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Improving the retrieval and dissemination of rare disease guidelines and research recommendations: a RARE-Bestpractices initiative

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ABSTRACT

Introduction: Guidelines on rare diseases (RD) are more likely to be produced by groups other than major guideline development organisations and therefore the retrieval and dissemination of guidelines on rare diseases will be more challenging than for more prevalent conditions. The EU-funded RARE-Bestpractices project includes the development of a collection of guidelines on rare diseases together with a complementary collection of research recommendations. The basis for development of this collection is presented.

Methods: To test recall and yield we conducted searches for a sample of RD reflecting a range of prevalence: Turner syndrome, Huntington's disease, and Costello syndrome. A systematic search was made of a range of sources including databases of major guideline producers, PubMed and a number of portals dedicated to RD together with Google searching. Comparisons were made of the structure and contents of existing databases of guidelines and research recommendations.

Results: From sources searched only 15 English language guidelines were retrieved across the 3 test RDs. Searching of major guideline databases was not an effective strategy; the highest number of relevant results was obtained through Google searches and pearl growing, i.e. using one authoritative resource to identify further related resources. Only two databases of research recommendations were identified, neither specific to RD.

Discussion: Searches of current databases of guidelines and repositories of information on RD were not effective for retrieving English language RD guidelines, with Google searching proving to be a more successful method. The yield from Google results ranged from 4% to 7%, meaning users would need to review a high number of results to identify relevant material. Therefore, there appears to be a need for a database that has high specificity and yield for RD guidelines.

Conclusions: We have demonstrated that existing resources do not allow for easy identification of RD guidelines and research recommendations. The resources being developed as part of the RARE-Bestpractices project are intended to meet this need.

KEYWORDS

guidelines, rare diseases, information retrieval, literature searching, search strategies, databases, collection development, research recommendations, uncertainties

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INTRODUCTION

Guidelines, defined by the World Health Organization as "systematically developed evidence-based statements which assist providers, recipients and other stakeholders to make informed decisions about appropriate health interventions", [1] have the potential to improve the quality of healthcare if they are disseminated to and implemented by their target audience. A high-quality guideline can be an expensive investment and some funders consider the prevalence of a disease as one factor in prioritising topics for guideline development. In such a policy environment, rare diseases (RD) may struggle to compete with more common diseases and as a result, rare disease guidelines may be more likely to be developed by consensus conferences, ad hoc expert groups, charities, or other organisations that may not have equivalent resources to devote to development, dissemination and implementation. Databases of guidelines, such as the Guidelines International Network (G-I-N) database and the National Guidelines Clearinghouse, exist to increase the dissemination of guidelines, but the handful of RD guidelines may be lost in the 'noise' of thousands of higher-prevalence disease guidelines. As a result of these factors, RD guidelines are likely to require more effort to identify, and are less likely to have adequate resources to support dissemination and implementation, than guidelines on common diseases.

The RARE-Bestpractices project funded by the European Union Seventh Framework Programme aims to address this disparity and improve the availability of high-quality best practice guidance, thereby supporting better care for people with RD. The project will deliver a sustainable networking platform that will support the exchange of high-quality knowledge and information, principally in the form of best practice guidelines and research recommendations, in concert with wide-ranging but complementary work relating to guideline methodology, value assessment of orphan medicines, and research dissemination. Within the RARE-Bestpractices project, work package 4 is led by Healthcare Improvement Scotland with the collaboration of Karolinska Institutet, Jamarau, Istituto Superiore di Sanità, Universitaetsklinikum Freiburg, and Universiteit Maastricht. A key objective of this work package is to deliver the information architecture and content for two databases devoted to RD knowledge and information, one for guidelines and one for research recommendations.

The RARE-Bestpractices project was proposed and funded based on the tacit knowledge and experience of RD specialists that RD guidelines and research recommendations require particular effort to retrieve and would benefit from dedicated tools and resources to facilitate their dissemination to patients, clinicians and researchers. Previous research has demonstrated that health information resources such as Medline and internet search engines perform less well when searching for rare disease information as compared to searching for information on common diseases [2-5]. One study tested the use of Medical Subject Headings (MeSH) Concepts versus MeSH Descriptors for improving the precision of searches for RD topics in PubMed [3]. Another study reported on the development of a new internet search engine for RD diagnostic queries (FindZebra) [4]. To our knowledge, no studies have examined information retrieval of RD guidelines or tested methods of improving the retrieval of RD guidelines. Guidelines are a valuable source of health information as they systematically identify, appraise, and synthesise existing evidence and then translate that evidence into recommendations that are expected to improve outcomes for patients. We set out to test recall and yield of existing databases and optimise search methods for RD guidelines.

METHODS

We carried out a literature search to assess existing research or practice in rare disease guideline searching or retrieval. Medline, Library Information Science and Technology Abstracts (LISTA) and Emerald databases were searched from 2003 to August 2013 combining 'rare disease guideline' and 'information retrieval' keyword terms. After sifting the 233 results for relevance, four documents were found to pertain to information retrieval in rare diseases, [2-5] although none of these papers concerns the location or provision of clinical guideline documents.

In the absence of a proven approach to guideline retrieval in the field of rare diseases, the aspects of the scoping work described below were carried out utilising search protocols that have been refined to support the scoping stage of the development of guidelines and standards in Healthcare Improvement Scotland (HIS).

The initial search strategy was based on the scoping search protocol for the Scottish Intercollegiate Guideline Network (SIGN) [6]. The purpose of the SIGN scoping search is not to exhaustively retrieve all guidelines but to identify key evidence documents which may influence the choice and/or remit of guideline topics commissioned by the organisation. The protocol refers only to large guideline databases such as the Guidelines International Network (G-I-N), National Guidelines Clearinghouse (NGC), and Evidence Search, a database of guidelines and other resources maintained by the National Institute for Health and Care Excellence (NICE).

In order to increase the coverage of the search, additional searches were conducted with a more comprehensive protocol used within HIS to support the development of clinical standards and quality indicators. This work necessitates an extensive search of resources to identify the maximum number of international guideline documents which may inform the development of national standards or indicators. The search protocol consists of 30 established guideline producers/databases, additional HTA and systematic review resources, primary literature search results (Medline and Embase), and a pragmatic internet search consisting of the subject term plus 'guideline' and limited to PDF document type in Google with the first 100 results to be checked.

Several RD information portals were also added to the protocol in order to increase sensitivity for RD topics: Orphanet,

National Organisation for Rare Disorders (NORD), Eurogentest, Dyscerne, and the Genetic and Rare Diseases Information Centre.

To test recall and yield of existing databases and optimise search methods, we conducted searches for a purposive sample of RD reflecting a range of prevalence. RD are defined in Europe as having a prevalence of 5 in 10,000 persons. Turner syndrome is an example from the high end of the prevalence spectrum with a prevalence of 1-5 in 10,000. Huntington's disease has a prevalence of 1-9 in 100,000. Costello syndrome is an ultra-rare disease, with approximately 150 cases reported worldwide [7].

Search strategies were specific to each individual resource and used both single keywords and more comprehensive search strings. The information retrieval technique of pearl growing was also employed. This refers to the process of using one authoritative resource to identify further related resources [8] and was proposed as an appropriate search method given that background reading and sifting internet search results may introduce the opportunity to identify relevant documents outside of a standardised search protocol.

The inclusion criteria for sifting the RD guidelines search results were: English-language documents published 2003-2013, described as guidelines, consensus statements, or best practice statements, AND containing recommendations. In keeping with the protocol used for sifting 'common' disease guidelines, we excluded documents that were not specific to the disease topic.

Finally, in addition to testing search strategies and information retrieval, we also conducted comparisons of the structure and contents of existing databases of guidelines and research recommendations, in order to identify the unique contribution that could be made by databases devoted to RD.

RESULTS

Test searches

The results from the searches for the three sample RD topics were sifted against the inclusion criteria. *Tables 1, 2, and 3* report the recall (total number of results returned), yield (number and proportion of results that met inclusion criteria), and reasons for exclusion for the three sets of searches. Most of the resources used within the existing SIGN and HIS protocols for retrieval of guidelines returned zero results on these RD topics. The tables report in detail results obtained from the seven key resources that produced the highest recall and the supplementary search technique of pearl growing. In total, only four guidelines on Turner syndrome were identified, [9-12] eleven guidelines on Huntington's disease, [13-23] and zero guidelines on Costello syndrome.

The two largest guideline-specific databases, G-I-N and NGC, produced a very low yield of guidelines for the three RD topics. Similarly, Evidence Search had a very low yield despite high recall, reflecting the imprecision of the search functionality as well as a low number of RD guidelines in the database.

The most common reason for exclusion was non-relevance to the clinical topic, indicating a poor specificity for RD topics in these resources, apart from Orphanet. Excluding documents in languages other than English meant that, given the very small number of relevant results, a significant number of guidelines were excluded. For example, Orphanet returned a total of eight guidelines for the three topics, but seven of the eight guidelines were in languages other than English.

For English-language guidelines, the highest number of relevant results was obtained through Google searches limited to PDF documents, and pearl growing.

Table 1. Turner syndrome guidelines retrieved, by source.

SOURCE	RECALL	REASONS FOR EXCLUSION	YIELD (%)
G-I-N database	2	Not English language	0 (0)
National Guidelines Clearinghouse	71	Not relevant	0 (0)
Orphanet	1	Not English language	0 (0)
Eurogentest	2	1 Not specific to Turner syndrome 1 Not a guideline	0 (0)
PubMed	27	3 Not English language 21 Not relevant	3 (11.1)
Evidence Search (NICE)	393	Not relevant	2 (0.5)
Google pdf first 100	--	96 Not relevant	4 (4)
Pearl growing	--	--	0
Total	596	De-duplication	4 (0.7)

Table 2. Huntington's disease guidelines retrieved, by source.			
SOURCE	**RECALL**	**REASONS FOR EXCLUSION**	**YIELD (%)**
G-I-N database	1	--	1 (100)
National Guidelines Clearinghouse	12	8 Not specific to Huntington's 3 Not relevant	1 (8.3)
Orphanet	5	4 Not English language	1 (20)
Eurogentest	65	64 Not relevant	1 (1.5)
PubMed	34	1 Not English language 29 Not relevant	4 (11.8)
Evidence Search (NICE)	52	Not relevant	0 (0)
Google pdf first 100	--	93 Not relevant	7 (7)
Pearl growing	--	--	6
Total	169	De-duplication	11 (6.5)

Table 3. Costello syndrome guidelines retrieved, by source.			
SOURCE	**RECALL**	**REASONS FOR EXCLUSION**	**YIELD (%)**
G-I-N database	1	Not English language	0 (0)
National Guidelines Clearinghouse	6	Not relevant	0 (0)
Orphanet	2	Not English language	0 (0)
Eurogentest	1	Not relevant	0 (0)
PubMed	1	Not relevant	0 (0)
Evidence Search (NICE)	53	Not relevant	0 (0)
Google pdf first 100	--	99 Not relevant 1 Not a guideline	0 (0)
Pearl growing	--	--	0
Total	64	De-duplication	0 (0)

Table 4. Comparison of three existing databases containing rare disease guidelines.			
COMPARISON CRITERIA	**G-I-N (WWW.G-I-N.NET)**	**NGC (GUIDELINE.GOV)**	**ORPHANET (WWW.ORPHA.NET)**
Access	Login required (limited free access)	Free access and free registration	Free access
Collections policy	Guideline documents produced by G-I-N members	Guidelines produced by specified types of formal organisations, in English, in the past five years, based on a systematic review of evidence and contain an assessment of benefits and harms	"summary recommendations for the management of patients, issued by official organisations"
Content development	G-I-N members	NGC searches and user suggestions	INSERM
Language	Multiple	English only	Multiple
Number of guideline records	6516	>2600	unknown
Document information	Bibliographic record, MeSH terms	Detailed information on guideline scope, methods, recommendations, supporting evidence	Hyperlink to document only
Quality assessment provided	No	No	No
Additional features	None	'Compare guideline' function, personalisation, topic alerts	'Search by sign' function

Comparison of guideline databases

In order to determine whether resources already existed with the same proposed scope and focus as the RARE-Bestpractices database, we included in the comparison only databases that were publicly available, international in scope, and inclusive of the full spectrum of diseases (i.e. not limited to a specific disease area, e.g. cancer). On this basis, we identified two international databases of clinical guidelines and the Orphanet collection of information on rare diseases for inclusion. We compared these three sources using eight criteria to determine whether there were any potential gaps in coverage of RD or in the information provided about the included guidelines. *Table 4* presents the characteristics of the existing guideline databases.

The G-I-N database (accessible at http://www.g-i-n.net/library) currently contains 6516 records of guidelines which have been produced by G-I-N members and which are published in many languages. Only details of the title and publisher of these guidelines is publicly available with further details accessible only to G-I-N members. Many of these guidelines will be freely available but will require further searching by non G-I-N member users via individual publishers' websites. The collection includes guidelines for common and rare diseases.

NGC is hosted by the US Department of Health and Human Services (http://www.guideline.gov). At present, for inclusion in the database, guidelines must be developed by "medical specialty associations; relevant professional societies, public or private organizations, government agencies at the Federal, State, or local level; or health care organizations or plans". The inclusion criteria also now require guidelines to meet rigorous quality standards relating to systematic review, evidence synthesis, and appraisal of benefits and harms. The size of the collection is not described but we estimate there are over 2600 guidance documents available. Both common and rare conditions are included in the collection. The guideline development methodology, a detailed synopsis and list of recommendations together with links to the publisher's website are provided in the database record.

Orphanet (www.orpha.net) covers almost 6000 rare diseases with information provided ranging from disease summaries and expert centres to guidelines and other treatment information. It is not possible to search for guidelines only but disease entries within the Orphanet Professional Encyclopaedia contain some direct links to guideline documents.

Comparison of research recommendation databases

There has been a much smaller number of initiatives to develop collections of research recommendations arising from gaps in the current evidence base than there are collections of guidelines. The databases considered in detail here are UK based, although we are aware of one being established in Sweden based on the UK DUETS database described below and other initiatives in Canada and Spain (personal communication). We have not identified any databases of research recommendations arising from international collaborations; however, international groups who have identified research recommendations have approached UK DUETS to use their quality assurance processes to verify uncertainties and include the uncertainties in UK DUETS. We found no databases specifically collating research questions on rare diseases.

The UK Database of Uncertainties of the Effects of Treatment (UK DUETS) was established in 2005 by the NHS in England and since 2010 has been hosted within NICE Evidence Services (http://www.library.nhs.uk/duets/). The collection comprises research questions arising from a range of sources including research uncertainties from surveys of patients, carers and professionals; research recommendations arising from evidence updates, guidelines and relevant and reliable systematic reviews; and ongoing primary and secondary research activity. Information on the recommendations includes: the source of the question; the citation to any relevant and reliable systematic review; systematic reviews which might if extended address the uncertainty if updated; the type of response required to address the uncertainty; and any ongoing research that might address the uncertainty. The date of review of the question is provided, but the process for question review and updating is not clear.

NICE hosts a separate database of research recommendations arising specifically from NICE products, such as guidelines, single interventional procedures, diagnostic reviews, technology assessments and guidelines from public health and social care. Information contained within the records includes the source of the question and its level of priority. Prioritisation of research recommendations is led by advisory groups developing the guideline or other output and a systematic approach to undertake this prioritisation process is defined in the published guide for developing research recommendations.

The UK DUETS database and NICE research recommendations databases use the EPICOT format to structure records of uncertainties and research questions. [24] This format comprises the following elements:

- What comprises the Evidence?
- What is the Population of interest?
- What are the Interventions of interest?
- What are the Comparisons of interest?
- What are the Outcomes of interest?
- Time stamp (date of recommendations).

The EPICOT format provides a structure for the formulation of research questions and has been recommended to avoid authors listing general or vague questions that make implementation problematic and provides an indication of the state of the evidence base at the time of original formulation.

Working closely with DUETS is the James Lind Alliance (JLA) (www.lindalliance.org/), established in 2004, and recently transferred to the UK National Institute of Health Research. This organisation facilitates patient and clinician groups, Priority Setting Partnerships, to identify uncertainties and then prioritise the research into treatment effects of greatest importance to them. The JLA process uses a range of methods of identifying areas of uncertainty including the use of surveys amongst patient and clinical populations as well as identification from the existing literature. Submitted uncertainties are included in the database in fields indicating the population, intervention, comparator and outcome (PICO) format and verified against sources such as the Cochrane Library, NICE and SIGN guidelines before being included in the prioritisation phase. A transparent method of achieving consensus as to the top 10 priorities in a particular topic area is then undertaken. Where identified uncertainties, e.g. regarding natural history of disease or communication approaches, are not suitable for inclusion in DUETS, Priority Setting Partnerships are encouraged to forward these to relevant organisations who can consider these within their own processes.

DISCUSSION

It was noteworthy that, for the three sample topics searched, only one of the documents retrieved and confirmed as a guideline was recorded in the two largest international databases, G-I-N and NGC. A possible explanation for this omission is that RD guidelines are often developed by small specialist groups which may not be aware of such dissemination facilities or have the resource to submit their guidelines to them. For example, a key guidance document for Turner Syndrome(9) was developed by a multidisciplinary panel of experts brought specifically to work on this publication. As such they may not qualify or may not wish to become G-I-N members and so would not be able to add their guideline to the database. Previous research has established that guidelines developed by professional societies or specialist groups are generally of lower methodological quality than guidelines developed by governmental bodies [25]. The NGC inclusion criteria relating to rigour of systematic review and evidence synthesis may therefore constitute a further barrier to the dissemination of RD guidelines.

Similarly, only one of the guidelines retrieved by our search was recorded in Orphanet. However, Orphanet did contain links to other references that would facilitate pearl growing, and additional records of non-English guidelines for each of the sample topics. The entry for Costello syndrome, for example, provides access to Spanish and French language guidelines [26,27] which were excluded by limiting our scoping search to English language documents. This demonstrates the importance of removing language restrictions in searching for RD guidelines, but also indicates a potential barrier to the dissemination and implementation of recommendations. Systematic reviewers of RD guidelines should be adequately resourced for translation. Funding bodies may wish to compare the cost of translating and adapting a good-quality guideline from another language with the cost of producing a de novo guideline.

The credibility of general purpose search engines to retrieve reliable and comprehensive coverage of health information has previously been brought into question [28]. However, more recent research has shown Google Scholar to be as, if not more, effective as PubMed at identifying health literature [29]. The results from our test searches indicate that Google is indeed an effective resource to locate RD guidelines, identifying nearly all of the retrieved guidelines in the first 100 results. Limiting to PDF document type appeared to be successful in improving specificity, given that most guideline documents published on the web are in this format. Also, the PDF documents are generally immediately available to view, and so reduce time and resource spent trying to access full text documents.

Previous research has demonstrated that, when searching for health-related information, internet users seldom read beyond the second page of results [30] and that both doctors and nurses report lack of time and lack of search skills as barriers to accessing online information [31]. Although the Google search results were limited to the first 100 results for practical reasons, the yield remained very low for all conditions and, despite using guideline terms in the search strategy, there were many irrelevant results. Thus, there is scope for a database tailored to RD guidelines to reduce the time and effort required to locate disease guidelines by allowing for more precise searches and a high yield of relevant results.

It is recognised that guidance documents may also be published in subscription-only resources and therefore might be excluded from the Google search by way of document type. In our three chosen examples this proved not to be the case as the PubMed search failed to identify any unique citations.

Huntington's Disease offers an example in which methods such as pearl growing may be useful in the location of RD guidelines. The journal in which six guidelines were published in 2012 by the European Huntington's Disease Network, Neurodegenerative Disease Management, is not indexed for Medline, meaning that these guidelines could not be retrieved via PubMed. Nor were five of these six guidelines obtained by the Google search strategy, which on analysis appeared to be the result of a metadata issue within the documents. Instead, references provided in the one retrieved guideline led to the identification of the other five.

In general, compared to our experiences in searching for guidelines on common diseases, we observed relatively low recall, very low yield, and very little duplication across sources. A larger proportion of guidelines addressed genetic testing, laboratory testing, and diagnosis. Guidelines were more likely to focus on a specific aspect of diagnosis or treatment (e.g. management of a specific symptom) and not to cover the full pathway of care.

The number of results would have been much greater had guidelines been included that were not specifically about the named diseases but that included these diseases within broader clinical topics. For example, guidelines on dementias or movement disorders may address in part, or be relevant to, Huntington's Disease; Turner's may be addressed in guidelines on growth hormone replacement, or growth failure in children; Costello syndrome is one of the RASopathies, a group of nine syndromes with some overlap in phenotypes. Using broader search terms and including guidelines from related diseases would present different challenges for information retrieval and applicability, compared with conventional search practices for guidelines on common diseases.

Although G-I-N and NGC are the largest guideline databases of which we are aware, they produced fewer relevant search results for RD topics than Google, indicating that RD guidelines and guideline developers are not well represented in their content or collection development methods. The yield for Google, however, ranged from 4% to 7%, meaning that the number needed to read in order to identify relevant results would be high. There appears to be a role for a database that has high specificity and high yield for RD guidelines.

Although NGC provides detailed information about the methodology of included guidelines, none of the three resources provides any quality assessment of guidelines. Information on guideline quality is important in deciding whether a guideline should be implemented or is suitable for adaptation. Such information could add value within a database of RD guidelines.

We identified only two databases of research recommendations, both hosted by NICE in the UK. Neither of these databases included uncertainties relating to the treatment of our three exemplar rare conditions, although uncertainties relating to RD are not excluded from these databases.

The James Lind Alliance is instrumental in ensuring research is of relevance to patients and clinicians and is not dominated by the priorities of researchers or industry. The method used to identify research priorities is based on the establishment of Priority Setting Partnerships. The majority of the established Partnerships have common diseases as their focus, although a Priority Setting Partnership for Lyme Disease published its research priorities in 2012. Uncertainties and research recommendations within UK DUETS cite any relevant and reliable systematic reviews, with the research recommendations mostly being based on the findings from systematic reviews. However, the updating process varies by the source of the record and submissions from individuals have not been reviewed since the original prioritisation meetings.

The records within the NICE database of research recommendations are less likely to be complete; however, there is a structured process for updating the records when the original guidance undergoes review and as a result the recommendations are more likely to be current than some of those within UK DUETS. There is overlap between the UK DUETS and NICE databases.

To be useful, research recommendations need to be sufficiently specific to allow a study to be defined. Despite attempts to ensure that records follows the EPICOT format, records within the UK DUETS database may not have these characteristics, such as the Dementia Priority Setting Partnership recommendation "what are the best ways to care for people from ethnic minority groups with dementia in all care settings?".

In the development of the RARE-Bestpractices database of research recommendations further issues need to be considered, including the inclusion of research recommendations of importance to clinicians, patients and carers and whether a process of prioritisation could be incorporated. We anticipate working closely with experienced teams such as those at NICE, UK DUETS and others to explore these issues.

This study is, to our knowledge, the first to test existing search protocols and resources in order to determine their usefulness and limitations in identifying RD guidelines and research recommendations. It demonstrates that RD guidelines and research recommendations may not be well represented in existing databases and provides evidence that unconventional search techniques may perform better in identifying RD guidelines. The study was conducted as a scoping activity and thus does not reflect a formal systematic review on any of the three selected RD topics, nor did it systematically search for research recommendations databases. Restricting the searches to English language documents clearly limited the retrieval of RD guidelines; future systematic reviews of RD guidelines should consider the potential impact of language restrictions on selection bias.

CONCLUSIONS

The results of our scoping work and test searches demonstrate that existing resources do not allow for rapid or complete identification of relevant RD guidelines and research recommendations, and that dedicated RD resources, tools and methods are therefore necessary. In a climate of scarce resources for RD guideline development and dis-

semination, and given evidence of gaps in RD coverage in existing guideline databases, the creation of new databases dedicated to RD guidelines and research recommendations is called for. The new guidelines database developed within the RARE-Bestpractices project is intended to meet the needs of multiple stakeholders. Clinicians, patients and policymakers will be able to quickly and easily identify relevant guidelines on specific topics without needing to navigate complex interfaces or conduct difficult searches. Guideline developers will be able to demonstrate the need for a particular guideline to funding bodies by demonstrating gaps in current guideline coverage, scope, or quality as recorded in the database. Researchers will be able to use the database to investigate the translation of evidence into guidelines, for example, or for epidemiological research into guideline coverage and quality. Similarly, a research recommendations database will ensure that RD guideline developers, researchers and patient organisations have access to a well-designed platform for disseminating these recommendations. Development of these resources will also entail the further development and testing of effective and innovative search strategies for RD guidelines. Dedicating these resources to RD will help to address the inequality that is potentially exacerbated where higher-prevalence disease guidelines and research recommendations are better resourced, better disseminated and more easily retrieved.

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REFERENCES

1. World Health Organisation (WHO). Guidelines for WHO Guidelines. Geneva: WHO; 2003 [updated 2003; cited 2013 Oct 31]; Available from: http://whqlibdoc.who.int/hq/2003/EIP_GPE_EQC_2003_1.pdf.
2. Beales DL. Beyond Horses to Zebras: Sicca Syndrome. Journal of Hospital Librarianship. 2011;11(4):311-24.
3. Darmoni SJ, Soualmia LF, Letord C, Jaulent M-C, Griffon N, Thirion B, *et al.* Improving information retrieval using Medical Subject Headings Concepts: a test case on rare and chronic diseases. Journal of the Medical Library Association. 2012;100(3):176-83.
4. Dragusin R, Petcu P, Lioma C, Larsen B, Jorgensen HL, Cox IJ, *et al.* FindZebra: A search engine for rare diseases. International Journal of Medical Informatics. 2013;82(6):528-38.
5. Laurent MR, Vickers TJ. Seeking Health Information Online: Does Wikipedia Matter? Journal of the American Medical Informatics Association. 2009;16(4):471-9.
6. Scottish Intercollegiate Guidelines Network (SIGN). SIGN 50: a guideline developer's handbook. Edinburgh: SIGN; 2011 [updated 2011; cited 2013 31 Oct]; Available from: http://www.sign.ac.uk.
7. Orphanet. [cited 2013 31 Oct]; Available from: www.orpha.net.
8. Ramer SL. Site-ation pearl growing: methods and librarianship history and theory. Journal of the Medical Library Association. 2005;93(3):397-400
9. Bondy CA, Turner Syndrome Study G. Clinical practice guideline - Care of girls and women with Turner syndrome: A guideline of the Turner Syndrome Study Group. Journal of Clinical Endocrinology & Metabolism. 2007;92(1):10-25.
10. Saenger P, Wikland KA, Conway GS, Davenport M, Gravholt CH, Hintz R, *et al.* Recommendations for the diagnosis and management of Turner syndrome. Journal of Clinical Endocrinology & Metabolism. 2001;86(7):3061-9.
11. Werther G. Turner Syndrome Management Guidelines Australasian Paediatric Endocrine Group November 2003. [cited 2013 31 Oct]; Available from: http://www.apeg.org.au/portals/0/documents/turner_posstate.pdf.
12. Wolff DJ, Van Dyke DL, Powell CM, Working Grp ALQA. Laboratory guideline for Turner syndrome. Genetics in Medicine. 2010;12(1):52-5.
13. Special Focus: A standard of care for Huntington's disease. Neurodegenerative Disease Management. 2012;2(1).
14. Armstrong MJ, Miyasaki JM, Amer Acad N. 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.
15. Brotherton A, Campos L, Rowell A, Zoia V, Simpson SA, Rae D. Nutritional management of individuals with Huntington's disease: nutritional guidelines. Neurodegenerative Disease Management. 2012;2(1):33-43.
16. Cook C, Page K, Wagstaff A, Simpson SA, Rae D. Development of guidelines for occupational therapy in Huntington's disease. Neurodegenerative Disease Management. 2012;2(1):79-87.
17. Hamilton A, Ferm U, Heemskerk A-W, Twiston-Davies R, Matheson KY, Simpson SA, *et al.* Management of speech, language and communication difficulties in Huntington's disease. Neurodegenerative Disease Management. 2012;2(1):67-77.
18. Hamilton A, Heemskerk A-W, Loucas M, Twiston-Davies R, Matheson KY, Simpson SA, *et al.* Oral feeding in Huntington's disease: a guideline document for speech and language therapists. Neurodegenerative Disease Management. 2012;2(1):45-53.
19. Harbo HF, Finsterer J, Baets J, Van Broeckhoven C, Di Donato S, Fontaine B, *et al.* EFNS guidelines on the molecular diagnosis of neurogenetic disorders: general issues, Huntington's disease, Parkinson's disease and dystonias. European Journal of Neurology. 2009;16(7):777-85.
20. Losekoot M, van Belzen MJ, Seneca S, Bauer P, Stenhouse SAR, Barton DE, *et al.* EMQN/CMGS best practice guidelines for the molecular genetic testing of Huntington disease. European Journal of Human Genetics. 2013;21(5):480-6.
21. Manley G, Lane H, Carlsson A, Ahlborg B, Mårtensson Å, Nilsson MB, *et al.* Guideline for oral healthcare of adults with Huntington's disease. Neurodegenerative Disease Management. 2012;2(1):55-65.
22. Potter NT, Spector EB, Prior TW. American College of Medical Genetics standards and guidelines for clinicals genetics laboratories: Technical Standards and Guidelines for Huntington Disease. 2006 [cited 2013 31 Oct]; Available from: https://www.acmg.net/Pages/ACMG_Activities/stds-2002/HD.htm.
23. Quinn L, Busse M. Physiotherapy clinical guidelines for Huntington's disease. Neurodegenerative Disease Management. 2012;2(1):21-31.
24. Brown P, Brunnhuber K, Chalkidou K, Chalmers I, Clarke M, Fenton M, *et al.* Health research - How to formulate research recommendations. British Medical Journal. 2006;333(7572):804-6.
25. Alonso-Coello P, Irfan A, Sola 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. Quality & Safety in Health Care. 2010;19(6).
26. Grupo de Trabajo sobre Cáncer en Síndromes Genéticos Polimalformativos (GT-CSGP). Síndrome de Costello. 2012 [cited 2013 31 Oct]; Available from: https://www.orpha.net/data/patho/Pro/es/CSGP-Costello-3.pdf.
27. Haute Autorité de Santé. Syndrome de Costello. 2012 [cited 2013 31 Oct]; Available from: https://www.orpha.net/data/patho/Pro/fr/PNDS_syndrome_de_costello.pdf.
28. Benigeri M, Pluye P. Shortcomings of health information on the Internet. Health Promotion International. 2003;18(4):381-6.
29. Nourbakhsh E, Nugent R, Wang H, Cevik C, Nugent K. Medical literature searches: a comparison of PubMed and Google Scholar. Health Information and Libraries Journal. 2012;29(3):214-22.
30. Eysenbach G, Kohler C. How do consumers search for and appraise health information on the world wide web? Qualitative study using focus groups, usability tests, and in-depth interviews. British Medical Journal. 2002;324(7337):573-7.
31. Younger P. Internet-based information-seeking behaviour amongst doctors and nurses: a short review of the literature. Health Information and Libraries Journal. 2010;27(1):2-10.