

Expensive orphan drugs that were included in the policy regulations for orphan drugs up to 2013 are evaluated by the Dutch Board of Health Insurance (CVZ).

Initiatives have been initiated in Europe by which price authorities, researchers and pharmaceutical companies collaborate with regard to the evaluation of orphan drugs in use⁴⁷. In October 2013, the Dutch law should include an article about cross-border healthcare. Through this legislation, cross-border treatment should become available. An article concerning expertise and reference centres has also been included in draft legislation. The NFU has started an inventory of expertise and treatment centres for rare diseases in UMCs that are supported by the Dutch Boards of Directors (June 2013).

⁴⁰ www.forumbg.nl. Also see www.gezondheidsraad.nl/nl/adviezen for advice about neonatal screening, PGD, preconceptional care

⁴¹ Nivel report "The relation between volume and quality of care, time for a broad approach" (2012)

⁴² The EUCERD and the Stuurgroep Weesgeneesmiddelen have established and published criteria for Centres of Expertise. The criteria are similar and relate to the same elements.

⁴³ www.eucerd.eu/wp-content/uploads/2013/06/OrphaCode_Leaflet.pdf

⁴⁴ www.vsop.nl/nl/wat-doen-wij/projecten/g-zorgstandaarden-de-patient-centraal/

⁴⁵ Research of Eurordis into the availability of orphan drugs (www.eurordis.org) In 2010, 93% of orphan drugs (60) was available in France, followed by 88% in the Netherlands, and 87% in Denmark

⁴⁶ Advice has been given to the Minister by the de NZa about the new policy (July 2013)

www.nza.nl/publicaties/nieuws/Verzekeraar-en-ziekenhuis-aan-zet-over-apart-declareren-geneesmiddel/

⁴⁷ Medicine Evaluation Committee (MEDEV); Clinical Added Value of Orphan Medicinal Products (CAVOMP); working group on coordinated access to orphan medicinal products (MoCA)

4.2 What is missing?

Diagnostics – what is missing?

One of the biggest problems for people with rare diseases remains that of receiving a timely diagnosis. For a group of people with rare diseases, it still seems impossible to give an exact diagnosis⁴⁸. The experience of parents and patients is that Dutch childcare centres and GPs do not normally consider the possibility of a rare disease. This can contribute to the fact that it might take years before receiving a diagnosis. The problem is partly the unfamiliarity and lack of experience with rare diseases in practice. Transfer of knowledge is also lacking (for example through ICT tools), and it is usually not known where expertise about the diagnostics of a specific condition can be found. Many rare diseases have a genetic component, this is often unknown to care providers and/or patients and their families, or it is not discussed. This could lead to a delay when giving a diagnosis. New methods for genetic diagnostics are still used insufficiently.

Organisation of care – what is missing?

Making a diagnosis is one aspect, finding a place where people have knowledge of the care and treatment of a specific disease is another. Although care for patients with a chronic disease is widely available in the Netherlands, patients and families that are involved with rare diseases experience a lack of coordination of care, and fragmentation of the little knowledge that is available. On the one hand this is caused by insufficient collaboration between professionals, on the other by the way in which current healthcare is organised and financed. These 'walls' within healthcare (for example between *care and cure*) do not promote an integral approach, especially not for diseases for which knowledge is scarce, and an integrated approach is necessary. Furthermore, only few hospitals offer a transition of healthcare for children with a rare disease to healthcare for adults. Within healthcare for adults, people are referred to different physicians for different symptoms that are all connected to the same rare disease, and often there is no multidisciplinary and integral approach. This requires a lot of direction from the patient. An expertise centre could have a crucial role in the coordination of care with a network of care givers around the patient.

In the long term, centres could be of more value in healthcare with regard to timely diagnostics, prevention of complications, organisation of care (at home – hospital), increasing knowledge about rare diseases, and research and implementation of new treatments. Due to decentralisation, certain parts of healthcare are now directed by municipalities (WMO). These parts should also be integrally added to a chain. Healthcare chains are not yet used in practice.

The lack of a uniform codification of rare diseases and registration of people with rare diseases is an important bottleneck in healthcare. People who are diagnosed with rare diseases cannot presently be found or recognised in Dutch hospital registrations (ZIS) and Dutch GP registrations (HIS, ICPC codes). There are only codes for 250 rare diseases in the ICD10. The lack of a specific code makes it difficult to find people with rare diseases in databases (hospital and other registrations), and does not promote collaboration within the area of healthcare (healthcare chain).

The Netherlands lacks an organisation that is formally authorised to appoint hospitals (or hospital departments) as Centres of Expertise based on uniform criteria. In theory, the special medical procedures legislation (Wbmv, article 8) offers possibilities to appoint centres for rare diseases within a legal framework laid down by the government⁴⁹. The Dutch Strategy concerning rare diseases of the Ministry of VWS (29.02.2012) states that appointing one or more reference centres for treating specific diseases or a group of related diseases by the government is not on the agenda in the short term⁵⁰.

Availability of treatment – What is missing?

⁴⁸ See for example www.undiagnosed.org.uk

⁴⁹ Concentration of care, combining knowledge and experience, making it accessible, distributing it for the development of knowledge and experience www.rijksoverheid.nl/documenten-en-publicaties/kamerstukken/2013/06/28/aanbiedingsbrief-overevaluatiewet-op-bijzondere-medische-verrichtingen-Wbmv.html

⁵⁰ www.rijksoverheid.nl/documenten-en-publicaties/notas/2012/03/01/de-nederlandse-strategie-met-betrekkingtot-de-zeldzame-ziekten.html

Off-label

Problems often arise with regard to the price of pharmaceuticals that are not registered for rare diseases on a regular basis. Health insurers are not obliged to reimburse such pharmaceuticals and comply with the advice of the CVZ concerning off-label use of pharmaceuticals for this purpose.

Expertise centres

In the present situation, care for certain rare diseases is not always purchased in each expertise centre. To solve this problem, it was recommended that rare diseases be declared as non-competitive, which would allow health insurers to reach agreements on the purchasing of care and treatment of rare diseases. In some cases this already takes place, but not for the group of rare diseases as a whole. The boards of directors of hospitals (and other organisations) that possess expertise centres could be held responsible for the continuous functioning of these expertise centres.

Availability of orphan drugs (intramural)

A number of academic hospitals have carried out research into the efficiency of some expensive orphan drugs with regard to policy regulations on orphan drugs. The final recommendation concerning orphan drugs for Pompe disease and Fabry's disease was issued by the CVZ.

The minister has decided to continue to price these pharmaceuticals for standard health insurance in 2013 based on this advice⁵¹. The decision about adding expensive orphan drugs to standard health insurance based on the results and cost efficiency research has limitations.

The strategy of the Ministry of VWS states that all orphan drugs will be covered by hospital funding in the future, but this does not affect entitlement⁵². This development could promote the implementation of an expertise centre, if these centres coordinate treatment and care for people with rare diseases, etc. The development of a consistent reimbursement policy in which the specific situation of the treatment of rare diseases with (orphan) drugs is advocated⁵³. It is relevant to regularly monitor the patient to see whether they still benefit from medication in case of pharmaceutical treatment, and to see if the dosage and frequency are optimal. An issue with this is that the researcher is also the treating physician of the patient. This could result in a moral dilemma within the treatment relationship.

4.3.1 Table for recommendations of Care (specifically in the area of diagnostics)

	Recommendations Diagnostics	1 st point of contact/ other party/parties
4.3.1.1	Improve alertness of rare diseases.	See recommendations: 2.3.1, 2.3.2, 3.3.1, 3.3.2
4.3.1.2	The number of diseases that can be detected with the heel prick test should be monitored periodically to see if it can be increased based on new insights.	VWS

⁵¹ www.rijksoverheid.nl/documenten-en-publicaties/kamerstukken/2013/01/30/kamerbrief-over-vergoedingweesgeneesmiddelen-voor-ziekte-van-pompe-en-ziekte-van-fabry.html

⁵² Correspondence VWS/GMT of 17 May 2013, transfer postponed to 2016.

⁵³ See also Paying for the Orphan Drug System: break or bend? Is it time for a new evaluation system for payers in Europe to take account of new rare disease treatments? Orphanet Journals of Rare Diseases 2012, 7:74 Hughes Wilson et al.

	The heel prick test shortens the time needed for diagnoses of rare diseases.	
4.3.1.3	Research or screening possibilities (for example cascade screening) can be implemented for the detection of genetic rare diseases.	FBG VKGN STOET (stichting opsporing erfelijke tumoren – organisation for detection of hereditary tumours)
4.3.1.4	More attention and information is needed about the genetic aspects of rare diseases.	VKGN in collaboration with The Erfocentrum

4.3.2. Table of Recommendations Organisation of Care

	Recommendations for Organisation of Healthcare	1st point of contact /other party/parties
4.3.2.1	Make Wbmv an umbrella organisation for expertise centres for rare diseases.	VWS
4.3.2.2	Appoint expertise centres in a transparent manner, making use of existing uniform criteria.	VWS
4.3.2.3	Directors are responsible for the adequate functioning of expertise centres over longer periods of time.	Boards of Directors of UMCs
4.3.2.4	In expertise centres, make use of multidisciplinary teams for children and adults with rare diseases, with a contact person (care coordinator). Attention is paid to the transition from child care to adult care.	NFU in collaboration with STZ
4.3.2.5	Expertise centres contribute to the foundation of healthcare standards and guidelines and work according to procedures established from these standards.	NFU in collaboration with STZ and VSOP
4.3.2.6	More focus is needed for NHG preconception care.	NHG

4.3.2.7	<p>More focus is needed for preconceptional hereditary advice (FBG detection) Carry out a pilot study that will offer more insight on possibilities and problems if needed.</p>	<p>VWS FBG</p>
4.3.2.8	<p>Care close to home ('care in the neighbourhood') needs to be coordinated better in collaboration with the expertise centre.</p>	<p>LHV</p>
4.3.2.9	<p>Develop a 'rare diseases' code (morbus rare) or make use of the 'Orphacode' (Orphanet).</p>	<p>RIVM (ICD/ICF) in collaboration with NHG (HIS), NFU (ZIS), Orphanet (Orphacode), VKGN (Cineas)</p>
4.3.2.10	<p>Create and maintain a database with information on people suffering from a rare disease, this should be a chargeable presentation. A patient does not always have to come to the centre, through ICT, collaboration with hospitals in the area could take place. For example E-health.</p>	<p>NZa Health insurers DBC-Onderhoud</p>
4.3.2.11	<p>People who suffer from rare diseases are often treated by several specialists, who often repeat examinations, such as scans and blood tests. Patients experience this as stressful, and often there is no need for it. Coordination of healthcare is needed.</p>	<p>ZN and Health insurers</p>

4.3.3 Table of recommendations for Availability of treatment

	Recommendations for Availability of treatment	1 st point of contact / other party/parties
4.3.3.1	For the development of the policy with regard to reimbursement of orphan drugs, one needs to take the specific features of the treatment of rare diseases (small diverse group of patients) into account.	VWS
4.3.3.2	Research of the natural course and of initiation and stopping criteria, dosage and frequency, could offer information about the efficient use of orphan drugs.	NFU and UMC's Nefarma and Biofarmin CVZ
4.3.3.3	Research and collection of data concerning the off-label application of pharmaceuticals for rare diseases is necessary – after positive advice from CVZ – for reimbursement purposes.	UMCs CVZ and Health insurers
4.3.3.4	Purchasing healthcare aligned with appointed expertise centres for rare diseases. Rare diseases to be declared non-competitive (implementation of limited contracting for expertise centres).	ZN and Health insurers
4.3.3.5	Implementing legislation for cross-border healthcare in the Netherlands.	VWS
4.3.3.6	Implementation of healthcare chain (DBC Chain) for rare diseases, in a similar way to Pilot CF	ZN Health insurers Quality institution

5. Research

Overview of the theme

Research in the area of rare diseases is broad-oriented: medical scientific or social scientific research. Research can be basic (looking for hereditary aspects or other pathogenesis, targets for pharmaceuticals), but also applied research with medication (before these are registered and in everyday practice - post registration), and research about the natural course. Research might also cover aspects involving living with a rare chronic disease and palliative care. Social scientific research could also cover issues in the healthcare system. The results of this last type of research could be relevant for developing policies and for the representation of interests. Ideally, these research fields come together in an expertise centre.

5.1 What already exists?

Subsidies for medical scientific health research are usually funded through ZonMw⁵⁴, and funds for specific diseases. There are funds that specifically focus on rare diseases, such as the Zeldzame Ziekten Fonds, the Prinses Beatrixfonds voor spierziekten, and the Dutch Cystic Fibrosis Stichting (NCFS). The NCFS is part of the collaborating health funds (SGF)⁵⁵. Fundamental and early clinical research with regard to rare diseases in the Netherlands has a good reputation abroad. Rare diseases is an area for which European and worldwide collaboration is very much desired. The numbers of patients are mostly limited in one member state, for pharmaceutical research as well as research regarding the natural course of a specific rare disease. European collaboration also takes place through ZomMw (E-Rare program), and through scientific organisations themselves. In E-rare, projects are funded involving collaboration among several researches from different European countries (member states or associated countries). In 2012, 11 projects were accepted, and Dutch researchers took part in eight of these projects. To reduce the 'gap' between basic research and therapy, ZomMw started the Priority Rare Medicines (PM-Rare) programme in 2009. In May 2012 three promising projects were awarded a subsidy of € 3 million per project. For these projects there is public-private collaboration. Many new diagnostic or treatment possibilities are developed by (spin-offs of) universities or small companies. In past years 'big' pharmaceutical companies also took an interest in the development of pharmaceuticals for small groups. Up-to-date overviews of orphan drugs that are available are published through Orphanet and the European Medicines Agency (EMA)⁵⁶.

For Dutch pharmaceutical MKB organisations, public or non-profit organisations, it is possible to request small subsidies from ZonMw (subsidy regulations for Orphan Designation, ODD support) for the costs of drafting and submitting a file to EMA for the request to appoint orphan drugs, an *orphan designation*. The Dutch contribution to the development of orphan drugs increased to twelve *orphan designations* in 2010⁵⁷.

In coming years much can be expected from new technological developments that could contribute to swifter diagnoses for rare diseases (such as array research, *exome sequencing*, *proteomics* or further additions to the heel prick test), and developments that contribute to a causal treatment for rare diseases, such as gene and cell therapy. Research regarding hereditary and exogenous factors could offer more insight into the causes of diseases, which will make it possible to provide better information (hereditary advice or preconceptional care) for patients and their families.

Creating and managing registers of rare diseases is very important for scientific research, as already indicated in the introduction to this chapter. Some examples are: the TI-Pharma project 'Sustainable Orphan Drug Development through registries and monitoring', the registration of metabolic diseases (www.DDRMD.nl), Treat

⁵⁴ ZonMw has the following main clients: The Dutch Ministry of Health, Welfare and Sport (VWS) and The Dutch Organisation for Scientific Research (NWO).

⁵⁵ www.gezondheidsfondsen.nl/home.aspx

⁵⁶ www.orpha.net/orphacom/cahiers/docs/GB/list_of_orphan_drugs_in_europe.pdf & <http://ec.europa.eu/health/documents/community-register/html/alforphreg.htm>

⁵⁷ STIGON Orphan drugs project (2006-2011).

NMD & CRAMP (both muscular diseases, www.isno.nl) or Eurocat (www.eurocatnederland.nl). In 2014, the European Committee will initiate the creation of a platform for the registration of rare diseases⁵⁸.

5.2 What is missing?

Clinical pharmaceutical research, which usually takes place in different countries around the same time, has not been conducted in the Netherlands for a number of rare diseases. The pharmaceutical companies have their own reasons for choosing the countries where they do research. One reason for not including the Netherlands for some research is the current regulations with regard to conducting phase I research with children⁵⁹.

With regard to the efficiency of research into orphan drugs for Fabry's and Pompe disease, it became clear that there is a need for an assessment framework, which could also lead to a better treatment due to research with small groups and therefore to the decision to reimburse the treatment. Furthermore, one should focus on research with regard to the results of care and treatment, for which the increased life expectancy and quality of life are considered^{60, 61}. In the discussion about expensive care and treatment, results are not yet considered as being significant.

For many patients who suffer from rare diseases the natural course of the disease is insufficiently known. More knowledge about the natural course of diseases will lead to early detection of complications, or even prevention of complications, and offers a better principle for research about the effectiveness and efficacy (efficiency and efficient use) of new pharmaceuticals. Genetic diagnostics could be improved with more research regarding gene variants, and research findings should be made available worldwide through databases⁶².

Basic scientific research in the Netherlands is of high quality, but its translation to clinical application or healthcare has room for improvement. Other suggestions for new research in the area of rare diseases are: disease transcending research of symptoms that are present for several rare diseases; research of possibilities for early detection, diagnostics, screening, preconceptional care and prevention of rare diseases, and research concerning the genetic components that are the partial cause of rare diseases, and the impact of rare diseases on everyday life. Publications about rare diseases could contribute to an increase in knowledge about rare diseases, especially very rare diseases.

Another aspect that should be focused on is research regarding the application of pharmaceuticals that are already available for the treatment of rare diseases (off-label use).

Patient registers could help to collect such research data, but this takes place insufficiently and not continuously. One of the reasons for this is that there is no uniform codification. The ICD-10 is often unsuitable for codifying rare diseases⁶³. The data of people with rare diseases are usually not updated for a long period, and are kept mostly only on a national basis. A lot of research that includes registration is only funded in the short term, and is not intended to be continuous. One possible threat for (medical) scientific research is the decrease or reallocation of government budgets. This could have consequences for research with regard to rare diseases. Furthermore, there are insufficient funds for research over a longer period of time.

⁵⁸ http://ihcp.jrc.ec.europa.eu/our_activities/public-health

⁵⁹ The Commissie Doek has proposed that these regulations be modified. Parliamentary examination of these proposals has not yet taken place.

⁶⁰ Research of the Van Creveldt Kliniek at Utrecht (Aging with haemophilia) has shown that a large percentage of the patients that were treated in the centre in 2007 were over the age of 40.

⁶¹ Verborgten Waarden. About the results of pharmaceuticals for society, Nefarma, November 2012.

⁶² Also see: www.lovd.nl/LSDBs

⁶³ A New Coding System for Metabolic Disorders Demonstrates Gaps in the International Disease Classifications ICD-10 and SNOMED-CT which can be Barriers to Genotype-Phenotype data Sharing. Sollie, A. et al. Human Mutation, 2013 (in press).

5.3 Table of recommendations for Research

	Recommendations for Research	1st point of contact / other party/parties
5.3.1	Improve tools for detection and recognition of rare diseases on the part of GPs, clinics and child healthcare.	NHG NCJ
5.3.2	Make rare diseases more known and easier to find in literature by adding the term rare disease or Orphan or Rare Disease to the text of the scientific article, as a search term.	Scientific organisations NFU and STZ
5.3.3	The scientific research field should continuously pay attention to: - medical and social scientific aspects of rare diseases; - the development of more and better diagnostic methods; - (new) therapeutic possibilities for rare diseases; - natural course of rare diseases - efficient and cost-effective research regarding orphan drugs.	ZonMw in collaboration with SGF and NFU, Nefarma and Biofarmind
5.3.4	Promote research regarding treatment with existing pharmaceuticals that are not (yet) registered for the concerning disease (off-label use).	ZonMw NFU (UMCs) Nefarma and Biofarmind
5.3.5	More research for the improvement of genetic diagnostics for more rare diseases (including exome and genome sequencing) and research regarding gene varieties and publication of these data in worldwide databases.	VKGN
5.3.6	Fund research into rare diseases in which different scientific disciplines (for example medical and social scientific) collaborate on a national and international basis.	ZonMw /E-Rare
5.3.7	Involve patients when choosing priorities for new research programmes, deciding upon final goals, registering the natural	ZonMw in collaboration with NPCF, SGF, VSOP

	course, quality of life research and research regarding palliative care for rapidly progressive diseases.	
5.3.8	International research is needed concerning renewed (HTA and MTA) methods for measuring the effectiveness and efficiency of orphan drugs.	ZonMw
5.3.9	Promote public and private collaboration for the development of treatments.	ZonMw in collaboration with the SGF, Nefarma & Biofarmind
5.3.10	Develop and finance a follow-up database (NEORAH) after heel prick tests for long-term research regarding the course of the condition.	VWS RIVM
5.3.11	Registers and bio banks should be an integral part of the Dutch expertise centres for rare diseases, with links to registration in other countries as far as this is possible. To do so, the management of a patient register/database of people with rare diseases should be funded. ⁶⁴	NFU ZN
5.3.12	Concentrate specific scientific research for (groups of) rare diseases for which expertise is already present at the centre. Develop this by using research, clinical excellence and innovation.	NFU
5.3.13	Remove barriers that slow the development of new diagnostic tools and new therapy for rare diseases. Broaden legal limitations that are included in the WMO for carrying out phase 1 and phase 2 research with children.	VWS (legislative adjustment) CCMO and METCs (implementation)

⁶⁴ Such as is already in place for the Palga registration <http://www.palga.nl>

6. More focus on patients with rare diseases

Overview of the theme

This theme concerns the general representation of interests and proactive engagement from the perspective of patients and their representatives in the broad area of living with a rare, often chronic disease. Patient organisations could play an important part for all themes that have been described in the previous chapters: improvement of knowledge and information, creating care path systems, prioritising research, or detecting issues with regard to diagnostics, care and treatment. Furthermore, this theme relates to the empowerment of patients with rare diseases.

6.1 What already exists?

There are several organisations for patients with a rare disease and their families to go to, for contact with fellow sufferers, information and advice. In the Netherlands, there are about 350-400 specific patient organisations focusing on particular diseases. Of these, a number of organisations focus on a cluster of rare diseases, for example for muscular diseases, metabolic diseases, blood disorders, chromosomal disorders. The government recognises a number of umbrella organisations and platforms that operate on a national level: the NPCF, CG-Raad, Platform VG and LPGGz.

Only these umbrella organisations receive operating subsidies from the Fonds PGO, a part of the VWS ministry⁶⁵. For a number of years the VSOP is the National contact point for rare diseases for the European umbrella organisation EURORDIS. The VSOP is a collaboration of 66 member organisations, most of them dedicated to rare and/or genetic conditions. Together with supporters and other patient organisations, the VSOP has a number of projects in the area of rare diseases. Unlike other countries funding is available (through Fonds PGO) for patient organisations in the Netherlands. The government has decided to allow patient and disability organisations up to 2015 to carry out mergers and collaborations, including initiatives using vouchers. In 2015, it will be seen whether such collaborations have made any progress. If insufficient collaboration has been achieved, stricter subsidy conditions will be enforced. This could lead to the reallocation of resources⁶⁶. Collaboration and merging is necessary for rare diseases, especially as there are so many diseases.

In 2013 a number of collaboration projects were initiated, using the voucher system. A number of these related to rare diseases. An overview of these projects has been added to the appendices.

6.2 What is missing?

It is important to implement a better structure to the representation of interests for people involved with rare diseases. Due to the rare nature of these diseases, there are a few generic aspects that might play a role in the development of new legislation or regulations or their implementation.

The umbrella organisations for chronic diseases have insufficient means to represent interests in the area of rare diseases, although they are consulted by the government.

Solutions of issues and policy decisions for more common chronic diseases usually offer no or insufficient answers for the specific situation of people with rare diseases.

Currently, there is no complete overview of all patient organisations or contact groups that exist for rare diseases in the Netherlands (also see recommendation 3.3.6).

A problem that arises is that there are currently no Dutch patient or parent organisations for very rare diseases. Patients can easily find each other all over the world with the help of the Internet, but people with very rare diseases often come across more problems in the Dutch healthcare system due to the unfamiliarity of the disease among healthcare providers, healthcare organisations, insurers and the government. An important condition to improve the organisation of input of patients with rare diseases is that the larger patient organisations for cross-border diseases and specific diseases should be available for new additions. In this manner, more empowerment is created. For very small groups or individuals, it is often impossible to join an organisation. The

⁶⁵ The Chronisch Zieken en Gehandicapten Raad (CG-Council) will merge with the platform for the mentally disabled in the Netherlands (Platform VG) at the end of 2013, which creates an umbrella organisation for physical and/or mental conditions and chronic diseases.

⁶⁶ www.fondspgo.nl/doc/pdf/Bijlage%201%20-%20Aangepast%20beleidskader%202013_32461.pdf

representation of interests in general is under pressure due to the changes in funding patient organisations (see 6.1.). A number of interest-representation initiatives are dependent on project subsidies, whereas the representation of interests should be a continuous focus point.

Patient organisations play an important role in creating the NPZZ. During a meeting that was organised by the VSOP (in 2012), people indicated they wanted to play a prominent role in the implementation and coordination of the NPZZ. However, there is no consensus yet within patient organisations about how this could be organised or achieved.

6.3 Table of Recommendations for More focus on patients with rare diseases

	Recommendations to increase the input of the patient	1st point of contact / other party/parties
6.3.1	Enhancing and expanding the collaboration of patient organisations with regard to generic aspects of rare diseases, namely representation of interests, is necessary.	VSOP in collaboration with CG Council and NPCF
6.3.2	This should be promoted for patient organisations to let fellow sufferers or small groups join (merging disease groups) and to collaborate more in the area of rare diseases. ⁶⁷	Fonds PGO in collaboration with NPCF
6.3.3	Patient organisations and health insurers need to work more closely. This will promote the development of care path and care chain systems, and improve the quality of care and purchasing care for people with rare diseases.	VSOP in collaboration with CG Council, NPCF, Health insurers

⁶⁷ NPZZ looks to the examples of Spierziekten Nederland (VSN) and of Volwassenen, Kinderen en Stofwisselingsziekten (VKS). For different pathologies, these organisations have created diagnosis groups.

7. Direction on a continuous basis

Overview of the theme

After several meetings with the actors involved (hearings, congresses) and within the advisory board, the recommendations from the NPZZ concept have been discussed, as has the subject of direction. This especially concerns the question: which organisation could be held responsible for activities performed further to this plan? Who would be able to monitor the connection between different projects and activities, especially for aspects that are not part of the responsibility of a stakeholder, or for which it is necessary to bear in mind the general picture. It was also asked who would focus on a future evaluation of the goals and results of the plan and monitoring activities that need continuous attention.

7.1 What already exists?

The (Dutch) National Plan for Rare Diseases was submitted to the VWS minister on 10 October 2013. In November 2013, the VSOP organised a conference about the National plan and the EUROPLAN project. The VWS ministry requested the Dutch Forum for Biotechnology Genetics (FBG) in their assignment letter of 2012 to contribute to solving the problems faced by people with rare diseases, and with regard to the assignment, to take responsibility for the plenary meeting between the relevant parties. This especially concerns the position of the patient, the development of orphan drugs and, as far this is necessary, advice given to the government. From Europe, the EUCERD will monitor the development of plans for rare diseases within Europe. The EUCERD has created a document with 21 indications with which data of the process and the results of the national plan can be recorded within each country⁶⁸. In 2013 several new projects were initiated in the area of rare diseases and orphan drugs, which were, amongst others, financed by the Fonds PGO⁶⁹ and by ZonMw⁷⁰. The first results of these projects are expected in 2014-2015.

7.2 What is missing?

Several of the actors involved have indicated that the focus should remain on a European policy for rare diseases in addition to all national plans, especially for aspects for which European collaboration and alignment is necessary, for example in the area of research.

No budget has been estimated for the implementation of the plan. In this way, the plan could be a motivation for starting activities, and the involved actors now have responsibility for covering the personnel and/or financial needs to implement activities. The VWS ministry should clarify who has the (delegated) responsibility for directing the proposed actions. Many involved actors are in need of a coordination point for rare diseases, at which the gathered knowledge from the field can be brought together, developed, and implemented further.

For this reason it should also be mentioned that such a group needs to have support and authority for taking decisions. An independent, scientific or joint coordination point is advocated. The following organisations have been mentioned: Kwaliteitsinstituut, ZonMw, RIVM, University or Health insurers⁷¹.

⁶⁸ www.eucerd.eu/wp-content/uploads/2013/06/EUCERD_Recommendations_Indicators_adopted.pdf

⁶⁹ www.pgosupport.nl/page/Voucherprojecten-2013

⁷⁰ www.zonmw.nl/nl/themas/thema-detail/zeldzame-ziekten-en-weesgeneesmiddelen/thema-detail/

⁷¹ The NFU has also been mentioned, especially with regard to appointing expertise centres. Patient organisations also recognise a role they could have for monitoring the plan (see 6.2)

7.3 Table of recommendations for Direction (coordination) on a continuous basis

	Recommendations for Direction on a continuous basis	1st point of contact / other party/parties
7.3.1	A director should be appointed who has primary responsibility for implementing the plan and promoting the activities of the plan.	Minister of VWS
7.3.2	An advisory body from the government that closely follows the activities of the plan, monitors them, and reports about progress and problems, is needed.	FBG

8. Conclusions and Priorities for the short- and medium-long term

The NPZZ describes what is already present, and what is still lacking. The plan has been created in addition to the strategy of the VWS minister. Many new projects have been initiated, in the area of scientific research as well as in collaborative projects of patient organisations. The outcomes and results of these are uncertain at this moment in time, but currently data are lacking about the delay in making a diagnosis, the natural course of rare diseases or the number of patients suffering from a rare disease in the Netherlands. Research in these areas is therefore very much desired. The NPZZ could motivate actors to gather such data and collaborate more. Practical recommendations are made in the plan to improve the situation of people with rare diseases in the short and long term.

Based on the discussions and consultations in the field, priorities can be allotted. With regard to the following, a proposal for prioritising subjects is given, based on currently available information. In addition to this, it would be desirable to implement actions that are currently considered as being long-term goals.

Urgent/short term, start of next year: 2014)

A few areas and corresponding recommendations can be designated as being urgent, pressing, or necessary.

- Appointing a director for the entire plan.
- Certainty with regard to the policy for expertise centres and EU reference centres, mainly concerning cross-border care legislation.
- Consistent policy with regard to entitlement and the price of orphan drugs.
- Promoting timely and adequate diagnostics and promoting awareness and knowledge of rare diseases among physicians and other care professionals.

Medium-long term (starting in 2 to 3 years)

Longer times are expected for the following recommendations, due to the complexity of the subject or diversity of the actors involved.

- Appointing centres based on uniform criteria, the presence of multidisciplinary care chain and care path systems.
- Coordination and alignment of care and information (*shared care and care chain*).
- Adequate financing of Healthcare (DBC chain).
- Continuous financing for running research programmes in the area of rare diseases and orphan drugs.

Long term (3 years or more)

Recommendations that will take a longer time to implement and/or for which it is unclear at this moment how (and when) these activities could start. Moreover, the introduction to this paragraph mentioned that it is desirable to implement some of these recommendations sooner.

- Financing new research/new programmes regarding rare diseases (medical science, social science).
- Adequate and uniform codification and national registration of rare diseases.
- Long-term research concerning the course of the disease, early treatment and measures to prevent and treat complications.
- Development of new therapies by Dutch researchers and companies.
- Evaluations of activities and results of the plan (NPZZ).

Continuous attention

A few aspects should be mentioned that need continuous focus, these do not benefit from a project-based approach, after which the focus is removed at the end of the project. This relates to aspects such as:

- Input by patients (or patient organisations) for creating policies, making priorities, and strong representation of interests for rare diseases;
- Adequate education and training for care givers and social workers with regard to rare diseases;
- Knowledge and education, early detection and awareness of rare diseases;
- Infrastructure for collecting knowledge about rare diseases and maintaining databases;
- Entitlement to and financing of adequate treatment of rare diseases.

A. Responsibility

The National Plan for Rare Diseases (NPZZ) was created under the responsibility of ZonMw, which appointed an advisory board (Klankbordgroep NPZZ) for this purpose (2012-2013). The advisory board had five meetings about the plan. Summaries of the meetings are published on the website of the NPZZ. Three versions of the plan were published through the website for public consultation (www.npzz.nl). Many people and organisations have contributed to the plan.

A chronological overview of the steps taken to draft the final version of the plan is given below.

- The themes helpdesk, information, healthcare, treatment, research, availability of treatment and availability of knowledge were discussed separately by the advisory board of NPZZ (2012-2013).
- These same themes were discussed by multidisciplinary work groups (meetings at end of 2011, a written round will start in 2013) and in a Hearing (April 2012).
- The first version of the NPZZ was presented and discussed during a public meeting and published on the website www.npzz.nl (August 2012).
- The second version was published on 29 January 2013 on www.npzz.nl.
- The feedback was collected and discussed in the meeting of the NPZZ advisory board in March 2013.
- The second version of the NPZZ was modified subsequent to this meeting and another feedback round followed within the advisory board (April-May 2013).
- The third version of the NPZZ was published on the website www.npzz.nl (May 2013).
- The third version was discussed with the Dagelijkse Bestuur of ZonMw (May 2013).
- The feedback on the third version was collected and discussed during the meeting of the advisory board (June 2013).
- The NPZZ was again modified based on the feedback, and a last feedback round took place within the advisory board NPZZ (June-July 2013).
- The final version of the plan, including editorial changes, was drafted (August - September 2013).
- The NPZZ was submitted to the VWS ministry by ZonMw (October 2013).

Advisory board

The composition of the advisory board for the National Plan for Rare diseases was as follows:

Chairperson: Dr J.F.F. Lekkerkerker

Members:

P.J.A. Bertens, Nefarma, The Hague
Prof. F.J.M. Gabreëls, paediatric neurologist, UMC. St. Radboud, Nijmegen
M. van der Graaff, CVZ, Diemen
J.G. Hanstede, Biofarmind, The Hague
Prof. C.B.H.W. Lamers, gastroenterologist, LUMC, Leiden
J. Lanphen, general practitioner, Blaricum
H. Meutgeert, VSOP & VKS, Zwolle
C.M.A. Rademaker, hospital pharmacist, UMCU-WKZ, Utrecht
G.W. Salemink, Physician M&G, ZN, Zeist
Prof. M. de Visser, AMC, Amsterdam
A. van der Zeijden, CG Council, Utrecht
V. Stoyanova, CBG, Utrecht

Observer from the VWS ministry:

H.J.J. Seeverens, internist, GMT department, up to 1 February 2013, after that advisory board member with personal title. Furthermore, EUCERD member up to 1 February 2013
P.S. Boom, Curative Care Department, from 1 June 2013

Secretaries:

J. Huizer, ZonMw, The Hague
S. van Weely, ZonMw, The Hague

Organisations

A number of organisations have discussed the plan with their executive boards, and have provided feedback to the advisory board, such as the Dutch Forum for Biotechnology and Genetics, ezondheidsraad/Beraadsgroep Genetica, Erfocentrum, Madurodamgroep (VSOP), NFU, VSOP (members and directors), werkgroep weesgeneesmiddelen (Biofarmind). The advisory group has also given a number of presentations, for example for NCMD Nijmegen, member consultation for VSOP, and during Orphan Cafés.

Individual contributions

A list of the other persons who have contributed to the plan can be found below⁷² (in alphabetical order):

T. Akkermans (NFVN); A. Antonisse (AstraZeneca); S. Beacher (Oscar Nederland); M. Beckers (NCJ); J. Bekenkamp (Noonan syndroom); J. Bolk (LUMC); R. Bos (CBG); Y. van der Bosch (Friedrich Wegener Stichting); F. Breedveld (NFU); M. Brouns-Van Engelen (Erfocentrum); H. Brunner (UMC St Radboud); I. Caubo (NFVN); S. Ying Chuah (KNMP); M. Cornel (Orphanet Nederland/VUmc); J. Crasborn (AGIS); M. Creemers (Genzyme); P. Deen (UMC St Radboud); K. Dolsma (Erfocentrum); C. van Doorne (ADCA); T. Drenthen (NHG); H. Droog (AA/PNH); G. Engel (FBG); B. Van Engelen (UMC St Radboud/NECC); P. Evers (NFK); P. Flapper (Shire); A. Franken (Isala/STZ); J. Frenkel (UMCU); W. Goossen (Results 4 Care);
F. de Groot (ToendersdeGroot); E. Hackenitz (ZonMw); M. Heijmans (NIVEL); M. Heldoorn (NPCF); M. Van Hest (Flockloose); J. Hofdijk (Casemix); C. Hollak (AMC); N. Hoogerbrugge (UMC St Radboud); M. Hooiveld (GlaxoSmithKline); H. Hurts (VWS/GMT); H. Jonker (Het Ondersteuningsburo); L. Ten Kate (VUmc /GR); N. Kien (Stichting EGV); J. Kimpen (NFU); C. Kleinegriss (Stichting NET-groep); N. Knoers (UMCU); H. Kruijswijk (Stichting Marijke); P. Leeflang; R. Legtenberg (PSR); C. Leijten (Prosensa);
B. Van der Lelie (Lysiac); R. Van der Linden (Medir); B. Leufkens (UU); M. Martens (VSOP); J. Van der Meer (Stichting EGV); I. Van Meijeren (LAM Nederland); M. Metzelaar (Pfizer); E. Mogendorff (TopGGZ); E. Moret (UU); R. Nugteren (RIVM); C. Oosterwijk (VSOP); H. Overkleeft (Universiteit Leiden); P. Van Overveld (Orphanet NL); I. Overwater (Erasmus MC); A. Van der Ploeg (Erasmus MC); H. Ploegmakers (STSN); D. Postma (KNMP); G. Postma (UMC St Radboud); I. Plug (Erasmus MC); A. Prenger (ZN); C. Van Ravenswaaij (UMCG); J. Roord (VUmc); E. Sauter-Lemmens (Orphan Europe); W. van Schaik (Nail Patella Syndrome); H. Schikan (Prosensa); M. Schmidt (NFU); C. Schrandt-Stumpel (MUMC+); J. Schrandt (MUMC+); R. Senf (Erfocentrum); L. Siderius (SSSH); J. Smeitink (UMC St Radboud/NCMD); C. Smit; A. Sollie (CINEAS); J. Span (CBG); A. Speijer (VSOP); A. Stiene (AA&PNH); P. Taschner (LUMC); M. Timmen (VSN); T. Van der Vaart (Erasmus MC); I. Vajda (VSOP); E. Van Veldhuizen (NVACP); G. Visser (UMCU); B. Voordouw (CBG/LUMC); M. Voorsluijs (M-Power); E. Vroom (Duchenne Parent Project); R. de Vruhe (ZonMw); G. Wagemaker (Erasmus MC/EUCERD); A. de Weijer (VSOP); S. Weinreich (VSN/VUmc); E. Van der Wiele; M. Wiers (SLE); P. Wiers (SLE); L. Wormhoudt (Genzyme); E. Yap (Lysiac)

⁷² These persons were members of a work group, attended a hearing or congress, or have contributed through Nationaal Plan Zeldzame Ziekten.nl to the plan. They have done so on a personal basis.

B. Summary of the strategy of the Ministry of Health, Welfare and Sport

In the strategy of the VWS ministry (29 February 2012) regarding rare diseases, the policy of previous years and the current situation are discussed⁷³. The influence of the government is mostly possible in general thematic areas, such as accessibility, quality and affordability of healthcare. Besides this, the government could help to solve certain specific problems by granting subsidies to appointed parties. However, the policy of the government has no direct influence on the individual relationship between a patient with a rare disease and the care providers or healthcare organisations. The strategy of coming years has been partially modified. In the strategy for coming years, a number of tasks have been assigned to ZonMw and to the Dutch Forum for Biotechnology and Genetics. Other aspects of the national strategy of the government are mostly a continuation of an already existing policy, and relate to:

Diagnostics and treatment

Diagnosing and treating patients is deemed to be specialist or referral care. The financial means that are made available by the VWS ministry through the academic component are meant for funding advanced care (80% care) and 20% is allotted to research and innovation. The government will not appoint centres in the short term.

Involvement of patient organisations

Patient organisations are involved through representatives and the advisory board of the NPZZ, and consulting is given through, among other things, the website of the National Plan and representation within the Dutch Forum for Biotechnology and Genetics (FBG). Patient organisations are financially supported by the government, through CIBG/Fonds PGO.

Screening

Screening policy concerning the heel prick test is expected to remain unchanged. Child healthcare systematically carries out screenings with essentially all children according to established regulations. The Stichting Opsporing Erfelijke Tumoren (STOET) registers families with a predisposition for hereditary tumours and is granted a subsidy from the VWS ministry.

Scientific research

The government funds scientific research through the Academic component, ZonMw programmes and Kader EU programmes.

Reimbursement of pharmaceuticals

Starting in 2014 (postponed to 2016), orphan drugs will only be funded through hospital financing. The government has no influence on the entitlement.

Registration of rare diseases

The government acknowledges that this is a difficult matter and not an optimal one. The government points out the European database for cancer, such a database could be used as a basis for a general registration system.

Involvement with European policies

A representative of VWS has a position in the EUCERD (European Committee for Experts On Rare Diseases).

⁷³ The complete text of the Dutch strategy with regard to rare diseases can be found on www.rijksoverheid.nl/documenten-en-publicaties/kamerstukken/2012/03/01/kamerbrief-over-de-nederlandsestrategie-met-betrekking-tot-de-zeldzame-ziekten.html

C. Overview of projects in the sphere of rare diseases

The NPZZ refers to different projects in the area of rare diseases. In this appendix, an overview of projects that were granted funding for the implementation of their project, initiated in 2012 or 2013, in which different organisations and different actors, both public and private, national or international, collaborate can be found. Furthermore, a large number of other initiatives or projects are planned, which could be important for rare diseases, but have not been added to the current overview. Projects of individual patient organisations for specific groups of rare diseases are not indicated in this overview. Most of the projects below will terminate in the period 2014-2015. It is obvious that the results of these projects can be used for creating the next National Plan, with new priorities.

Table 1. Projects of patient organisations in collaboration with other patient organisations or other partners (funded by the Fonds PGO or Innovatiefonds)

Project name	Goals / overview of activities project	Participants/Partners	Time span
Expertise in rare conditions from the perspective of patients	The goal of the project is to record knowledge about a number of rare diseases by visiting a number of expertise centres. The basis for this is a list of criteria that expertise centres should meet according to the project partners. www.expertiseinkaat.nl	VKS in collaboration with Longfibrose Patientvereniging, Klub van Lange mensen, PKU vereniging, Vasculitis Stichting, Vereniging Nee-eten.	2013
Care standards for rare conditions	The project's goal is to develop 16 care standards for rare conditions (www.zorgstandaarden.net).	VSOP in collaboration with patient organisations with which care standards will be developed.	2012-2014
Heard, seen, and known. Innovation by participation in policies for people with rare conditions.	This project includes: an annual policy symposium concerning implementation of the National Plan for Rare Diseases; a Multistakeholder platform (Madurodamgroep); a workgroup on Genetics, pregnancy and ethics; organisation of the annual Rare Diseases Day. The development of a point of contact, info desk and portal.	VSOP in collaboration with AIS Nederland, CMTC-OVM, Dit Koningskind, Helpende Handen, HME-MO vereniging, Jeugdreuma Vereniging Nederland, NPV, Contactgroep AA & PNH, Vereniging Tietze en costochondritis patiënten, FSIGN, Ehlers Danlos Patiënten, SCCH.	2013-2015
From care 1.0 to care 2.0. Innovation by participation in quality in	This project includes: Creation and expansion of the website for healthcare standards; the improvement of primary	VSOP in collaboration with Paget, Fragiele X, NFVN, SAS, VSN, HCHWA-D, Dwarslaesie NL,	2013-2015

healthcare and prevention for people with rare conditions	healthcare (especially care by general practitioners) by promotion and implementation of the brochure 'the patient as a carrier of information' and developed healthcare standards for rare diseases. Furthermore, the development of care advice and of a user version of healthcare standards.	Bijniervereniging, NVACP, SCCH.	
Patients in perspective. participation in healthcare research and development of treatments for people with rare conditions.	This project includes: Data for innovation (annual meeting for patients, researchers, and developers of medical products); attending patient organisations (mostly partners) for possible subsidisation; participation in the work group for medical scientific research and medical databases, and the child and disease work group. Exploring healthcare research and therapy development and patient registers.	VSOP in collaboration with Stichting kind en ziekenhuis; HCHWAD: HEVAS, Stichting DES, Stichting Noonan Syndroom, Vereniging Allergiepatiënten, Vereniging ouder couveusekinderen; Galactosemievereniging, NL vereniging Hemofiliepatiënten.	2013-2015
The mentally disabled: care in the future	The goal of this project is to develop a care module: transition for people with a mental disability.	VSOP in collaboration with PlatformVG, UMC St. Radboud Nijmegen, Academisch Ziekenhuis Maastricht, Elkerliek Ziekenhuis Helmond, Amphia Ziekenhuis Breda, Maasstad Ziekenhuis Rotterdam and Hogeschool Rotterdam.	2013-2015
Increasing the input of the patient	The goal of the project is to create a means of providing information in a similar way to the Medical Home Portal/Chronic care model. An important element of the portal is early detection and diagnostics. Patient organisations and experts will offer information to promote timely	Stichting perspectief in collaboration with Stichting Shwachman Support Holland, Oscar Nederland, Sarcoidose Belangenvereniging Nederland, FOP Stichting Nederland, Stichting Rubenstein Taybi, Stichting	2013-2015

	diagnostics in primary care (child health clinic, GP, general specialist). There are plans to connect with the Digital Kind Dossier, to make information from before the diagnosis available after the diagnosis to promote early detection.	Perspectief, Stichting Lapos, Nederlandse vereniging voor hereditair angio oedeem en quincke's oedeem, Stichting Marshall Smith	
Syndrome Research Foundation, Stichting Veteranenziekte, Vereniging Ouders van Wiegendoodkinderen. Zorgpad Neuro-Musculaire Aandoeningen (NMA).	To create a multidisciplinary NMA care chain, focused on the quality of life with an NMA, enhancing the desired life purpose of the patient by allowing him to be in charge of directing. The alignment focuses on relations between care givers, patients and the care givers/family care givers.	UMC St. Radboud, RMC Groot Klimmendaal en Siza, Vereniging Spierziekten Nederland (VSN).	Started in 2013

PGO projects

Through the link below, an overview of all voucher projects that were initiated in 2013 can be downloaded.

www.pgosupport.nl/page/Voucherprojecten-2013

Table 2. Projects within the ZonMw programme Priority Medicines for rare diseases (PM Rare)

All projects can be found on: www.zonmw.nl/pmrare

Antisense therapy for several major rare diseases. Prof. dr. G.J.B. van Ommen / LUMC	Duchenne muscular dystrophy. The researchers are trying to make the defected gene work better through so-called exon skipping. In collaboration with Prosenia and GlaxoSmithKline, it is being seen whether this method works. Furthermore, exon skipping is studied to see if it is also applicable to Huntington's disease and CADASIL.	2012-2016
Gene-corrected stem cells for curative treatment of SCID. Prof. dr. F.J.T. Staal / LUMC	This research is focused on the immune disorder Severe Combined Immuno Deficiency (SCID). Children with this condition lack white blood cells, which are crucial for a well-functioning immune system. They can be treated with bone marrow transplantation. The idea is to treat these small patients with gene therapy.	2012-2016

<p>Towards treatment of MELAS syndrome: drug development based on newly identified compounds. Prof. dr. J.A.M. Smeitink / UMC St. Radboud</p>	<p>The subsidy supports the research for new treatment methods for MELAS syndrome, a rare hereditary metabolic disease. To carry out this research a multidisciplinary team was formed, consisting of public and private parties. For 5 years, Mercachem, Khondrion and UMC St. will contribute their expertise to develop a treatment.</p>	<p>2012-2016</p>
<p>Treating the cognitive deficits associated with NF1 using the HCN channel agonist lamotrigine. Prof. dr. Y. Elgersma/Erasmus MC/ENCORE</p>	<p>Children with the condition Neurofibromatosis type 1 (NF1) often also have learning, concentration or behavioural difficulties. Erasmus MC researches have found the cause of these problems with mice with an NF1 mutation. Mice are administered medication (lamotrigine) that stimulates the HCN channel, the brain functions normally again, and the learning problems disappear. To test if Lamotrigine could help children with NF1 as well, researchers will carry out a clinical trial.</p>	<p>2013-2015</p>
<p>A novel technology to improve Enzyme Replacement Therapy for Mucopolysaccharidosis I and Fabry disease. Prof. dr. C.E.M. Hollak/Academisch Medisch Centrum</p>	<p>The proposed project will focus on studies in cell cultures and relevant mouse models, to provide a proof-of-principle that GSHPEG liposomes containing lysosomal enzymes leads to better clearance of accumulated substrates in the clinically relevant tissues as compared to unshielded enzyme. The AMC, with its clinical and laboratory expertise on LSDs, combined with to-BBB's experience in generating GSH-PEG liposomes containing drugs and their knowledge on targeting the brain, will create an optimal platform for this study. Collaboration with the Stem Cell & Neurotherapies</p>	<p>2013-2015</p>

	<p>Lab in Manchester provides essential expertise for this project on MPS I brain pathology in the mouse model and on antibody studies in MPS.</p>	
<p>Thyroid hormone analogue therapy of patients with severe psychomotor retardation caused by mutations in the MCT8 thyroid hormone transporter. Prof. dr. ir. T.J. Visser, Dr. W.E. Visser/ Erasmus MC</p>	<p>Thyroid hormones are important for a normal brain development and metabolism. Patients with mutations in an important thyroid hormone transporter (MCT8) have a serious mental disorder and abnormal thyroid hormone values. The goal of this research is to reduce the serious effects of this pathology, or to prevent them: by restoring the functioning of the thyroid hormone on a cellular level, and to normalise the abnormal thyroid hormone levels. Researchers hope to achieve this by administering a substance that is derived from the thyroid hormone. This substance is then absorbed by the cell through a different route than through MCT8, and mimics the functioning of the thyroid hormone.</p>	<p>2013-2015</p>
<p>Preventing arrhythmias and sudden cardiac death in long QT syndrome type 3 through pharmacological late sodium current inhibition. Prof. dr. A.A.M. Wilde/ Academisch Medisch Centrum</p>	<p>Long QT syndrome type 3 (LQT3) is a rare genetic disorder caused by mutations in the SCN5A gene encoding the cardiac sodium channel, and is characterized by prolonged QT intervals on the ECG, and increased risk for sudden death due to ventricular tachyarrhythmias, in particular torsades de pointes. Compared to other LQT subtypes, LQT3 patients are particularly at risk of sudden death, and cardiac arrest (rather than syncope) is often the first clinical event. Pharmacological treatment options for LQT3 are limited. At the moment, high risk LQT3 patients are treated with implantation of an implantable</p>	<p>2013-2015</p>

	<p>converter defibrillator (ICD), often in combination with beta blockers. ICD implantation however has serious complications and a tremendous impact on the quality of life.</p>	
<p>Informatiepunt weesgeneesmiddelen A. van der Sande/ Biofarmind</p>	<p>The Advice centre for orphan drugs will function as a portal for research and business, adding to expertise in the area of research and development of new therapies (orphan drugs) for rare diseases. This new advice centre will be a valuable source of information for applied research, companies, etc. with the final goal of accelerating the flow from research to the patient. This is important for the researcher, patient, the industry and the government www.weesgeneesmiddelen.info</p>	2012-2013

Table 3. Projects with Dutch researchers that were funded within the European project E-rare in 2012

For an overview of all funded projects see: www.e-rare.eu/all-funded-projects

Acronym Project	Coordinator	Title
Cure-FXTAS	Renate Hukema	Experimental approaches towards therapeutic intervention for Fragile X-associated Tremor Ataxia Syndrome
SpliceEB	Marjon Pasmooij	Splicing therapies for Dystrophic Epidermolysis Bullosa
TARGETCdLS	Frank Kaiser	Targeting unknowns in causes and phenotypes of the Cornelia de Lange Syndrome
PPPT-MJD	Philipp Koch	Towards the understanding of pathological protein processing and toxicity in Machado-Joseph Disease
Eur-USH	Kerstin Nagel-Wolfrum	European young investigators network for Usher syndrome
ALSdegeneration	Eran Perlson	The molecular basis for neurodegeneration and muscle atrophy in ALS

HEART DM	Nicolas Charlet-Berguerand	Exploring the mechanisms of heart dysfunctions in myotonic dystrophies
PYRAMID	Jan Herman Veldink	Phenotype Research for ALS modifier discovery
EMINA-2	Andreas Hermann	European Multidisciplinary Initiative on Neuroacanthocytosis – 2
COQ-iPSC	Pablo Menendez	Coenzyme Q10 Deficiency Syndrome: Understanding the genotype-phenotype association and metabolic dysfunction through generation of induced pluripotent stem cells (iPSCs) from patient-specific uncorrected and genetically-corrected cells
EuroDBA	Alyson MacInnes	European Diamond-Blackfan Anemia Consortium

An overview of European projects for rare diseases in the area of public health can be found on: http://ec.europa.eu/health/rare_diseases/projects/index_en.htm.

A total overview of European projects for rare diseases in the area of research and development of treatments can be found on: http://ec.europa.eu/research/health/pdf/rare-diseases-howeurope-meeting-challenges_en.pdf and http://ec.europa.eu/research/health/medical-research/rarediseases/index_en.html

D. Sources

*National Plan for Rare Diseases*⁷⁴:

The preparatory document and final report of the Hearing on the National Plan for Rare Diseases in April 2012 can be downloaded from: www.npzz.nl/hearing_12_april/.

The first version of the National Plan for Rare Diseases and the report of the congress about the National Plan on 28 August 2012 can be downloaded from: [www.npzz.nl/plan-voor-zeldzame-ziekten/eerste-versie-npzz/](http://www.npzz.nl/plan-voor-zeldzame-ziektenderde-versie/conceptplan-voor-zeldzame-ziekten/eerste-versie-npzz/).

Information about the work groups (2011) and advisory board of the National Plan for Rare Diseases (2012) can both be found on: www.npzz.nl/werkgroepen/ and www.npzz.nl/werkgroepen-nationaal-plan/.

On the website of the NPZZ, several documents supplied by different patient organisations and other groups involved with rare diseases and orphan drugs can be found in the background information section. www.npzz.nl/achtergrondinformatie/ingekomen/.

Other documents:

Other documents that can be found on the website are indicated below. Furthermore, we offer a number of website addresses for more information.

⁷⁴ Information of the website www.npzz.nl will eventually (after 2014) be transferred to www.zonmw.nl and possible other websites that will be referred to then.

Policy

- Recommendation of the COUNCIL of the European Union (Council of ministers) concerning actions in the area of rare diseases, 8 June 2009. This RECOMMENDATION includes seven areas of action: www.npzz.nl/wp-content/uploads/2011/08/Aanbeveling-vd-Raad-ZZjuni-2009.pdf
- Directives and recommendations were described in the EUROPPLAN project (2008-2011) to facilitate the definition, implementation and monitoring of the National Plans or Strategies. The document with the recommendations focuses on the seven areas of action of the Council Recommendation (see previous section): www.npzz.nl/wpcontent/uploads/2011/08/Vertaling-EUROPLAN-aanbevelingen-NL.pdf
An overview of all national plans: www.europlanproject.eu/_newsite_986989/plans.html
- The VSOP organised the conference Nationale dagen Zeldzame Aandoeningen in November 2010 with regard to the EUROPLAN project. Following this EUROPLAN Project (EUROPPLAN-2), the VSOP is organising a conference in November 2013. For the reports of the conference in 2010 see: www.npzz.nl/wp-content/uploads/2011/08/Verslag-Nationale-Dagen-Zeldzame-Aandoeningen-2010.pdf
- The most up-to-date reports and other information about activities in the area of rare diseases in Europe and different member states can be found on the website of the Comité van Experts in the area of rare diseases (EUCERD): www.eucerd.eu
- The Dutch Forum for Biotechnology and Genetics (FBG) submits monitoring reports on a regular basis in the area of rare diseases. The monitoring reports can be downloaded from the website www.forumbg.nl/documenten, for example about cascade screening heart conditions in newborns. Comments on opinions of the government and/or advisory bodies about preconceptional care or off-label use of pharmaceuticals for rare diseases can also be found on this website.

Information and research

- Orphanet (www.orpha.net) issues monthly newsletters in English. In these newsletters, a general overview of activities in Europe (for example concerning the progress of national plans) and articles about new discoveries with regard to rare diseases can be found, in fundamental scientific areas as well as with regard to healthcare. Besides newsletters, the Orphanet website also offers elaborate information about rare diseases and orphan drugs. Since 2013 most of the information is also available in Dutch. www.orpha.net/consor/cgi-bin/index.php?lng=NL. The team of Orphanet Nederland has the website www.orphanet.nl
- In the area of research into rare diseases, the International Rare Diseases Research Consortium (IRDIRC) was founded in 2010. This consortium consists of researchers and organisations that invest in research regarding rare diseases. The consortium aims to develop 200 new therapies for rare diseases by 2020, as well as fresh possibilities for diagnosing the rarest diseases. In the Netherlands, Prosenia and ZonMw are connected to with this. More information can be found on www.irdirc.org.
- At the request of Stuurgroep Weesgeneesmiddelen, dr. Wouter Boon carried out research in 2010 and 2011 regarding the efficiency of research into orphan drugs. In his report Efficiency of research into orphan drugs: analysis and future prospects from 2011, an analysis (of practise and literature) can be found, and recommendations are made for the future. The report can be downloaded, but also ordered from ZonMw. www.npzz.nl/wp-content/uploads/2011/08/WGM-Onderzoek-doeimatigheid-Eindversie.pdf
- In 2010 and 2011, the Stuurgroep Weesgeneesmiddelen consulted treating physicians, hospitals, umbrella organisations of hospitals (NFu and STZ), Zorgverzekeraars Nederland (ZN), patients and parents about possible criteria to distinguish expertise for rare conditions. The report is called Expertise for rare diseases in the Netherlands: Findings and conclusions resulting from consultations by the Stuurgroep Weesgeneesmiddelen (2010-2011). The report can be downloaded from www.npzz.nl/wpcontent/uploads/2011/12/exp-centra-samenvatting-aangepaste-versie-2012.pdf
- The EUCERD has established (similar) criteria as well for European networks. This report can be downloaded from the website of the EUCERD: www.eucerd.eu/?post_type=document&p=1962
- In 2010, the European Committee conducted a survey on 'European awareness of rare diseases'. A total of 26,574 Europeans were interviewed, 1,024 of whom were Dutch. 76% of the interviewed subjects considered the description 'rare disease are diseases that a limited number of people suffer from and need very specific care' most applicable (63% was the average for the EU). In the Netherlands, the diseases haemophilia (83%) and Duchenne Muscular Dystrophy (73%) were the most well-known. The same percentage of people interviewed in the Netherlands (33%) had actually never heard of anyone

with a rare disease. People are not aware of the real problems that people with a rare disease suffer from, said 93% of Dutch interviewees (completely agree, agree more than disagree). A total of 58% of the interviewees did not agree with the statement that the Netherlands is dealing with more important health issues than making rare diseases a priority. For the full survey, go to: www.npzz.nl/wp-content/uploads/2011/10/Eurobarometer-zeldzame-ziekten-2010.pdf

- The relationship between volume and quality of healthcare: time for a broad approach.

Utrecht/Nijmegen/Rotterdam: Consortium Onderzoek Kwaliteit van Zorg, 2012,

Zuiderent-Jerak T, Kool T, Rademakers J (red.) More information:

www.nivel.nl/node/2430?database=ChoicePublicat&preref=1002244

- Normal care for an abnormal patient: rare diseases at the GP clinic. Huisarts en Wetenschap, 50 (2007)

www.nivel.nl/node/2430?database=ChoicePublicat&preref=2297

- Life with a rare chronic condition: experiences of patients in healthcare and everyday life. NIVEL, 2003.

www.nivel.nl/node/2430?database=ChoicePublicat&preref=1001079

- Several literature references for problems of people with rare diseases. Equality Analysis: UK Plan for Rare Diseases, February 2012:

www.euoplanproject.eu/_newsite_986989/Resources/docs/NATIONALPLANS_UK_EqualityAnalysisPlanRD.pdf

E. Definitions

The Nationaal Plan Zeldzame Ziekten (NPZZ) centres on rare diseases and pharmaceuticals for rare diseases that are known as orphan drugs. For a better description of these, please consult the definitions below that are generally accepted within Europe.

It was chosen to use the term rare disease in the NPZZ, of course this includes rare congenital conditions or syndromes. For the abbreviations of different definitions and organisations mentioned in this plan, please consult the list of abbreviations (Appendix F).

What is a rare disease?

Rare diseases are life threatening or chronically debilitating diseases with such a limited prevalence, that combined efforts are necessary to prevent a high morbidity and perinatal and early mortality (as well as a serious decrease of the quality of life or social economic potential). Although these diseases are rare, there are so many different kinds that millions of people are affected. Currently, there are an estimated 5,000 to 8,000 different rare diseases, which affect 6 to 8% of the population during their lives⁷⁵. Despite the typical low prevalence of rare diseases, it is estimated that between 27 and 36 million people in the EU are annually affected by them. It is estimated that 75% of rare diseases are already present in childhood. 30% of children with a rare disease die before the age of five⁷⁶. It is suspected that 80% of rare diseases are hereditary⁷⁷.

A rare disease affects physical and psychological functioning, and often leads to financial consequences, for example travelling more often and hospital visits⁷⁸.

In Europe, a disease is also called rare when no more than 5 in 10,000 inhabitants (=1:2000) in the European Union suffer from this condition. This definition is used by European authorities as a measurement and number for promoting the development of pharmaceuticals for rare diseases.

Rare diseases that are more known to 'the general public' are for example cystic fibrosis, with 1,300 patients in the Netherlands, and the blood disease haemophilia, with 1,600 patients in the Netherlands. All malignant diseases that affect children are also rare. About 400 children are affected each year. Furthermore, clusters of very rare conditions that are less known, such as muscular or metabolic diseases, exist. This concerns groups of very rare diseases. Each year an estimated 900 children are born with one of the 600 metabolic diseases. 125 pathologies are represented with Vereniging Spierziekten Nederland (VSN).

An estimate of the VSN is that there are 13,000 people with a muscular disease in the Netherlands. These are not all members.

What is an orphan drug?

Pharmaceuticals for rare diseases are called orphan drugs (OD) or Orphan Medicinal Products (OMP). In regulation (EC) no. 141/2000 regarding orphan drugs it is stated that a pharmaceutical can be appointed as an 'orphan drug' if it is used for the diagnosis, prevention or treatment of a life threatening or chronically incapacitating condition, of which a maximum of 5 per 10,000 people of the Community suffer at the time of the request with the European authorities EMA.

In Europe several measures have been taken to promote the development of orphan drugs. Important characteristics of regulation (EC) 141/2000 regarding orphan drugs⁷⁹ are: Low costs for advice on creating

⁷⁵ Publicatieblad Europe's Unie. Recommendations of the Council, 8 June, 2009. (2009/C 151/02).

⁷⁶ Eurordis survey 2007.

⁷⁷ Eurordis survey 2005 & Guillem, P et al. Rare diseases in disabled children, an epidemiological survey, Archives of diseases in childhood, February 2008.

⁷⁸ Life with a rare chronic condition. Experiences of patients in healthcare and everyday life. NIVEL (2003) & Wallenius, E et al. Nordic Journal of Nursing Research and Clinical Studies (2009) & Rare Disease Impact Report: Insights from patients and the medical community, Shire 2013.

⁷⁹ Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:018:0001:0005:EN:PDF>

research protocols and registration requests, central registration in the European Community, and ten years of market exclusivity.

A manufacturer can request the European status of orphan drug from the European assessment authority, EMA ('designated') in an early stage of the development of a product for a rare condition. The pharmaceutical product is then in its research phase and not available on the market. After more clinical trials are performed, the manufacturer offers the registration file. After a positive opinion from the EMA, the orphan drug is granted marketing authorisation, which is valid in all EU member states. The EMA can grant the registration with an obligation to strictly monitor the pharmaceutical product in practise (registration under exceptional circumstances, because few data are known, and considering the limited patient population. This means that the manufacturer needs to show additional results to the EMA of a running or new clinical trial on a regular basis.

Several new treatments have entered the market due to these measures, some for very rare diseases with very small groups of patients.

Individual member states should also adopt measures for national promotion. Reimbursement and payment of orphan drugs is a national matter. The prices of orphan drugs however are established in a European context.

F Abbreviations

The most commonly used abbreviations and names of organisations from the NPZZ with any references to a website address can be found below:

Add-on	An Add-on is connected to DBC-zorgproduct, and is meant for special kinds of healthcare, such as expensive pharmaceuticals (>€10,000 per patient per year) (situation in August 2013)
AJN	Artsen Jeugdgezondheidszorg Nederland. Scientific organisation of physicians working in JGZ (http://ajn.artsenet.nl/Home.htm)
Biofarmind	Vereniging Biotechnologische Farmaceutische Industrie (www.biofarmind.nl)
CAVOMP	Project about the added value of orphan drugs (measured in everyday life) (CAVOMP=Clinical Added Value of Orphan Medicinal Products). See the recommendations of EUCERD (www.eucerd.eu/?post_type=document&p=1446)
CBG	College ter Beoordeling van Geneesmiddelen (www.cbq-meb.nl)
CCMO	Centrale commissie mensgebonden onderzoek (www.ccmo-online.nl)
CG Raad	Chronisch Zieken en Gehandicaptenraad (www.cg-raad.nl)
CHMP	Committee of the European assessment authority that decides upon access to the market (see EMA website)
CINEAS	Codification system of the Klinische Genetica Nederland
COMP	Committee of the European assessment authority for appointing an orphan drug (see EMA website)
CVZ	College voor Zorgverzekeringen (management of healthcare packages) (www.cvz.nl)
DBC and DBC-Onderhoud	Diagnose Behandeling Combinatie The organisation of DBC-Onderhoud offers information in the area of DBC-zorgproducten (healthcare products) and other kinds of care performance (www.dbconderhoud.nl)
DG Research and Innovation	Directoraat-generaal Onderzoek en Innovatie of the Europe's committee develops, amongst other things, research programmes in the area of research and innovation (also business) http://ec.europa.eu/research/index.cfm

DG SANCO	Directoraat-generaal Gezondheid en Consumenten of the European Committee develops, amongst other things, research programmes in the area of public health. http://ec.europa.eu/dgs/health_consumer/index_en.htm
EMA	European pharmaceuticals assessment authority, situated in London. Reports of meetings of the COMP and CHMP and patient information about registered orphan drugs can be found on the website of EMA (www.ema.europa.eu)
E-Rare	European collaboration in the area of research regarding rare diseases (www.e-rare.eu)
Erfocentrum	www.erfelijkheid.nl
EUCERD	European Committee for Experts on Rare diseases. (www.eucerd.eu)
EUROCAT	Registration of congenital conditions in the North of the Netherlands (www.rug.nl/research/genetics/eurocat/) and Europe (www.eurocat-network.eu)
EUROPLAN	European project regarding National Plans for rare diseases (www.europlanproject.eu)
EURORDIS	European umbrella organisation for rare disease patient organisations (www.eurordis.org)
FBG	Dutch Forum for Biotechnology and Genetics (www.forumbg.nl).
Fonds PGO	Subsidies for patient organisations (http://www.fondspgo.nl/)
ICD code	International Classification of Disease (WHO)
ICF code	International Classification of Functioning (WHO)
LHV	Landelijke Huisartsen Vereniging (http://lhv.artsennet.nl/home.htm)
LPGGz	Landelijk Platform GGZ (http://www.platformggz.nl/lpggz/)
NCJ	Nederlands Centrum Jeugdgezondheid (www.ncj.nl/)
NEFARMA	Vereniging innovatieve geneesmiddelen Nederland (www.nefarma.nl)
NFU	Nederlandse Federatie Universitair Medische Centra (UMC's) (www.nfu.nl)

NHG	Nederlands Huisarts Genootschap (www.nhg.org)
NPCF	Nederlandse Patiënten en Consumenten Federatie (www.npcf.nl)
NPZZ	Nationaal Plan Zeldzame Ziekten (www.npzz.nl)
NZa	Nederlandse Zorgautoriteit (www.nza.nl)
NVZ	Nederlandse Vereniging van Ziekenhuizen (www.nvz-ziekenhuizen.nl)
Orphacode	Code for rare diseases in Orphanet (www.orpha.net)
Orphanet (EU and NL)	www.orpha.net or www.orphanet.nl
PGO support	Network organisations for patients and disability organisations (http://www.pgosupport.nl/)
Platform VG	Platform for people with a mental disability, their families and representatives (www.platformvg.nl)
RIVM	Rijksinstituut voor Volksgezondheid en Milieu (www.rivm.nl)
SGF	Samenwerkende Gezondheidsfondsen (http://www.gezondheidsfondsen.nl/home.aspx)
STZ	Stichting Topklinische Ziekenhuizen (www.stz-ziekenhuizen.nl)
UMC	Universitair Medisch Centrum. All eight UMCs have joined forces under the umbrella organisation NFU (www.nfu.nl)
VKGN	Vereniging Klinische Genetica Nederland (www.vkgn.org)
VKS	Volwassenen en kinderen met Stofwisselingsziekten (www.stofwisselingsziekten.nl)
VSN	Vereniging Spierziekten Nederland (www.spierziekten.nl)
VWS	Ministerie van Volksgezondheid, Welzijn en Sport http://www.rijksoverheid.nl/ministeries/vws
VSOP	Vereniging Samenwerkende Ouder en Patiëntenorganisaties for rare and genetic conditions (www.vsop.nl)
Wbmv	Wet op bijzondere medische verrichtingen (Dutch Special medical procedures Act)
WHO	The World Health Organisation www.euro.who.int
ZonMw	ZonMw funds healthcare research and promotes the use of

	developed knowledge to improve healthcare and health (www.zonmw.nl) http://www.zonmw.nl/nl/themas/thema-detail/zeldzame-ziekten-enweesgeneesmiddelen/ thema-detail/
ZN	Umbrella organisation of Healthcare insurers (Zorgverzekeraars Nederland) (www.zn.nl)
ZZF	Zeldzame Ziekten Fonds (www.zzf.nl)