ORIGINAL ARTICLE

Report of an international workshop to explore the utility of the AGREE II instrument for appraisal of rare disease guidelines

Michele Hilton Boon[1], Jenny Harbour[2], Karen Ritchie[2], Lorna Thompson[2], AGREE II workshop participants for the RARE-Bestpractices Consortium[3]

[1]MRC/CSO Social and Public Health Sciences Unit, University of Glasgow, Glasgow, UK
[2]Healthcare Improvement Scotland, Glasgow, UK
[3]For Consortium membership see end of article

Open access

Correspondence to
Lorna Thompson
Delta House
50 West Nile St
G1 2NP Glasgow, UK
Tel +44 (0)141 2256880
Email lorna.thompson2@nhs.net

Competing interests
The authors declare they have no competing interests.

Funding information
The research leading to these results has received funding from the European Union Seventh Programme (FP/2007-2013) under grant agreement n. 305690.

Received 8 April 2015
Accepted 27 July 2015

The Rare Diseases and Orphan Drugs Journal has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under Grant Agreement n. 305690 RARE-Bestpractices project www.rarebestpractices.eu.
Sole responsibility lies with the authors and the European Commission is not responsible for any use that may be made of the information contained therein.

Abstract

Aims and background. RARE-Bestpractices is a four-year European collaborative project that has as one of its primary goals the facilitation of global access to trustworthy guidelines on rare diseases. This paper describes the findings of a workshop held with representatives of ten RARE-Bestpractices partner organisations to explore the utility of the AGREE-II instrument for the quality appraisal of rare disease guidelines.

Methods. Participants viewed the online AGREE-II overview tutorial and worked in small groups to complete appraisals of two guidelines on Huntington's disease. Participants discussed their views on using the instrument to appraise rare disease guidelines.

Results and discussion. All domains and items of the AGREE-II instrument were considered relevant to appraising the quality of the selected guidelines; additionally, it was possible to identify information within the guidelines to support a judgment on the score for each item. Discussion on areas of difficulty or disagreement has resulted in a set of notes on how to address problems of interpretation that may commonly be encountered when applying AGREE-II to rare disease guidelines.

Conclusion. The AGREE-II instrument is applicable regardless of the small patient numbers, potentially small volume of evidence, and other limitations typically encountered in rare disease guidelines.

Key words

Guidelines, rare diseases, AGREE II instrument.

Introduction

RARE-Bestpractices is a four year collaborative project funded by the European Union Seventh Framework Programme. One of the primary goals of the project is to promote and facilitate communication on the management of rare diseases by facilitating global access to, and dissemination of, trustworthy guidelines on rare diseases. To this end an online database of guidelines, on topics ranging from diagnosis and treatment to the organisation of care, is being developed by RARE-Bestpractices partners to provide professionals, patients and policy makers with robust and up to date information on the care of individuals with rare diseases [1].

A previous study by members of the RARE-Bestpractices project explored the utility of existing databases for identifying guidelines on rare diseases. Based on a low search yield for three rare conditions in the largest two guideline specific databases the authors concluded that rare disease guidelines may not be well represented in existing databases and provided a novel search strategy for their identification [2]. This approach to identification of rare disease guidelines is being used to retrieve guidelines on a range of rare conditions for inclusion in the RARE-Bestpractices guideline database.

Following identification of guidelines, an assessment of their methodological quality is required to ensure that the most robust and trustworthy guidelines can be highlighted. A systematic review identified 40 tools for appraisal of guideline quality [3] with the most comprehensively validated of these being the Appraisal of Guidelines for Research & Evaluation (AGREE II, http://www.agreetrust.org/).

The AGREE II instrument is an internationally recognised assessment tool which consists of 23 items arranged into six quality domains [4, 5]. Each domain represents a

unique dimension of guideline quality, and from the item scores (range 1-7) a quality score for each domain is calculated.

The six domain scores are judged as independent factors and so cannot be aggregated into a single quality score. Overall guideline quality is a separate judgement based on the assessment process as a whole and is considered alongside the question of whether the appraiser would recommend the guideline for use, for use with modifications or would not recommend use. It is suggested that each guideline is assessed by at least two appraisers (preferably four), in order to increase the reliability of the assessment [6]. Practical application of the AGREE II instrument includes its use as the basis of the guidance accreditation process of the National Institute of Health and Care Excellence [7].

This article reports on an international workshop delivered by the RARE-Bestpractices partners which aimed to:

- provide participants with experience of using the AGREE II instrument in a multidisciplinary environment;
- stimulate discussion on appraisal of rare disease guidelines, and from this, develop an informal consensus on the utility of the AGREE II instrument for appraising rare disease guidelines within the context of the RARE-Bestpractices database.

Methods

With a view to specifying AGREE II appraisals as a feature of the RARE-Bestpractices guideline database, members of the RARE-Bestpractices consortium were invited to participate in a two-day workshop to explore the utility of this instrument for appraisal of rare disease guidelines. The workshop took place in Edinburgh, Scotland in October 2014. The employing organisation and geographic location of participants are described in Table 1. There were 13 participants. Clinicians, guideline developers, patient organisations and policy makers were represented.

As an introduction to the AGREE II instrument the participants watched the AGREE II Overview Tutorial (http://www.agreetrust.org/resource-centre/agree-ii-training-tools). This tutorial provides an avatar-guided overview of the AGREE II instrument, briefly describing each of the items from the six quality domains and introducing how the scoring should be conducted.

Following a preliminary discussion of potential issues that could arise in the use of the AGREE II instrument for appraising rare disease guidelines, participants formed four groups to simultaneously conduct an appraisal of a guideline on nutritional management for Huntington's disease [8]. To provide further experience in using the AGREE II instrument, a second guideline, on the pharmacological management of chorea in Huntington's disease [9] was then appraised.

The two guidelines were chosen pragmatically from those identified in a previous study [2] as examples that covered drug and non-drug interventions, and that provided sufficient information to support informed judgement on most if not all AGREE items. Within the time limitations of the workshop, only two guideline appraisals could be completed.

Results and discussion

The first appraisal took approximately 90 minutes to complete. Ratings for overall quality, which summarise the methodological assessment, ranged from 1 to 3 (on a scale of 1-7 where seven indicates highest quality).Three of the four groups recorded that they would, despite this low quality-score, recommend the guideline with modifications, with one group not reaching consensus on a judgement.

The workshop participants then discussed issues arising in the application of the AGREE II instrument. There was variation both within and among groups in the scores assigned. This was particularly apparent for items within

Table 1. Organisations participating in the guideline evaluation workshop

Organisation	Location
DEBRA Ireland	Dublin, Ireland
The European Academy of Paediatrics	Bruxelles, Belgium
EURORDIS, European Organisation for Rare Diseases	Paris, France
Fundación Canaria de Investigación y Salud	Las Palmas de Gran Canaria, Spain
Healthcare Improvement Scotland	Glasgow, UK
The Children's Hospital at Westmead and The University of Sydney	Sydney, Australia
Istituto Superiore di Sanità	Rome, Italy
University of Maastricht	Maastricht, The Netherlands
Murdoch Children's Research Institute	Melbourne, Australia
Newcastle University Upon Tyne	Newcastle, UK

the 'rigour of development' and 'editorial independence' domains. These variations arose both from differences in the interpretation of the methodological descriptions in the AGREE II guidance document and from identification or interpretation of material within the guideline being examined.

Other issues related to scoring of the AGREE II items highlighted by workshop participants included:

- judgement 'generosity' can be influenced by mood, context and appraisal workload;
- information within the guidelines is not always easy to find so appraisal can be a time consuming process;
- knowledge of the rare disease can influence the appraisal rating given a clinical subject expert may identify quality issues not apparent to non experts;
- although for some items there was wide variation in scores, the overall quality judgement was consistently low across the groups.

Two principles were emphasised and agreed by the group. Firstly, it is as important that guidelines for rare diseases are high quality as it is for guidelines for common conditions; therefore quality standards should not be lowered for rare disease guidelines. Paradoxically, however, the three groups who recorded a judgement recommended the guideline for use with modifications despite a low quality score. This discrepancy related to the value placed on a guideline that was unique in addressing its topic and reluctance to reject it in the absence of other guidelines. Later in the workshop the view that guidelines should not be categorised as 'recommended for use' simply because there are few available was emphasised within the group. Secondly, although it may be challenging to achieve, participation of patients and their carers or representatives is viewed as vital for the development of a high quality rare disease guideline.

The second appraisal took approximately 40 minutes to complete with groups assigned specific domains within the AGREE II instrument for more detailed consideration of the application of each domain in the context of a rare disease guideline. No overall quality rating was made due to the domains being allocated across the participants. The participant pairs were then invited to present to the whole group a detailed discussion of the application of the AGREE II items in light of their growing experience of using the tool in the context of rare disease guidelines.

Following completion of the second guideline appraisal, participants concluded that the AGREE II instrument is appropriate for evaluation of rare disease guidelines but that some notes to supplement the AGREE II manual should be developed to support appraisals of rare

Table 2. Notes on use of the AGREE II instrument for guideline quality evaluation in rare diseases

AGREE II Domain	Points to consider
Scope and purpose (Items 1-3)	Rare disease guidelines should be able to address all of the items concerned with scope and purpose.
Stakeholder involvement (Items 4-6)	Although it is likely that one professional group may dominate, comprehensive stakeholder involvement is as important to the development of guidelines for rare diseases as it is for common diseases. Scoring of these items should recognise this principle and reflect the extent to which the guideline addresses each item.
Rigour of development (Items 7-14)	The AGREE II quality rating does not depend on the quantity or type of published evidence but on the rigour of the systematic methods used to identify, select and synthesise evidence and the transparency with which the guideline development group report how they reached recommendations. For item 13 (external review by experts) – the experts should include patients, carers, and/or patient groups.
Clarity of presentation (Items 15-17)	When scoring item 16 there may not be a range of options for management of the (rare) condition or health issue. In this case the item would be considered 'not applicable' and scored as '1'.
Applicability (Items 18-21)	The extent to which a guideline can provide information on potential facilitators to guideline implementation and describe resource implications may be limited for rare disease guidelines where the implementation setting is likely to encompass diverse healthcare contexts. The information provided may be country-specific, healthcare system-specific, or generic.
Editorial independence (Items 22-23)	For many rare diseases there are likely to be only a small number of experts worldwide. This may limit the potential for editorial independence. Scores should reflect how this was addressed.
Overall guideline assessment	Before selecting 'yes with modifications', consider whether resources are available to modify the guideline and any copyright issues. The existence of only a few or only one guideline on a topic should not prevent a judgment of 'no' on question 2 as it is worthwhile to indicate that better quality guidelines are needed.
Notes section	Indicate if the guideline is the only (known) guideline on available on the topic. Indicate any research recommendations which the guideline identifies.

disease guidelines. Discussion focused on the particular items of AGREE II where difficulty or disagreement was experienced and additional notes for appraisers was developed from these points as summarised in Table 2. It is intended that these notes will be used and further refined during the course of the project as a wider community of researchers and clinicians apply the AGREE II tool in practice, while building the repository of appraised guidelines.

Conclusions

One of the key objectives of the RARE-Bestpractices project is to support the development and global dissemination of trustworthy guidelines for the management of rare conditions. It was recognised early in the project that establishing a process for appraising guidelines was essential as not all guidelines, for rare or common conditions, are of equal quality [10].

The workshop described here was designed to test a method for undertaking this quality assessment and has demonstrated that use of the AGREE II instrument is feasible for the appraisal of the methodological quality of rare disease guidelines. During the course of testing the AGREE II instrument specific challenges relating to the appraisal of rare disease guidelines were identified and supplementary notes have been produced to support quality assessment of these guidelines.

As a report of an exploratory workshop, this study inevitably has limitations. The workshop was designed to test the feasibility of the AGREE II quality appraisal tool and to enable discussion of the broader issues around quality assessment for rare disease guidelines. It employed neither formal qualitative research methods nor formal consensus methods. It is further limited in exploring only one appraisal tool and testing this tool on only two guidelines due to time limitations. However, this study does represent a step towards further research into the quality appraisal of rare disease guidelines and may stimulate those developing guidelines for care and treatment of individuals with rare diseases to consider methodological aspects associated with guideline quality.

The supplementary notes provide clarification on scoring of some AGREE II items, such as the potential lack of a range of available treatment options or a paucity of experts on the condition. The notes emphasise that items in the 'rigour of development' domain are applicable regardless of the number of people affected (few), volume of published evidence (potentially small), type of studies (randomised or non-randomised) or number of existing guidelines (potentially few). The AGREE II instrument and additional notes will be integrated into the RARE-Bestpractices guidelines database providing patients, clinicians, and policy makers with a detailed assessment of the quality of the methodology used to develop the guideline. The project aims to recruit between two and four appraisers for each guideline in the collection.

Acknowledgements

The authors wish to acknowledge the participation and expertise of the following partners: Antonio Atalaia, Mathieu Boudes, Paula Bray, Avril Kennan, Paola Laricchiuta, Cristina Morciano, Merryn Pearce, Liesbeth Siderius, Mar Trujillo-Martin and Henk van Kranen. Thanks also to Melissa Brouwers, principal investigator, AGREE Next Steps Consortium for advice and support, and to our colleague Ali McAllister for her help in preparation of the manuscript.

Members of the RARE-Bestpractice Consortium

Domenica Taruscio, Istituto Superiore di Sanità, Italy
Cristina Morciano, Istituto Superiore di Sanità, Italy
Paola Laricchiuta, Istituto Superiore di Sanità, Italy
Sabina Tonon, Istituto Superiore di Sanità, Italy
Joanne Auld, JAMARAU, UK
Thomas Sejersen, Karolinska Institutet, Sweden
Desirée Gavhed, Karolinska Institutet, Sweden
Karen Ritchie, Healthcare Improvement Scotland, UK
Lorna Thompson, Healthcare Improvement Scotland, UK
Jenny Harbour, Healthcare Improvement Scotland, UK
Panos G. Kanavos, London School of Economics and Political Science, UK
Pierpaolo Mincarone, National Research Council, Italy
Carlo Giacomo Leo, National Research Council, Italy
Saverio Sabina, National Research Council, Italy
Roberto Guarino, National Research Council, Italy
Fabio Palazzo, National Research Council, Italy
Giuseppe Ponzini, National Research Council, Italy
Juliette Senecat, EURORDIS, European Organisation for Rare Diseases, France
Mathieu Boudes, EURORDIS, European Organisation for Rare Diseases, France
Yann LeCam, EURORDIS, European Organisation for Rare Diseases, France
Graziella Filippini, Associazione per la Ricerca sull'Efficacia dell'Assistenza Sanitaria, Centro Cochrane Italiano, Italy
Roberto D'Amico, Associazione per la Ricerca sull'Efficacia dell'Assistenza Sanitaria, Centro Cochrane Italiano, Italy
Silvia Minozzi, Associazione per la Ricerca sull'Efficacia dell'Assistenza Sanitaria, Centro Cochrane Italiano, Italy
Cinzia Del Giovane, Associazione per la Ricerca sull'Efficacia dell'Assistenza Sanitaria, Centro Cochrane Italiano, Italy
Holger Schünemann, Universitaetsklinikum Freiburg, Germany
Joerg Meerpohl, Universitaetsklinikum Freiburg, Germany
Alfonso Iorio, Universitaetsklinikum Freiburg, Germany
Lisa Schell, Universitaetsklinikum Freiburg, Germany
Tsonka Miteva-Katrandzhieva, Bulgarian Association for Promotion of Education and Science, Bulgaria
Rumen Stefanov, Bulgarian Association for Promotion of Education and Science, Bulgaria
Georgi Iskrov, Bulgarian Association for Promotion of Education and Science, Bulgaria
Pedro Serrano-Aguilar, Fundación Canaria de Investigación y Salud, Spain
Lilisbeth Perestelo-Perez, Fundación Canaria de Investigación y Salud, Spain
Maria M. Trujillo-Martín, Fundación Canaria de Investigación y Salud, Spain
Jeanette Pérez Ramos, Fundación Canaria de Investigación y Salud, Spain
Amado Rivero, Fundación Canaria de Investigación y Salud, Spain
Angela Brand, Universiteit Maastricht, Netherlands
Jonathan Lal, Universiteit Maastricht, Netherlands
Henk van Kranen, Universiteit Maastricht, Netherlands
Kate Bushby, Newcastle University Upon Tyne, UK
Antonio Atalaia, Newcastle University Upon Tyne, UK
Liesbeth Siderius, The European Academy of Paediatrics AISBL, Belgium

Jose Ramet, The European Academy of Paediatrics AISBL, Belgium
Manuel Posada, Institute of Rare Diseases Research, Instituto de Salud Carlos III, Spain
Manuel Hens-Pérez, Institute of Rare Diseases Research, Instituto de Salud Carlos III, Spain
Ignacio Abaitua, Institute of Rare Diseases Research, Instituto de Salud Carlos III, Spain
Francisco Javier Manzanares, Institute of Rare Diseases Research, Instituto de Salud Carlos III, Spain
Veronica Alonso, Institute of Rare Diseases Research, Instituto de Salud Carlos III, Spain
Kathryn North, Murdoch Childrens Research Institute, Australia

References

1. Taruscio D, Morciano C, Laricchiuta P, Mincarone P, RARE-Bestpractices Consortium. RARE-Bestpractices: a platform for sharing best practices for the management of rare diseases. Rare Dis Orphan Drugs 2014;1(1):5-10.
2. Hilton Boon M, Ritchie K, Manson J. Improving the retrieval and dissemination of rare disease guidelines and research recommendations: a RARE-Bestpractices initiative. Rare Dis Orphan Drugs 2014;1(1):20-9.
3. Siering U, Eikermann M, Hausner E, Hoffmann-Eßer W, Neugebauer EA. Appraisal tools for clinical practice guidelines: a systematic review. PLoS ONE 2013;8(12):e82915.
4. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. Development of the AGREE II, part 1: performance, usefulness and areas for improvement. CMAJ 2010;182(10):1045-52.
5. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. Development of the AGREE II, part 2: assessment of validity of items and tools to support application. CMAJ 2010;182(10):E472-8.
6. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in healthcare. CMAJ 2010;182(18):E839-42.
7. National Institute for Health and Care Excellence (NICE). Process manual for accrediting producers of guidance, advice and recommendations for practice: a guide for producers and stakeholders. London: NICE; 2014. [cited 30 Jan 2015]. Available from: http://www.nice.org.uk/Media/Default/About/accreditation/nice-accreditation-process-manual.pdf.
8. Brotherton A, Campos L, Rowell A, Zoia V, Simpson SA, Rae D. Nutritional management of individuals with Huntington's disease: nutritional guidelines. Neurodegen Dis Manag 2012;2(1):33-43.
9. Armstrong MJ, Miyasaki JM, American Academy of Neurology. Evidence-based guideline: pharmacologic treatment of chorea in Huntington disease: report of the guideline development subcommittee of the American Academy of Neurology. Neurology 2012;79(6):597-603.
10. Alonso-Coello P IA, Solà I, Gich I, Delgado-Noguera M, Rigau D, et al. The quality of clinical practice guidelines over the last two decades: a systematic review of guideline appraisal studies. Qual Saf Health Care 2010;19(6):e58.