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Methodology for production of best practice guidelines for rare diseases

Brief title: Methodology for guideline production

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ABSTRACT

Best practice guidelines for clinical management have increasingly become useful tools for patients and health care professionals in several disease areas. This is the case not least in the area of rare diseases, where scarcity of expertise is a well known and far too common cause of late or wrong diagnosis and care. However, in order for clinical guidelines to be useful and trustworthy, they must adhere to principles of how they are developed and updated, including a basis of best available evidence. Because of the potential great importance of well made best practice guidelines for rare diseases, we here describe work within the RARE-bestpractices EU project aim to address this topic by I) delineate the current state of existing best practice guidelines, as well as processes and tools for developing, updating, and adapting guidelines in the field of rare diseases, II) define and agree on methodological quality standards for best practice guidelines on rare diseases, III) develop pilot best practice guidelines for a specific rare condition, implementing the agreed methodological quality standards and IV) to develop a graphical representation of the sequence of activities in best practice guidelines, which are useful for helping in understanding key steps, for allowing a faster development of information systems supporting the enactment of the modeled process, and for monitoring the effectiveness, efficiency and equity of the implemented guidelines.

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INTRODUCTION

Best practice guidelines for clinical management have increasingly become useful tools for patients and health care professionals in several disease areas [1]. Major reasons for the importance of developing best practice guidelines are that they contribute I) to allowing physicians and other health care professionals to make recommendations based on best available evidence, II) to allowing patients to ensure that their management follow recommendations based on best available evidence, and III) to allow for a common basis of diagnosis and clinical management in clinical multicenter trials. These general advantages of best practice guidelines are even more important in the field of rare diseases. The scarcity of expertise in rare diseases is a well known and far too common cause of late or wrong diagnosis and care [2]. Further, it is even more important for rare diseases than for common diseases to rely on recruitment of patients from multiple centers in clinical trials, and it is hence crucial that patients in the study are diagnosed in the same way, and have a similar background care in order to optimize the chance to detect the true effect of a certain therapy. However, in order for clinical guidelines to be useful and trustworthy, they must adhere to principles of how they are developed and updated, including a basis of best available evidence [3-6]. It should be emphasized that best available evidence for rare diseases rarely is present in the form of meta-analyses of big randomized trials, but more frequently is based on smaller trials of varying quality, and sometimes on expert opinion when evidence is lacking [4]. Presently, we lack an overall understanding of principles currently employed in development of care guidelines for rare diseases, we lack an overview of which guidelines for rare diseases exist and a common platform to find and disseminate these, and we lack consensus on what methodological principles, common to all rare diseases, should be adhered to when developing new guidelines [4-5,7-8]. Because of the potential great importance of well made best practice guidelines for rare diseases, we therefore in this work aim to address this topic by I) delineating the current state of existing best practice guidelines, as well as processes and tools for developing, updating, and adapting guidelines in the field of rare diseases, II) defininge and agree on methodological quality standards for best practice guidelines on rare diseases, III) developing pilot best practice guidelines for one or two specific rare conditions, implementing the agreed methodological quality standards and IV) developing a graphical representation of the sequence of activities in best practice guidelines, which are useful for helping in understanding key steps, for allowing a faster development of information systems supporting the enactment of the modelled process, and for monitoring the effectiveness, efficiency and equity of the implemented guidelines. To accomplish this, several RARE-Bestpractices partners participate, covering a range of experience and expertise (*Table 1*). This paper presents the work process adopted in the methodology of developing rare best practices guidelines.

Table 1. Overview of rare-bestpractices tasks for methodology in best practices guideline production for rare diseases (Continues)

TASK:	TASK LEADER:	OTHER MAJOR TASK PARTICIPANTS:	TIMELINE (FINISHED BEFORE):
Present state of guidelines for rare diseases	**Graziella Filippini**, Italian Cochrane Center and Network (AREAS-CCI), Italy	• JAMARAU, UK • Healthcare Improvement Scotland (HIS), UK • Karolinska Institutet, Sweden	31 January 2014
Methodology for producing best practice guidelines	**Holger Schünemann**, University Medical Center Freiburg, Germany	• Istituto Superiore di Sanità, Italy • Karolinska Institutet, Sweden • HIS, UK • AREAS-CCI, Italy • Fundación Canaria de Investigación y Salud (FUNCIS), Spain • Istituto Superiore di Sanità, Italy • Bulgarian Association for Promotion of Education and Science (BAPES), Bulgaria • National Research Council, Italy • EURORDIS, France	31 August 2014
Production of pilot best practice guideline(s)	**Thomas Sejersen**, Karolinska Institutet, Sweden	• JAMARAU, UK • Consiglio Nazionale delle Ricerche, Italy, • AREAS-CCI, Italy • BAPES, Bulgaria • FUNCIS, Spain • Istituto Superiore di Sanità, Italy • EURORDIS, France	31 december 2015

[1] *Grading of Recommendations Assessment, Development and Evaluation*, http://www.gradeworkinggroup.org

Overview of rare-bestpractices tasks for methodology in best practices guideline production for rare diseases (Continued)			
Patient version of a pilot best practice guideline	**Juliette Senecat**, EURORDIS, France	• Karolinska Institutet, Sweden	30 June 2016
Graphical representation of the sequence of activities in best practice guidelines	**Saverio Sabina**, National Research Council, Italy	• Karolinska Institutet, Sweden • University Medical Center Freiburg, Germany • AREAS-CCI, Italy • BAPES, Bulgaria • FUNCIS, Spain • Istituto Superiore di Sanità, Italy • EURORDIS, France	31 December 2015

PRESENT STATE OF BEST PRACTICE GUIDELINES AND GUIDELINE METHODOLOGY IN THE FIELD OF RARE DISEASES

One of our first goals is to gain information on already existing or planned best practice guidelines and programmes dedicated to rare diseases in the EU at a member state level. To realize that goal a survey will be developed.

The two main objectives of the survey are:

1) To gain information on already existing or planned best practice guidelines and programs dedicated to rare diseases in EU member states.

2) To investigate methods in use for the development of best practice guidelines and reports on rare diseases by developers.

The information gathered will contribute to the RARE-Bestpractices Consortium discussion on the definition of quality standards for developing best practice guidelines on rare diseases, which is one of the main goals of the project

METHODS

Survey

Participants:

Participants in the survey are Health Ministries and local or national agencies which develop BP guidelines in all the European Countries. We will contact participants by email through contact details found on publicly accessible institutional websites and we will ask for the person in charge to answer on behalf of the institution.

Investigator:

The survey will be conducted by the Italian Cochrane Network (Italy), with the support of the RARE-Bestpractices partners JAMARAU (United Kingdom), the Karolinska Institutet (Sweden), Healthcare Improvement Scotland (United Kingdom) and Istituto Superiore di Sanità (Italy).

Survey implementation:

Survey and questionnaire structure:

A questionnaire will be sent online to all Health Ministers and local or national agencies which develop best practice guidelines (or the person(s) in charge to answer on behalf of the institution) of the EU countries. The survey will be conducted by the Italian Cochrane Network (Italy), with the support of the RARE-Bestpractices partners JAMARAU (United Kingdom), the Karolinska Institutet (Sweden), Healthcare Improvement Scotland (United Kingdom) and Istituto Superiore di Sanità (Italy). The survey consists of several sections. The first of these should be completed by all respondents. This section includes questions on the availability of any national or local programme or other types of initiative dedicated to rare disease best practice guidelines and the current needs and future scenarios in the field of best practice guidelines on rare diseases at a national level. The other parts of the survey will be completed only by the EU countries that have declared to have a national programme on rare disease guidelines, or are developing it. This part of the survey aims to obtain general information on national programme(s) on rare disease guideline; the methodologies used to develop them, and how they are disseminated and updated.

Criteria used to construct the questionnaire (domains): the questionnaire addressing the methodologies used to develop, disseminate and update best practice guidelines have been built on the basis of the international articles, handbooks and validated check lists (Appraisal of Guidelines for Research & Evaluation II – AGREE, Conference on Guideline Standardization – COGS, SIGN guideline developer's handbook, PNLG Manuale metodologico).

Structure of the questionnaire:

The first part of the survey contains both closed questions with single or multiple choices and open-ended questions about the existence or not of a national programme to develop guidelines on rare diseases already implemented, in development or planned. If such a programme does not exist, the reasons for that are asked.

The latter part of the survey contains both closed questions with single or multiple choices and open-ended questions asking general information on national programme(s) on rare disease guideline (already implemented or in development or planned) such as sponsoring, participants, duration, criteria used to choose the topic. In this part are included both closed questions with single

or multiple choices and open-ended questions on the methodologies used to develop, disseminate and update already implemented national programme(s) on rare disease guidelines. The following aspects are investigated:

Multidisciplinary panel of national programme on guidelines (if existing): compositions of panel, criteria to select participants, way of disclosure of conflict of interest;

Methodology for literature review: definition of clear clinical questions (according to the PICO(S) approach: **P**atients characteristics, **I**ntervention assessed, **C**ontrol intervention, **O**utcome measures, (**S**tudy design)), comprehensive bibliographic searches, ways for selecting studies for inclusion and data extraction, ways of methodological quality assessment of included studies, ways of performing data synthesis;

Grading system: existence and description of grading the level of evidence and/or the strength of the recommendations;

Cost-effectiveness: formal/informal analysis performed;

Consideration of harms, i.e adverse/negative effects of the intervention: formal/informal analysis performed;

Way of reaching consensus among panelists for formulating recommendations: description of the methods used;

Peer review: description of the peer review process: internal/external, experts and or patients involvement;

Dissemination and implementation process: description of the methods and instruments used;

Updating of the guideline: regular update planned, frequency of updates.

Organizational aspects: The contact participants will be found on publicly accessible institutional websites. Health Minister websites and European Public Health Association websites will be checked to find a contact of the person in charge of answering the questionnaire. The partners of the RARE-project will be asked to help in looking for the contacts from their respective European country. Contact data will be stored in an excel database.

The online system: The survey will be managed using a functional module of the RARE Bestpractices Guidelines database. This module has been purpose designed for consulting audiences online in regards to documents and questionnaires. The process works as follows: firstly the questionnaire is developed and loaded into the system by a registered author or a system administrator (in this instance this is being managed by the RARE-Bestpractices partner JAMARAU). It is then published, along with related documentation to the system's Discussion Board. The Discussion Board is one component of the system's public interface, designed to provide respondents with a point of access to consultation documents and questionnaires. Once the information and questionnaire are available on the Discussion Board, respondents are notified of their availability and provided with instructions and a password that will allow them to access the information and survey via the online consultation interface, where they will be able to read the information provided and submit their responses to the questionnaire. When a respondent submits their feedback the system will automatically email a copy, converted into a standard PDF document, to the author of the questionnaire (whose name is published on the Discussion Board). It will also copy the response to the email address provided by the respondent. A third copy is also forwarded to JAMARAU for record keeping purposes. And the information is also stored in system to enable the production of statistical data at the end of the consultation period. At the end of the consultation period, the system will remove the discussion item from the bulletin board and send the author a consolidated report of feedback, grouping responses to enable the information to be compared and analysed to inform future discussions. The consolidated report is not sent to all respondents, but it is copied to JAMARAU, again for record keeping purposes.

Data analysis: Data collected with the survey will be stored in a database. Answers of the open ended questions will be analyzed qualitatively, the results summarized and displayed in a narrative way. Answers of the closed ended questions will be analyzed quantitatively, the results summarized with descriptive statistics and displayed in a graphic format.

Timeline: Questionnaires will be completed by the end of November 2013; data analysis and summary of the results will be provided by the end of January 2014.

METHODOLOGY FOR PRODUCING BEST PRACTICE GUIDELINES

The best methodology for assessing the confidence in estimates of effect (also known as "quality of evidence") and for developing recommendations for rare diseases based on a multi-stage process will be agreed on in this task. This process will be informed by a review of current methods and procedures for development of guidelines and recommendations for rare diseases. The process will involve working through prepared examples based on the GRADE approach that the GRADE

Working Group has applied successfully in the development of its methodology [10-11]. For this purpose we will use five examples of systematic reviews and develop health care questions (i.e. questions meaningful to health) for rare diseases that lend themselves to guideline development [12]. We will prepare evidence summaries [13-14] and recommendations [15-16] as examples for at least three of these examples and develop another 3 health care questions using the full GRADE approach. These examples will be explored and challenges and advantages identified during a **one-day workshop in Rome with key participants of this proposal in addition to invited experts in the field**. During this workshop the examples of health care questions will be finalized and, following the workshop submitted to external advisors. These key questions and finalized examples will then be discussed with the GRADE Working Group that consists of over three hundred individuals with interest in guideline development. The GRADE working group will provide suggested solutions for the identified challenges.

This work is facilitated by Dr. Schünemann being co-chair of the GRADE Working Group. After obtaining feedback from the GRADE Working Group, the identified examples of questions meaningful to health will be finalized with the RARE-Best-

practices consortium. We will use the three identified health care questions and complete another exercise online where we will identify another two heatlh care questions of relevance. We will then prospectively prepare evidence profiles and mock evidence to recommendation frameworks for these five examples. All relevant stakeholders in this proposal will be invited for comment online for final feedback before a second workshop. **In a second workshop** with participants of this proposal we will finalize the methodology and involve all relevant stakeholders for final feedback before the second workshop. During the second workshop at the University Medical Center Freiburg we will prepare mock recommendations with all participants by assigning roles of relevant stakeholders to participants in the workshop and by simulating commonly used guideline recommendations development processes such as described in various publications by WHO and the GRADE Working Group. We will particularly invite consumer and patient representatives.

Timeline: The task to agree on recommendations of methodology to use for best practice guideline development for rare diseses will be finished by end of August 2014.

DEVELOPMENT OF PILOT BEST PRACTICE GUIDELINE(S) USING AGREED METHODOLOGY

A pilot will be conducted to test the methodological quality standards in the collaborative development of a guideline for one or two specific rare conditions, implementing the methodological quality standards and common tools/formats set up and discussed in the section above. Any challenges observed will be discussed among all project partners in order to ameliorate the guideline development protocol. This task is in turn strictly linked with the task on representation of processes embedded in the guidelines to be developed (see below).

Timeline: A pilot guidelines using agreed methodology will be produced before end of December 2015.

PATIENT VERSION OF A PILOT BEST PRACTICE GUIDELINE DEVELOPED ACCORDING TO AGREED METHODOLOGY

EURORDIS, the European Organisation for Rare Diseases, has developed knowledge about the needs of rare disease patients regarding the development of health care guidelines. The Eurordis Care surveys on Experiences and Expectations of Rare Disease Patients on Diagnosis and Care in Europe, whose results were published in the book The Voice of 12 000 Patients [2] intended to contribute to the establishment of standards and guidelines for the management of rare diseases, as well as to promote equal access to diagnosis and care for rare diseases throughout Europe. These surveys have highlighted that rare disease patients experience difficulties and delays for obtaining an accurate diagnosis, that rare diseases require complex care and that a low level of coordination and communication between health professionals prevails. Difficulties and inequalities of access to medical and/or social services result in differences in quality of life and in life expectancies across Europe. As a result, the implementation of "strategies of care" is a necessity for people living with rare diseases. Patient needs include speeding up correct diagnosis, reducing misdiagnosis and ensuring that the correct treatment is administered in the proper healthcare context. Patients also express the need of raising awareness of healthcare professionals regarding the complexity and the peculiarities of rare diseases.

The development of guidelines is of high relevance in this context. In health care, guidelines can be defined as "systematically developed statements which assist providers, patients and stakeholders to make informed decisions about appropriate health care for specific circumstances, including clinical interventions, public health activities, or government policies. Health care guidelines provide recommendations that describe in detail what the recommended action is and under what circumstances it should be performed".

I. To better address patients' needs, guidelines should be informed by the best available evidence, and should be broad, comprehensive, including paramedical treatments, use of medical devices, physiotherapy, nutrition, surgery and complementary treatments. Health care guidelines should promote a multidisciplinary approach for the care of rare disease patients as well as provide reliable information to guide and orientate treatment.

In the framework of the RARE-Bestpractices project, EURORDIS will act as a transversal partner in the different work packages, ensuring the involvement and the capacity-building of patient organizations across Europe. EURORDIS will build capacities of rare diseases patient organizations and of people living with rare diseases on the importance, use and benefits of health care guidelines and Health Technology Assessment.

In our work package, dedicated to the development and to the implementation of the methodology for health care guidelines for rare diseases, EURORDIS will ensure that this methodology places patients' needs foremost. As part of the project, EURORDIS will be in charge of a task which entails the development of a patient version of the developed pilot best practice guideline. EURORDIS will be supported in this task by the work package leader, Karolinska Institutet.

To best ensure the involvement of patients and their families in the development process of the patient version of the pilot guideline, EURORDIS will rely on its large network of patient organizations and patient representatives across Europe.

II. A dedicated patient working group will be created in order to ensure that patients' opinions are represented at the different stages of the development process. The patient version of the pilot best practice guideline will provide a summary of recommendations made for health professionals, in a language adapted for patients and their families.

Timeline: A patient version of the pilot guideline(s) will be available before the end of June 2016.

GRAPHICAL REPRESENTATION OF BEST PRACTICE GUIDELINES

Some criticism have been raised that can prevent an appropriate use of best practice guidelines. Guideline developers tend to focus on specific tasks rather than processes like care plans which are extended in time [2, 17].

Guideline users face challenges in understanding guidelines' messages and question their rigor, limiting their trustworthiness [17]. Bridging the gap between clinical research and everyday healthcare practice requires the identification of ways that help guideline users (clinicians, patients, and others) to understand and implement guidelines using the best available tools [18]. In this regard Rosenfeld *et al.* points out the importance of having one or more clinical algorithms that graphically display decision logic and sequences of activities, especially when dealing with complex or unclear situations [19]. Moreover, they outlined that including an algorithm in a guideline can rapidly convey the scope and organization of the guideline and can result in faster learning, higher retention, and better compliance by the practice community [19]. With regard to the compliance of clinical pathways to the best practice guidelines, it is worth considering Quality-of-care indicators that are expected to be increasingly integrated in the guideline development process with standardized criteria [18]. Such indicators, defined in relation to the identified critical points of the recommended processes, are useful for monitoring the effectiveness, efficiency and equity of the implemented guideline.

Nowadays Computer Science has provided several standards, methods and tools that combine the intelligibility of a graphical notation with the power of a formalism that allows an automatic translation of process modeling into information systems for supporting the enactment of such process and tracking and analysis of flows. This allows the use of process-oriented Health Information Systems able to formally models guidelines, workflows, or care pathways hence providing support for clinical decisions that extend over time.

RARE-Bestpractices is committed to propose a method for represent algorithms that graphically display decision logic and sequences of activities included in best practice guidelines and will test it in a specific case (pilot best practice guideline).

Timeline: A graphical representation of the sequence of activities in best practice guidelines, which are useful for monitoring the effectiveness, efficiency and equity of the implemented guideline, will be completed by the end of December 2015.

CONCLUSION

The project here, part of the RARE-Bestpractices, describes aims at improving development of, and access to, best practice guidelines for rare diseases, with the goal to collect available guidelines, describe methodology presently in use, and to reach consensus on a common methodological basis for best practice guideline development for rare diseases. The ultimate goal of this is to achieve improved diagnosis and care for patients with rare diseases.

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[1] Definition of the Glossary developed as a deliverable of the RARE-Bestpractices project, WP4, and based on WHO and IOM definitions.

[11] The European Organisation for Rare Diseases (EURORDIS) is the voice of 30 million people affected by rare diseases throughout Europe. EURORDIS represents over 500 rare disease patient organisations in more than 50 countries, covering at more than 4000 rare diseases.