Deutscher Ethikrat

The Challenges of Providing Care for Rare Diseases

AD HOC RECOMMENDATION

Berlin, 23 November 2018

In Germany alone, as many as four million people live with one of the 7,000 to 8,000 rare diseases that have been identified.[1] Most of these diseases are hereditary, and they can often be life-threatening or cause chronic impairment and disability. In the European Union, a disease is considered rare if no more than five out of 10,000 people are affected.[2] Precisely because of their rarity these diseases often do not receive enough attention. Therefore, special efforts are needed to ensure that fewer people fall ill, fewer infants and children die from these diseases, patients' quality of life is improved and their physical and mental capacities are maintained as much as possible. The considerations presented in this Recommendation have a wider relevance not least because the overall number of people with rare diseases constitutes a considerable proportion of the population.

Living with medical, social and economic vulnerability

People with rare diseases face a variety of problems. They often receive the wrong diagnosis or receive the right one only after significant delays. Furthermore, they are adversely affected by a lack of information about their condition and a lack of practical support in everyday life. Specialist institutions with appropriate qualifications are often difficult to reach. Patients carry a psychological burden due to social exclusion, a lack of understanding in their environment and few opportunities to contact other fellow sufferers, who often live far away. This can lead to feelings of isolation. Since the healthcare system is geared to the most widespread diseases, the provision of effective medical care for those with rare diseases and the promotion of research to improve diagnosis and treatment of these conditions are impeded by structural, medical and economic obstacles.

Patients often go through years of ordeals before receiving the right diagnosis, and all too often getting the correct diagnosis depends on serendipitously finding the right doctor. Once a rare disease has finally been recognized the patient usually faces poor prospects as the vast majority of these diseases have few effective therapies. Moreover, there tend to be few scientific studies as well. Information about rare diseases is usually difficult to obtain and qualified professionals are often in short supply. Frequently, there is also a lack of multi-professional care – which most patients require – to help people cope with everyday life and psychological stress.

Through modern medical research and intensive work by medical experts diagnostic tools have improved significantly, particularly in the area of molecular biology. Also, for some rare diseases symptomatic therapies and even causal treatments have been found, resulting in considerable improvements in the quality of life and the life expectancy of patients. The treatment for cystic fibrosis, for example, is an impressive case in point.[3] However, patients with rare diseases are rarely cured; rather, they usually require lifelong, intensive therapeutic care due to the chronicity of their condition. This poses special challenges for the healthcare system in light of the structural and economic limitations it faces, particularly with regard to the provision of adequate, appropriate, economical and necessary care mandated by Section 12 of SGB V (Book V of the Social Code). These challenges include providing medical care that meets the generally recognised standard of medical knowledge for all people with rare diseases, while taking the ethical aspects described below into account.

Ethical aspects

People with rare diseases form one of the most vulnerable groups in society. On the one hand, their vulnerability arises from the severity and chronicity of their disease and the heavy strain put on their family, which can be aggravated when it comes to family planning or if other family members are affected by the same disease. On the other hand, isolation and poor access to supportive resources – a result of the structural orientation of the healthcare system towards common diseases, in particular the most widespread diseases – also contribute to their vulnerability.[4] The marginalised position of people with rare diseases, like that of other vulnerable groups, puts them at risk of having their suffering not adequately mitigated and their interests not adequately represented. In addition to the general ethical principles of respect for self-determination, beneficence and non-maleficence, the principle of justice is also very important with respect to this group (this includes individual capabilities and distributive justice).[5]

There is a general consensus that a society based on solidarity must give all its members a fair chance of obtaining adequate treatment in the event of illness, regardless of whether their disease is common or rare. In Germany, patients with statutory health insurance have the right to receive suitable and effective treatment and to have the costs covered, as laid down in Section 12 of SGB V. However, from the perspective of justice it is also necessary to consider the economic viability of potential treatments. Consequently, when considering how to prioritise different healthcare services in order to distribute the scarce resources of the healthcare system fairly, it is often argued quite reasonably that interventions with solid supporting evidence and a high degree of individual benefit (measured, among other things, in so-called quality-adjusted life years) should be preferred over interventions with poor evidence and a low degree of individual benefit. This is especially relevant when the treatment in question is expensive, which is often the case for rare diseases. With a view to establishing fair access to adequate healthcare it should also be

1 Cf. Eidt et al. 2009a, 1.
2 Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products (OJ 2000, L 18, p. 1).
3 Cf. Nährlich/Burkhart/Wiese 2017.
4 Cf. International Bioethics Committee 2011.
5 Cf. Dabrock 2012.

kept in mind that the comparatively small number of cases of rare diseases makes it much more difficult to achieve the same degree of evidential support for treatments that can be expected when therapies for common diseases are approved or reimbursed.[6]

Furthermore, recently it has also been pointed out that the treatment of rare diseases could be considered a pilot project for the future design of the healthcare system. Given the growing importance of so-called precision medicine – i.e. medical care that is increasingly personalised, predictive, preventive, participatory, biomarker-based and big data-driven[7] – even the more widespread diseases will increasingly be differentiated into subgroups as well. In general, it is argued that the healthcare system must be overhauled in order to be better prepared to address the impact of this development in a fair, efficient and effective manner. In particular, medical care for people with rare diseases should be reorganised in the present time to put in place the necessary structures to respond to this general trend in medicine. This is another important ethical argument in favour of paying close attention to the distribution of resources and the specific vulnerability of people with rare diseases.

This requires special protective measures to prevent people with rare diseases from receiving poor or inadequate care and to make sure they are empowered and involved so that their needs are reflected in the planning of research and care in a fair and adequate way.[8]

Protection against poor and inadequate care

The first step to prevent people with rare diseases receiving poor and inadequate care consists in establishing appropriate training and further education within the health professions. To accomplish this end, it seems sensible to make the issue more prominent during medical school and in the training programmes of other healthcare professions. Currently, these training courses focus on common diseases for obvious reasons of ensuring comprehensive care. Knowledge and skills for treating rare diseases are often neglected, however. Insofar as medical school, for example, is designed to address the requirements of general practice and primary care utilised by large parts of the population, special efforts and incentives are necessary to at least make students aware of the specific challenge of treating rare diseases. Even after students have completed their training, specific continuing education and training programmes should be offered to ensure that the necessary knowledge and skills in the field of rare diseases will be available to meet demand.

Moreover, the ethical principles of beneficence and non-maleficence imply the need for high-quality care. Often, patients with rare diseases can only obtain such care in specialist centres or outpatient clinics established specifically for this purpose. In order to provide the specific care patients with rare diseases need in an adequate and at the same time economical way, the additional commitment that institutions (mostly universities) have to make to meet these objectives should be supported by sufficient funding. In practice, however, the establishment of such specialist outpatient clinics or centres tends to be hindered by red tape. Prioritisation might have to be regarded as unavoidable, but it must not affect the level of staff and equipment available for diagnosis, therapy and prevention that is required to cover basic care.[9] As a rule, basic care is administered in a centralised way. Additional services that facilitate decentralised care for patients with rare diseases – who are often chronically ill and live scattered across the country – may also be indicated, for instance online counselling or online training. However, these also require appropriate financial support.

Empowerment

Disadvantages caused by the marginalisation of vulnerable groups must be remedied by targeted measures of empowerment and participation. The aim of empowerment is to get people with rare diseases involved more closely in decisions affecting them in order to better reflect their wishes and interests.[10] Allowing patient representatives and support organisations to participate can improve the quality of care because people affected by rare diseases are often connected with fellow sufferers elsewhere in Europe or even worldwide; frequently they have acquired specialist knowledge about their disease which in some cases can even exceed their doctor's knowledge. Centrally organised, clear and easily accessible information is particularly important for people who are searching for the right diagnosis, available medication or the opportunity to participate in a study.[11]

Moreover, people with rare diseases should also participate when structural decisions regarding the healthcare system are made. If patient groups are included, research can be reorganised more quickly to respond to a lack of treatment options in a given area and cooperation between specialist outpatient clinics and primary care can be improved. If prioritisation of services is considered indispensable, then these decisions should not be made without considering the views of the patients who will be affected by them.

In order to be able to fulfil their participatory functions adequately, patient organisations should be free from conflicts of interest as much as possible and operate independently and

6 Cf. Biller-Andorno/Lie/ter Meulen 2002.
7 See Hood et al. 2004.
8 Cf. ten Have 2016.
9 On the problem of prioritisation see: Zentrale Ethikkommission bei der Bundesärztekammer 2007.
10 Cf. Schicktanz 2015.
11 Examples include the central information portal for rare diseases ZISPE (https://www.portal-se.de), the care compendium for people with rare diseases (https://www.se-atlas.de) and the international portal for rare diseases and orphan drugs Orphanet (http://www.orpha.net) [2018-11-05]. International databases for physicians include http://www.findzebra.com, http://disease-discovery.udl.cat and http://compbio.charite.de/phenomizer [2018-11-05].

transparently.[12] Conflicts of interest can arise, for example, when patient organisations are instrumentalised by pharmaceutical companies or when different groups of individuals organised in a self-help group – such as patients and their relatives – have different interests. Such conflicts of interest must be prevented by providing public funding on the one hand and by establishing democratic organisational structures on the other. In particular, public funding can help to lessen one-sided dependencies on commercial companies.

National Action League for Rare Diseases

Over the last few years, some efforts have already been made to improve the situation of people with rare diseases. In 2010, the "National Action League for People with Rare Diseases" (NAMSE) was established in response to a recommendation issued by the European Union. NAMSE is a forum of 28 partner organisations, including representatives of key stakeholders in the healthcare system and of patient organisations. These organisations collaborate to identify fields of action, determine priorities and generate recommendations. The League has developed a National Action Plan for Rare Diseases which was published in 2013.[13] It puts forward a total of 52 suggestions focusing on the four areas considered essential: "specialist centres for rare diseases", "faster diagnosis", "accessible information" and "intensification of research". However, according to a recent NAMSE report, in 2017 only eight of the 52 measures had been fully realised, 21 were in the process of being implemented and ten were in the planning stages.[14] NAMSE's work has a particularly strong impact on patient participation and hence on the quality and transparency of decisions.

Medication for rare diseases: Hoping for therapy

When trying to compensate for the disadvantages caused by the low incidence of rare diseases, pooling existing resources and facilitating networking is crucial, especially in the field of scientific research. In this area too, special efforts are needed, for instance in the form of promoting compensatory measures, to allow people with rare diseases to benefit equally from scientific research. Such measures include for example recurring funding programmes for research into rare diseases with the aim of developing evidence-based diagnostics, therapy and prevention.

In the year 2000, an EU regulation regarding so-called "orphan medicinal products", also known as orphan drugs, came into effect. This term designates drugs that only benefit a comparatively small number of patients and therefore would not be developed and manufactured by pharmaceutical companies without economic incentives.[15] When a drug gets classified as an orphan drug, pharmaceutical manufacturers receive certain advantages in the form of fee exemptions, accelerated processing of drug approval applications and a ten-year right to market exclusivity. This is conditional on the disease being life-threatening or chronically debilitating. In Germany, the additional medical benefit of an orphan drug is considered proven if it has been approved by the European Medicines Agency, making the drug eligible for reimbursement right away. The determination of additional benefit undertaken by the Federal Joint Committee merely serves as a basis for negotiating price reductions between health insurers and manufacturers. Only if the gross annual turnover of the drug exceeds the threshold of 50 million euros is proof of additional benefit in accordance with Section 35a (1) of SGB V required for reimbursement.

This EU regulation has resulted in approximately 140 approved orphan drugs becoming available to patients since 2000.[16] Often these orphan drugs represent the first therapeutic option patients have ever been offered. The medications are designed to help patients live longer or at least have a better quality of life despite all the disadvantages of their disease. Successful examples include drugs for the muscle disorder Pompe disease, for chronic myeloid leukaemia[17] (a type of blood cancer), and for pulmonary hypertension.

In 2016, sales of orphan drugs accounted for approximately 3.7 percent of total drug expenditure in the outpatient sector in Germany.[18] In 2017, the annual cost of drug therapy increased to as much as 1.2 million euros per patient for some orphan drugs.[19] Many orphan drugs lose their special status and thus their market exclusivity after some time; however, they remain costly if cheaper generic drugs are not brought to market. On the one hand, the number of orphan drugs is still small compared to the large number of diseases in need of treatment: In 2017, there were about 7,000 to 8,000 rare diseases but only approximately 1,700 orphan drug research projects and 140 "active" orphan drugs.[20] On the other hand, there are concerns about potentially creating incentives to claim the advantages of the orphan drug approval process for diseases that are not in fact rare.[21] Practices such as artificially reducing the number of cases in order to achieve rare disease status, for example, by splitting indications to create subtypes of a disease, must be opposed effectively.[22]

Orphan drugs now represent one in four medications with a new active substance introduced into the German market.[23] Therefore, it seems increasingly important to establish better

12 Cf. Beier et al. 2016.
13 Nationales Aktionsbündnis für Menschen mit Seltenen Erkrankungen 2013.
14 Cf. Nationales Aktionsbündnis für Menschen mit Seltenen Erkrankungen 2017.
15 See footnote 2.
16 Cf. European Medicines Agency 2018.
17 After the introduction of a new class of drugs, the ten-year survival rate of patients with chronic myeloid leukaemia rose from 10 to 90 percent. Cf. Woessner/Lim/Deininger 2011.
18 Cf. Verband Forschender Arzneimittelhersteller 2017, 13.
19 Cf. Glaeske/Ludwig 2017, 7.
20 Cf. Verband Forschender Arzneimittelhersteller 2017, 5, 16.
21 Cf. Wörmann 2015.
22 See for example Daniel et al. 2016.
23 Cf. for example Glaeske/Ludwig 2017, 41.

safeguards against inadequate testing of active substances and to enforce clear conditions for their approval. This helps ensure the right of patients with rare diseases to receive drugs of the same quality, safety and efficacy as other patients.[24] In addition, within the framework of physicians' freedom to choose therapies even patients whose disease is not rare can be prescribed inadequately tested active substances, which is concerning.[25]

In some EU countries, patients do not have access to high-priced orphan drugs because the local healthcare system does not cover the costs. The European Organisation for Rare Diseases (EURORDIS) has criticised pharmaceutical companies for the opaque pricing of orphan drugs. The organisation demands that prices of these drugs should be reduced to between one-third and one-fifth of their current prices by 2025. To accomplish this, EURORDIS suggests that the different national healthcare systems coordinate their approach to price negotiations with manufacturers with one another and tie drug prices to evidence-based benefits for patients.[26]

Therefore, the criteria for determining the benefits for patients need to be critically evaluated. Measurements using diagnostic devices might show an improvement in a particular value that reaches statistical significance, if only just – for example, an increase in muscle strength of a few percent in the case of a hereditary muscle disorder. While this may satisfy the formal requirements for counting as an actual therapeutic effect, it hardly creates a noticeable improvement in health or quality of life for the patient in question. From an ethical and economical perspective it is therefore important to develop appropriate parameters to determine efficacy; these should focus more strongly on the overall benefit for the patient. The participation of patient organisations is crucial here as well. Another reason for this is that given the limited resources of the healthcare system, the allocation of resources should be based on the overall benefit for individual patients. Funding extremely costly therapies of questionable benefit ultimately absorbs resources that could deliver much better outcomes to the same group of patients elsewhere (e.g. funding local care in specialised outpatient departments).

In addition, patient registries are an essential tool to support orphan drug research. They facilitate the pooling and more efficient use of locally available knowledge and allow specialists and patients to interact via networking. However, in order to guarantee the quality of the data it is necessary to reduce conflicts of interest on the part of the operators. Such conflicts of interest can occur, for example, if a registry is run entirely by a pharmaceutical company or a single physician. Thus, specific systems of incentives are needed, such as independent financing and external evaluation.

24 Cf. ibid., 10.
25 Cf. Gottwald/Huster 2013.
26 Cf. Eurordis 2018, 5.

Provision of care: centres and networks

The provision of care in specialised centres is of major importance for patients with rare diseases. Due to the small number of patients per disease, high-quality care can only be delivered by highly qualified specialists working in specialised facilities. The minimum number of cases required to ensure appropriate quality of care for rare diseases can only be achieved within specialist outpatient clinics or centres. Moreover, clinical research should be coordinated across national borders.

The complex process of multi-professional diagnosis and treatment of rare diseases is very time-consuming because it involves providing guidance and engaging in specialised training, cooperation and exchange with other experts, both nationally and internationally. Moreover, it requires quality management (e.g. through patient registries) and special efforts to conduct research (e.g. to recruit enough patients for studies). In addition, patients should be able to access care close to their home regardless of where they live. This must be ensured with the cooperation of general practitioners and paediatricians and by means of modern information and communication technologies (e.g. in the form of telemedicine).

The infrastructure needed in centres for rare diseases and the work done there are expensive. Moreover, the operation of such centres requires increased workloads with regards to both medical and non-medical services such as psychosocial care or nutritional counselling.[27] Although the Federal Ministry of Health has affirmed that additional funding for centres for rare diseases can theoretically be granted,[28] there are indications that the financing difficulties have not yet been resolved.[29]

There are two further remuneration instruments for specialist outpatient clinics: The first, specialist outpatient medical care in accordance with Section 116b SGB V, allows physicians to bill for outpatient services. This is intended to help break down the separation between the outpatient and inpatient sectors. However, this measure involves an extremely complex application procedure which the Federal Joint Committee (GBA) has only defined for a handful of rare diseases so far:[30] Marfan syndrome, pulmonary hypertension, tuberculosis[31] and cystic fibrosis. The second additional financing option consists in flat payments made to university outpatient departments (in accordance with

27 Cf. Eidt et al. 2009, 36.
28 As stated by Federal Health Minister Hermann Gröhe on the occasion of the 10th European Rare Diseases Day on 28 February 2017, cf. also the corresponding press release: https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/4_Pressemitteilungen/2017/2017_1/170224_14_PM_Tag_der_Seltenen_Erkrankungen.pdf [2018-11-05].
29 Cf. for example https://www.rechtsdepesche.de/dkg-empoert-ueber-kuendigung-der-zentrenfinanzierung/ [2018-11-05] or https://www.gkv-spitzenverband.de/gkv_spitzenverband/presse/pressemitteilungen_und_statements/pressemitteilung_599680.jsp [2018-11-05].
30 See Jenschke 2017.
31 Although tuberculosis is one of the most common lethal infectious diseases worldwide, it is considered a rare disease in Germany.

Section 117 and 120 no. 2 and no. 3 SGB V). However, this is only available to universities and usually does not cover the cost of the treatments provided.

Since the network of institutions participating in the provision of healthcare is extensive, it is often difficult for patient organisations to identify the individual responsible for a given issue and hold them accountable for any problems in the delivery of care. Many patients find it incomprehensible that it continues to be impossible to staff outpatient clinics with the necessary teams of therapists because of the cost, while on the other hand expensive drugs that only have a minor effect are eligible for reimbursement. Taking cystic fibrosis as an example, a team of experts for this disease costs only about one percent compared to the annual cost of medication which can run into six figures and is incurred throughout life.[32]

Moreover, networking between different centres in Europe can also improve care for rare diseases. Projects such as the European Reference Networks endeavour to standardise diagnostic procedures, share expertise and monitor the quality of treatment.[33] However, such activities are usually dependent on an appropriate form of remuneration as well.

Recommendations

Provision of care

Centres for rare diseases should be established nationwide. They should be sufficiently funded in order to offer chronically ill patients the opportunity to receive appropriate specialist care in the long term. Further, these centres should facilitate multi-professional care and provide guidance for patients navigating the healthcare system. Certification of these centres should be mandatory, and they should establish or participate in registries and conduct research on rare diseases and on the treatment and care of patients.

For quality assurance purposes, the work done at the centres should be evaluated on a regular basis. Also, centres should engage in a structured exchange of knowledge and experience.

Self-help friendly healthcare

Given the unique problems people with rare diseases face, the healthcare system should be organised in a way that promotes self-help: The experiences gained in self-help groups and patient organisations should be utilised in medical counselling – including genetic counselling – to improve diagnosis, treatment and prevention. Close cooperation between patient organisations and healthcare providers should be encouraged to better address the needs and interests of patients.

Patient organisations wishing to contribute to such forms of participation should meet the requirements of transparency and independence formulated by the Bundesarbeitsgemeinschaft Selbsthilfe (Federal Association of Self-Help Organisations) and the "Forum chronisch kranker und behinderter Menschen" (Forum for Chronically Ill and Handicapped People) of the Paritätischer Gesamtverband (Federation of Welfare Associations), in particular independence from commercial enterprises.[34]

Patient registries

In the case of rare diseases especially, patient registries are invaluable when it comes to collecting evidence after the approval of a new drug. The creation of patient registries should therefore be encouraged. However, the operators of patient registries must be selected carefully. In order to avoid conflicts of interest and to ensure the quality of the data, registries should be subject to external quality control, and they should never be managed by a single physician or a single pharmaceutical company. Adequate data protection must be in place, and data should be made available to third parties for scientific research.

Research

Research to improve diagnosis, treatment and prevention of rare diseases should be promoted.

The participation of patients in the development of publicly funded research projects, and in decisions about their prioritisation if necessary, should also be promoted.

Information and training

Medical students, physicians completing additional training and members of other healthcare professions should learn about the specific challenges in the diagnosis, therapy and prevention of rare diseases. Accessible training programmes that provide continuing education and training should be established. These should teach the current state of knowledge to those providing the various levels of care (general practitioners or specialist institutions).

Moreover, patients with rare diseases should have access to specific and age-appropriate training programmes in the context of visits to outpatient clinics, rehabilitation centres or in the form of online services. These measures should be considered part of the overall treatment plan; hence the cost should be covered by the agencies providing healthcare funding.

32 Cf. Eidt et al. 2009b.

33 Cf. https://www.eurordis.org/european-reference-networks [2018-11-05].

34 See Bundesarbeitsgemeinschaft Selbsthilfe von Menschen mit Behinderung, chronischer Erkrankung und ihren Angehörigen; Deutscher Paritätischer Wohlfahrtsverband 2016.

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