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**What type of evidence is
currently being
considered in the
development of clinical
practice guidelines for
rare diseases?¹**

¹ Translation of the executive summary of the rapid report V10-01 “Welche Evidenz wird für die Erstellung von Leitlinien für seltene Erkrankungen derzeit herangezogen?” (Version 1.0; Status: 28.03.2011). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Background

In the European Union (EU) diseases are classified as rare if they occur with a prevalence of not more than 5 per 10 000 inhabitants. In many cases these rare diseases are life-threatening or have a severe chronic course. An estimated 5000 to 8000 different rare diseases exist; in Germany up to 4 million people suffer from a rare disease (overall EU: approx. 27 to 36 million).

In recent years, numerous national, European, and international initiatives have been started in order to raise public awareness and improve the health care of affected patients. In its regulation (EC) No. 141/2000 of 16 December 1999, the European Parliament and the Council of the European Union determined that “patients with such conditions deserve the same quality, safety and efficacy in medicinal products as other patients; orphan medicinal products should therefore be submitted to the normal evaluation process.” The research report of the German Federal Ministry of Health (BMG), called “Measures to improve the health situation of people with rare diseases in Germany” (2009), assumes that, by means of clinical practice guidelines (CPGs) and patient pathways, treatment quality in the area of rare diseases can be improved. At the same time the report asks whether the development of CPGs on rare diseases is possible and meaningful, as the evidence base is often weak.

Research question

The underlying question of the present rapid report is how CPG developers and health technology assessment (HTA) agencies handle the evidence on rare diseases for the development of CPGs or HTA reports.

The aim of the project was therefore the systematic search for existing approaches to handling evidence on rare diseases for the development of CPGs, as well as the summarizing presentation of the methods identified. This was performed on the basis of a) manuals on CPG development, b) methods papers by relevant HTA agencies, and c) CPGs on selected examples of rare diseases.

In addition, it was to be examined whether different requirements for the evidence base are set for CPGs on rare diseases compared to other CPGs.

Methods

A systematic search for CPG manuals was conducted in the CPG databases of the (German) Association of the Scientific Medical Societies (AWMF²), the Guidelines International Network (G-I-N), and the National Guideline Clearinghouse (NGC), as well as via a search of websites of multidisciplinary and specialist CPG providers. In addition, a systematic search

² Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften

for HTA manuals was conducted via the websites³ of member organizations or partners of the International Network of Agencies for Health Technology Assessment (INAHTA), Health Technology Assessment International (HTAi), as well as the European Network for Health Technology Assessment (EUnetHTA).

Furthermore, CPGs on 21 selected rare diseases were searched for in the CPG databases of AWMF, G-I-N and NGC. Finally, a supplementary, orientating and non-disease-specific search for CPGs on rare diseases was performed on the website www.orpha.net.

The searches took place between October 2010 and January 2011.

The extracted information on the handling of evidence in the development of CPGs and HTA reports on rare diseases was summarized descriptively and analysed. The following areas for the analysis were prespecified:

- Topic finding and prioritization of CPG or HTA topics
- Information on the methods of the literature search
- Information on the specification of the relevant study types
- Information on methods and criteria of the evidence assessment
- Information on the methods of evidence synthesis
- Information on the wording of recommendations

Results

A total of 125 documents were included in the present rapid report: 62 CPG manuals, 24 HTA manuals, and 39 CPGs on rare diseases.

Very little information on the underlying research question of the rapid report could be extracted from the CPG and HTA manuals. In particular, only sporadic references to or instructions on the handling of evidence on rare diseases could be found. These were identified in 7 CPG manuals and 5 HTA manuals. In addition, in 9 CPG manuals and 3 HTA manuals, topic-related or indirect methodological references were identified, e.g. information on the consideration of the prevalence of a disease or general information on the handling of small populations. A manual published by the French Haute Autorité de Santé (HAS) specifically addressed the development of CPGs on rare diseases.

No information on the present research question could be obtained from the CPGs. Only few CPGs provided any information on methods. These were the CPGs published by HAS, which formed the majority of CPGs identified. These documents were developed within the

³ <http://www.inahta.org> and <http://www.eunetha.net>

framework of the French national programme on rare diseases and usually referred to the corresponding HAS manual on the development of CPGs on rare diseases.

Topic finding and prioritization of CPG or HTA topics

In 11 manuals, information on topic finding and prioritization of CPG or HTA topics were identified. In most manuals the prevalence of disease was a criterion for topic finding and/or the prioritization of topics for the development of CPGs or HTAs, mainly in the sense of the preferential consideration of diseases with a high prevalence. In 2 manuals, the danger of discriminating against groups due to the prevalence/rarity of a disease was addressed, without however suggesting a specific approach.

Methods of the literature search

Two manuals included information on the literature search, which referred to the option of handsearching to identify small studies, as well as to the inclusion of grey literature to identify unpublished studies. Specific strategies for the search for evidence/information on rare diseases were not described.

Specification of the relevant study types

Five manuals provided information on the specification of relevant study types for the investigation of rare diseases. Case-control studies were described as a meaningful study type, in particular for research questions referring to the aetiology of rare diseases or for small populations; case reports and case series were also mentioned. One manual explicitly emphasized that a small affected population, such as is present in rare diseases, was not in principle a reason to deviate from the hierarchy of evidence, and that patients with rare diseases also have the right to reliable information on treatment options. In cases where parallel comparative studies are not possible, there is the option of adequate documentation of the course of disease and treatment.

Methods and criteria of the evidence assessment

Information on the quality of studies with small sample sizes or references to study design and analysis were identified in 8 manuals. For example, the reduced informative value of evidence from studies with small populations was addressed, caused, amongst other things, by the low precision of effect estimates, by decreased statistical power, by the difficulty in recording adverse events, and by the differences in the characteristics of the study population despite randomization. As an additional problem it was noted that, due to the necessity of adjustment calculations, larger patient numbers were usually required for non-randomized controlled trials (non-RCTs) than for RCTs. In addition, in one manual the assessment of (valid) surrogate endpoints, as well as the acceptance of p-values greater than 5%, were described as being potentially meaningful for the detection of statistical relevance.

Methods of evidence synthesis

Only little information could be identified on evidence synthesis methods that specifically referred to rare diseases or small populations. Two manuals recommended the meta-analytic summary of smaller studies in general. In addition, one manual described the greater weighting of larger and high-quality studies compared to smaller ones and those of weaker quality, without specifically referring to rare diseases.

Wording of recommendations

Seven manuals provided information on the wording of recommendations for rare diseases or small populations. However, no manual made concrete detailed specifications. In particular, no distinction was made regarding the wording of recommendations for common diseases. One manual mentioned aspects to be considered in the balancing of costs and benefits. Furthermore, 2 manuals emphasized the importance of a consensus process in the case of weak evidence from clinical studies. One manual noted that any potential weakness of the evidence base should be explicitly described.

Rare diseases are hardly addressed in CPG and HTA manuals. In particular the documents do not contain structured and detailed instructions on the handling of evidence on rare diseases within the framework of CPG development. The analysed sample of CPGs on rare diseases did not contain detailed methodological background information on this topic either. Due to the insufficient information base, further methodological questions could not be answered.

Conclusions

The handling of evidence on rare diseases has hardly been addressed in manuals on the development of CPGs or HTAs. There are only a few isolated references to methodological approaches from which, however, no consistent methodological specifications on the development of CPGs on rare diseases can be inferred. Neither can information be inferred from the documents that suggests a fundamentally different approach and evidence base for the development of CPGs on rare diseases.

Key words: rare diseases, systematic review, methods on guideline development

The full report (German version) is available under www.iqwig.de