Deliverable D4.1 - Procedures manual for collection of guidelines and research recommendations

Platform for sharing best practices for management of rare diseases

(*RARE-Bestpractices*)

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Contents

Introduction

The purpose of this document is to set out procedures for collection and processing of documents to be included in the RARE-Bestpractices guideline and research recommendation databases. The points considered here are

- topic selection
- sources
- search strategies
- document management
- data extraction procedures
- future collection development.

Process and procedures for the guideline and research recommendation collections are discussed separately.

Some aspects of the processes described here are dependent on the structure and function of the online database platform; it should be kept in mind that it may be necessary to amend some procedures once the database infrastructure is finalised.

Guidelines database

1. Overview

Guidelines are 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. Healthcare guidelines provide recommendations that describe in detail what the recommended action is and under what circumstances it should be performed.

A key aim of the guidelines database is to enable the discovery of rare disease (RD) guidelines, currently scattered across multiple databases and web sites, via a single point of access. Work programme 4 (WP4) is charged with the retrieval and processing of guideline documents to create a model collection (Deliverables 4.2, 4.3, 4.4).

The retrieval and processing of existing guidelines can be broken down into four separate stages (see figure 1).

Compartmentalisation allows for the generation of four discrete outcomes;

- topics list
- guideline document list
- database content for guideline documents
- AGREEII appraisals for each guideline.

This approach offers an advantage in that one person need not execute all aspects of collection development; WP4 partner contribution can be better matched to existing skill sets and available time, and training requirements can be met more readily. Additionally, although a linear process, there is no requirement for each stage to occur immediately after the preceding step e.g. a guideline document set can be retrieved for a specific condition and then held until such time as resource is available to process the documents for inclusion in the database.

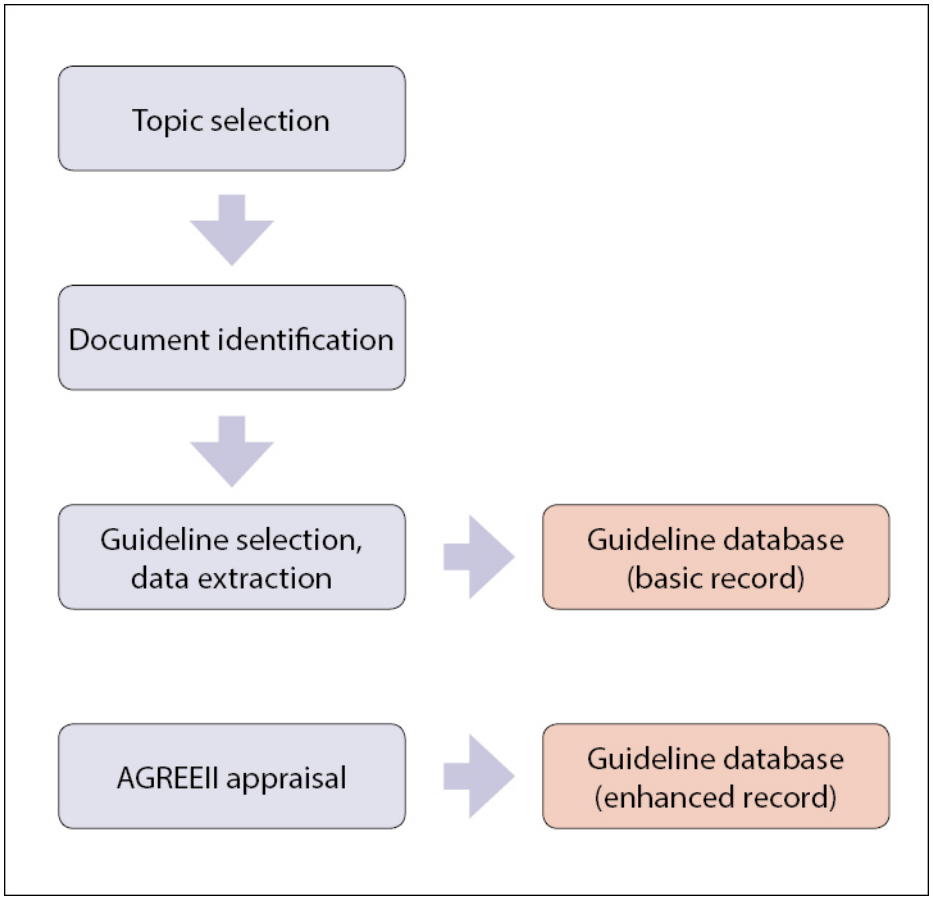

Figure 1 Guideline collection development process

2. Topic selection

2.1. Model collection

There are over 6000 recognised rare conditions; selection of a manageable number of diseases is required to develop the model collection of guidelines.

Several methods have been used to identify conditions which will be included in the initial collection. The number of conditions covered by the model collection shall be dependent on the capacity of WP4 partners.

An initial list of disease topics has been derived from the following sources.

Search protocol development test conditions

A purposive sample of high, medium and low prevalence RDs was identified and used to develop methods for guideline retrieval and processing. These conditions shall be included in the database model collection.

Project partner areas of interest

RARE-Bestpractices partner organisations and advisory board members were invited to nominate disease topics of particular relevance or importance within their respective areas of expertise.

CKS topic suggestions

The National Institute for Health and Care Excellence (NICE) clinical knowledge summaries (CKS)(1) provide up to date summaries of the evidence base for over 300, mostly common, conditions.

In May 2013, a message was submitted to the Oxford Centre for Evidence Based Medicine online mailing list inviting list members to suggest rare conditions for inclusion in the CKS tool. Healthcare Improvement Scotland (HIS) has been able to access the suggestions that followed. This has identified 20 rare diseases, directly identified as priority conditions by the clinical community.

European Academy of Paediatrics (EAP)

EAP members were invited to validate the selection of topics identified from the above sources and to propose additional topics.

EURORDIS Federation

The Council of European Rare Disease Federations was approached to suggest disease topics for inclusion.

The federations comprise national patient organisational networks for a specific disease or groups of diseases. There are currently 41 federations registered with EURORDIS, each of which was asked to nominate one rare condition for inclusion in the database model collection. Where a federation represents more than one specific disease, conditions known to have existing clinical guidelines were to be given priority in order to ensure some population of the database.

Engagement with the patient federations has generated a list of conditions and groups of conditions which represent the interests of existing patient organisations across Europe. In addition, consultation with patient organisations has served to disseminate the activities of RARE-Bestpractices to the wider rare disease community and potentially encourage further collaboration from patient groups. Engagement with the council has been facilitated by EURORDIS.

The list of topics identified for initial inclusion in the guideline database appears in Table 1. Further topics may be added or substituted in the event that RBP stakeholders or members of the rare disease community identify additional conditions of interest.

1.	Addison's disease	23.	Herpes simplex encephalitis
2.	Alstom Disease	24.	Klinefelter's syndrome
3.	Anal atresia	25.	Joint hypermobility syndrome
4.	Aniridia	26.	Huntington's disease
5.	Bardet Biedl Disease	27.	Long QT syndrome
6.	Biliary atresia	28.	Lichen sclerosus
7.	Brucellosis (human)	29.	Hirschsprung's disease
8.	Carcinoid syndrome	30.	Lyme disease
9.	Catastrophic antiphospholipid syndrome	31.	Mitochondrial disease (multiple disorder)
10.	Coarctation of the aorta in the newborn	32.	Multiple myeloma
11.	Congenital anaemias	33.	Myasthenia gravis
12.	Congenital cataract	34.	Noonan syndrome
13.	Congenital myasthenias	35.	Osteosarcoma
14.	Costello syndrome	36.	Paroxysmal nocturnal haemoglobinuria
15.	Cushing's syndrome	37.	Phaeochromocytoma
16.	Cushing's disease	38.	Phenylketonuria
17.	Cystic fibrosis	39.	Porphyrias
18.	Duchenne Muscular Dystrophy	40.	Progressive Subnuclear Palsy
19.	Epidermolysis bullosa	41.	Turner syndrome
20.	Gaucher's disease	42.	Spinal muscular atrophy
21.	Giant cell arteritis	43.	Waldenström Macroglobulinemia
22.	Hereditary Spastic Paraplegia (Strümpell-Lorrain disease)	44.	Wolfram Disease

Table 1. List of topics identified for initial inclusion.

2.2. Disease topic inclusion criteria

Further development of the collection, both within and after the duration of the RARE-Bestpractices project, will allow and encourage clinicians, patients and carers, guideline developers, information professionals or any other interested stakeholder to submit rare disease guidelines for inclusion in the database.

In order to maintain the database as rare disease specific resource, additional topics will be required to meet criteria for a rare disease: all conditions included in the RARE-BestPractices databases must possess an assigned Orpha number* **OR** must be shown to affect fewer than 5 in 10000 persons in Europe**.

** Orpha numbers refer to index numbers associated with the Orphanet(2) classification of rare disease (http://www.orphadata.org/cgi-bin/inc/product3.inc.php). The Orphanet classification system has identified over 6000 conditions as meeting criteria for rare disease status, each of which has been assigned an Orpha Number.*

*** Accepted definition of a rare condition in Europe (3).*

3. Document identification

This stage of the process aims to identify a set of documents for each condition which potentially meet the inclusion criteria for the guideline database.

Publication selection will normally be made on the basis of information provided in document titles and abstracts. The documents identified at this stage will be scrutinised further during the next stage of the process where, after accessing full text, a final decision will be made as to which publications meet the database inclusion criteria.

3.1 Guideline information resources

HIS carried out scoping work to examine the retrieval and yield of known guideline resources; a full explanation is provided elsewhere (4).In summary, guideline information resources currently used in the development of HIS projects were tested for recall and yield using a sample of three rare conditions. The findings demonstrated low yield in all resources but highlighted internet and primary literature searching as being most effective in identifying rare disease guideline documents. On the basis of this scoping work, a short search protocol has been developed.

The resources listed in the protocol (Table 2) do not require member subscription to access basic guideline information. Search techniques required to identify guidelines are relatively straightforward and require minimal knowledge or experience of literature searching. It is intended that the open access and simple searching features of the included resources will facilitate participation of the maximum number and range of partner and stakeholder contributors.

The search for existing rare disease guidelines is intended to be systematic but not exhaustive. The protocol represents the minimum set of resources to be searched for each disease topic. Discovery of documents through references, citations or sign posting (described as ‘pearl growing’) has also been found to be a useful method to locate guidelines (4). Searchers are therefore at liberty to include potentially relevant material sourced out with the listed protocol e.g. from patient organisations. The source of each identified document will be recorded in a standardised search history spreadsheet.

It should be noted that future amendments to the protocol may be considered dependent on feedback from participating stakeholders once topic searches have been rolled out on a larger scale. The procedure manual should be flexible enough to allow changes to address unforeseen barriers to effective and efficient collection creation and development.

Resource	URL
Orphanet	http://www.orpha.net/consor/cgi-bin/Disease.php?lng=EN
G-I-N	http://www.g-i-n.net/
National Guidelines Clearinghouse	http://www.guideline.gov/
EuroGentest molecular testing	http://www.eurogentest.org/index.php?id=700
EuroGentest clinical utility gene cards	http://www.eurogentest.org/index.php?id=668
NICE Evidence Search	http://www.evidence.nhs.uk/
Google (first 100 PDFs)	www.google.com
PubMed	www.http://www.ncbi.nlm.nih.gov/pubmed/

Table 2. Guideline resources to be searched within the protocol.

3.2 Search strategies

Searchers are advised to undertake background reading to familiarise themselves with the topic condition and to identify disease synonyms which can be used as keywords for searching.

A guidance document (see Annex 1 'Guideline searcher instruction manual') providing detailed search and result management techniques relevant to each resource will be made available to stakeholders involved in this part of the process.

Results are reported, by each group involved in the search, in a excel spreadsheet whose template has been prepared by HIS (see Annex 2).

HIS information specialists will provide additional literature search support as necessary throughout the duration of the RARE-Bestpractices project.

3.3 Search results inclusion criteria

The purpose of the search stage of the process is to identify potentially relevant documents based on bibliographic records, abstracts or a brief assessment of the document content. The detailed examination of retrieved documents and application of inclusion criteria form part of the guideline selection and data extraction stage.

Documents retrieved in the searches which clearly do not fit the inclusion criteria (see Table 3) will not be recorded on the search history document. However, the total number of results returned from each resource and duplicate documents will be recorded in order to monitor resource yield and inform possible future amendments to the search protocol.

	Inclusion	Exclusion
Document type	Any document produced by a stakeholder group which is described as a guideline, consensus statement, or best practice statement **AND** contains recommendations* for practice.	Patient information documents. Local (e.g. hospital) care protocols or pathways. Publications produced by individual authors who are not part of a guideline development group.
Year	Published within 10 years	
Language	English, French, Spanish, Dutch, Italian, German	
Topic	Directly relating to the named condition. Guidelines on single interventions for the named condition.	Generic symptom management e.g. dementia management. Reviews of single interventions which do not contain recommendations.
Format	PDF, web document, print document, journal article, eBook	Text books

Table 3. Search results inclusion and exclusion criteria.

** Genetic testing documents may not include recommendations as such. Any testing protocol described as best practice or consensus should be included in the first instance.*

3.4 Results management

Participating searchers will be required to record basic bibliographic details of the resources in order to facilitate full text document retrieval in the next stage of the process.

Searchers will also be asked to record medical coding assigned to the disease, to list all synonyms used to search for guidelines and to detail any additional sources of documents outside of the search protocol.

Full details of required fields and the format of recording are described in the search guidance document (see ‘Guideline searcher instruction manual’).

3.5 Output

The end product of this stage of the collection process will be a single spreadsheet per disease listing all potentially relevant retrieved documents.

4. Guideline selection and data extraction

Participants in this phase of the collection process will be required to access full text versions of the documents identified during searching, decide whether the documents meet the inclusion criteria and extract the data required to populate the database record.

4.1 Accessing full text

Full text access is required to ascertain the suitability of the document for inclusion in the collection and to allow accurate recording of details for the database records. Where full text access requires a subscriber login, WP4 participants may only access resources available to them through their home institution.

Availability of full text documents will be recorded in the search history form. If, for a given topic, the participant cannot access the full text of any document identified, the document will be reallocated to HIS. If the participant can access some but not all full text documents, the participant will create complete records from the available full text. The remaining documents will be noted as ‘full text not accessible’ on the spreadsheet and the reason provided e.g. no subscription access. HIS will periodically collate and reallocate these documents.

4.2 Document selection

Full text documents allow a more accurate assessment of documents against the inclusion criteria (Table 3). HIS and WP4 participants will be available as necessary to provide a second opinion where it is uncertain if a document meets criteria for inclusion in the database.

Reasons for exclusion will be recorded in the search history form.

4.3 Data extraction

A standardised set of bibliographic information, content coverage and methodological details shall be recorded for each document identified as meeting the database inclusion criteria.

4.3.1 Fields of the database

Table 4 illustrates the proposed data fields to be recorded. This includes required fields for standard information available from all documents and optional fields for information which may not be available, e.g. links to other databases, or requires additional resource e.g. AGREEII appraisal.

Specific information	**How it will be used**	**Associated information required**
Citation for guideline (title, author, date, hyperlink etc) (required field)	To retrieve records by keyword To allow users to access fulltext guideline To be exported as part of reference list or as file (Word, EndNote Library)	Fields for data input to match import filters for citation management software/Vancouver reference format
Language (required field)	To allow users to limit searches by language of guideline document	Standard list of international languages
Name of condition(s) covered by guideline (required field)	To search and retrieve records by disease topic To allow browsing by disease topic To index guidelines as they are entered into the database	Controlled vocabulary of disease names. Selection of this will require input from partners. MeSH terms or Orphanet index terms are possibilities. Search by symptom and body system have also been proposed; these would also require controlled vocabularies. Clinical input would be required to index documents by symptom and/or to link the diseases table with the symptoms table.
Clinical coding (required field)	Linked to controlled vocabulary, to allow maximum interoperability and futureproofing	ICD-10, ICD-11, OMIM, SNOMED datasets would need to be stored in tables and linked to the index vocabulary
Document scope (required field)	To give the user an overview of the type of information offered within the guideline.	Content creator should complete the following fields to describe the scope of the guideline. Choose yes/no for each of the following items to indicate whether they are addressed in the guideline. • Diagnostic methods • Drug interventions

		• Non-drug interventions • Rehabilitation • Social care • Economic/costing information Also, each item should have a text box that allows the content creator to provide a brief synopsis of the scope. For two additional fields, 'healthcare settings' and 'healthcare professions' the content creator should be able to select multiple options from a controlled vocabulary.
Document quality – full AGREE II criteria (optional)	To give content creators the option of presenting the results of AGREE II appraisal of the guideline/conformity with AGREE II criteria To give users the option of viewing results of AGREE II appraisal within a guideline record	Content creator should be able to indicate the number of appraisers involved and then to provide a value from 1-7 for 24 items (23 AGREE II criteria and overall rating). There should also be an optional text box for overall comments on guideline quality. OR Guideline developer should be able to enter text or upload a document describing how their methodology conforms to AGREE II criteria
Document methodology – key items (optional)	To give users a snapshot of guideline quality in terms of key areas of risk of bias To give users a quick and easy way to identify better-quality guidance	Content creator should select yes, no or unclear against five criteria: The views and preferences of the target population (patients, public, etc.) have been sought. Systematic methods were used to search for evidence. The strengths and limitations of the body of evidence are clearly described. The methods for formulating the recommendations are clearly described. Competing interests of guideline development group members have been recorded and addressed. Users should be able to limit advanced searches only to guidelines with 'yes' ticked for any or all of the five criteria selected by the user
Supporting information (optional)	Users will be able to access links to additional information relevant to this guideline available from the guideline	External hyperlinks with brief descriptive text, e.g.: Pathway for chronic pain assessment: http://www.ckp.scot.nhs.uk/Published/PathwayViewer.aspx?id=609 Patient booklet:

	developer (e.g. search strategies, development methods and manuals, implementation tools available from the guideline organisation's website)	http://www.sign.ac.uk/pdf/pat136.pdf Search strategy: http://www.sign.ac.uk/pdf/SIGN136_Search_Narrative.pdf Alternatively, the content creator may wish to simply provide a link to the guideline developer's website.
Links to other databases (optional)	Users will be able to access links to records of the same document in National Guidelines Clearinghouse (if available) and Pubmed (if available)	External hyperlinks
Full text (optional)	Subject to permission being granted by the copyright holder, the full text of the guideline or key recommendations may be uploaded to the database	PDF files or large text files/Word documents, provided by the guideline developer Copyright statement relating to the document including permitted uses and contact details of the rights holder (required)

Table 4 Proposed fields for guidelines database

4.3.2 Output

A finalised list of database fields, methods and applications used to record data and methods and applications used to upload records to the database platform will be dependent on the construction of the database infrastructure.

This procedure manual may require to be updated to provide details of method and process to generate database content once the database specification has been finalised.

5. AGREE appraisal

The aim of critical appraisal is to interrogate and describe aspects of how a research output has been produced, in order to understand the strengths and limitations of the output, and to support judgments of confidence in its conclusions/recommendations. The Cochrane Collaboration approach to critical appraisal focuses on risk of bias – those aspects of how a study has been undertaken that can potentially bias the results (for example, blinding and allocation concealment in RCTs). Critical appraisal can be understood as distinct from, but in some ways overlapping with, procedural manuals and standards for reporting. All relate to the diffuse concept of "quality" but refer to different perspectives and audiences. For example, the Cochrane Risk of Bias (5) tool lists 6 criteria for *evaluating* RCTs; the CONSORT statement lists 25 criteria for good quality *reporting* of RCTs (6); and the MSF field research guide lists 39 steps to be followed in *conducting* an RCT (7).

The AGREE II tool is widely used for critical appraisal of guidelines. This tool includes 23 items reflecting six domains of guideline "quality", with varying degrees of relevance to risk of bias. Many of the AGREE II criteria map directly to aspects of GRADE methodology that have been explored, or are being explored, within RARE-Bestpractices, principally within domain 3, rigour of development (e.g. strengths of limitations of evidence; methods of formulating recommendations). Other AGREE II domains and criteria have not yet been explored in depth in our discussions to date, (e.g. stakeholder involvement and editorial independence). The AGREE tool is used internationally for the appraisal of clinical practice guidelines. The tool itself, the accompanying manual, and instructional materials are available from: http://www.agreetrust.org/about-the-agree-enterprise/

WP4 aims to provide, in the database of rare disease guidelines, information about the quality of those guidelines. The use of a critical appraisal tool such as AGREE II involves making a judgment about what degree of quality is achieved by a guideline against various criteria. Making that judgment requires some knowledge as to what degree of quality is achievable, what barriers to quality exist, and how guideline developers can overcome them.

At a workshop facilitated by WP4 in Edinburgh in October 2014 RARE-Bestpractices partners concluded that the AGREEII instrument is appropriate for evaluation of rare disease guidelines but that some additional guidance for those undertaking the appraisals be developed. A summary of the workshop and the additional guidance is available in the project document 'WP4 Guideline Evaluation Workshop October 2014'.

6. Process management

Healthcare Improvement Scotland (HIS) shall co-ordinate the collection development process for the duration of the RARE-Bestpractices project.

HIS will record progress for each condition as it moves through the stages noted in Figure 1. WP4 partners will take ownership of database record production for specific individual conditions. Ideally this will translate to one WP4 partner completing all stages of the process for a specific condition. If this is not possible due to resource limitation or any other factor, the partner will return completed work to HIS and any remaining process stages for that individual condition will be reassigned accordingly.

Methods for uploading records to the guideline database will be determined by the database infrastructure. This procedure manual will be updated to include any additional process management steps required to co-ordinate the input of guideline records to the database once the specification has been finalised.

7. Future collection development

Records will continue to be added to the database for the duration of the project. In the event that the list of conditions identified for the initial collection is exhausted, project partners will be invited to suggest new topics and/or HIS will select further diseases from existing rare disease lists.(2)

Active searching

Database content may continue to be generated following the protocol detailed above. Searching may be carried out by out by any rare disease stakeholder. Resource for the co-ordination of this activity would need to be secured.

Publication alerts

Alerts can be set up and monitored for new rare disease guidelines added to the G-I-N and the National Guideline House guideline databases. Automated search alerts (using a generic rare disease search strategy) can also be implemented for primary literature resources. Resource would be required to monitor and implement alert services.

Research recommendations

8 Overview

A research recommendation (RR) is defined as a statement that describes “the need for further research, and the nature of the further research that would be most desirable” (Cochrane Handbook for Systematic Reviews of Interventions, 2011).

RRs arise from translating gaps or uncertainties in the evidence base for disease prevention, diagnosis or management into specific statements which can be used to prioritise research efforts and resources.

Uncertainties can be identified in different ways. The James Lind Alliance (JLA) http://www.lindalliance.org/, for example, works with patients, carers and clinicians to illicit and then prioritises uncertainties for individual conditions. Guideline developers such as the National Institute for Health and Care Excellence (NICE) and the Scottish Intercollegiate Guideline Network (SIGN) identify uncertainties through the guideline development process.

In both these examples, the uncertainties are said to exist where no up to date and reliable systematic review successfully addresses the issue. JLA undertake a literature search for systematic reviews as part of their methodology in order to validate suggested gaps in the evidence as true uncertainties. NICE and SIGN undertake systematic review of the evidence in order to develop guidelines; uncertainties are identified when there is a lack of evidence or where evidence is conflicting.

Existing definitions of uncertainties reflect the defining role of systematic reviews.

NICE define an uncertainty as “a question that cannot be resolved by reference to reliable and up-to-date systematic reviews of existing research evidence” (https://www.evidence.nhs.uk/evidence-search-content/process-and-methods-manual/nice-data-users-profilefolders-fwilkie-desktop-nhs-evidence-process-and-methods-manual-march-2012.pdf) .

JLA describes a treatment uncertainty as having either “no up-to-date, reliable systematic reviews of research evidence addressing the uncertainty about the effects of treatment or where up-to-date systematic reviews of research evidence show that uncertainty exists”

(http://www.jlaguidebook.org/jla-guidebook.asp?val=10).

The RARE-Bestpractices project will adopt a similar approach, defining an uncertainty as any aspect of disease diagnosis or management where no up-to-date reliable systematic review of the evidence has been carried out or where up-to-date, reliable systematic review of the evidence has identified inadequate or conflicting information to direct effective care.

9 Identification of uncertainties

The RARE-Bestpractices project shall identify uncertainties and corresponding research recommendations from existing high quality systematic reviews.

9.1 Cochrane reviews

It is imperative that uncertainties are gathered only from high quality systematic reviews; low methodological rigour may result in the identification of false uncertainties where further research is not required.

An agreement has been reached with the Cochrane Collaboration which will allow RARE-Bestpractices to reproduce uncertainties identified in published Cochrane reviews on rare conditions. Cochrane reviews are recognised as a gold standard in systematic reviewing. By limiting the model collection to RRs developed from uncertainties identified through Cochrane reviews, database users can be confident that the RARE-Bestpractices research recommendations reflect genuine evidence gaps where investing further research resources would be useful.

A search of the Cochrane Library has been carried out using generic terms for rare disease and keyword terms for the list of diseases identified for the guideline database collection (see section 2.1). NICE identifies a systematic review as being up-to-date when it has been published or updated within the last 2 and half years ((https://www.evidence.nhs.uk/evidence-search-content/process-and-methods-manual/nice-data-users-profilefolders-fwilkie-desktop-nhs-evidence-process-and-methods-manual-march-2012.pdf)) and so search results were limited to reviews published after 2012 . The resulting set of reviews will be used to identify known areas of uncertainty in rare conditions.

The standard format of a Cochrane review requires the authors to make specific comment on the implications of the review for future research. This usually includes a description of any uncertainties identified through the review process and specific advice on what future research should be undertaken to fill these gaps.

RARE-Bestpractices will utilise the ‘implications for research’ sections of the Cochrane reviews to create the research recommendation model collection.

10 Validation and currency of uncertainties

Users of the RARE-BestPractices research recommendation database must be confident that records held within the resource truly represent topics where further research would be of benefit to the rare disease community. This requires that the uncertainties used to develop research recommendations have been validated and also that new or ongoing research carried out after or in response to a published research recommendation is identified; these studies may potentially provide evidence to remove uncertainty. Identifying ongoing studies can additionally help to prioritise research initiatives; uncertainties which already have studies underway may be thought of as lower priority in terms of research need.(8)

10.1 Validation

Uncertainties and corresponding research recommendations identified in published Cochrane reviews shall not undergo any further validation due to the high methodological quality of the Cochrane review process.

10.2 Currency

The model collection shall consist of research recommendations from Cochrane reviews published in or after 2012, falling within the NICE criteria for current systematic reviews ((https://www.evidence.nhs.uk/evidence-search-content/process-and-methods-manual/nice-data-users-profilefolders-fwilkie-desktop-nhs-evidence-process-and-methods-manual-march-2012.pdf)).

It is proposed that the database will automatically generate a notice to appear in database records when the systematic review used to generate a research recommendation becomes over 30 months old and therefore may no longer be current. The implementation of this feature will form part of the ongoing discussion between HIS and Jamarau regarding database development and functionality.

10.3 Ongoing studies

The Cochrane Handbook recommends that review authors identify ongoing trials as part of the review development process (Handbook pt2 section 6.2.3 http://handbook.cochrane.org/). However, methods and reporting of ongoing studies in completed reviews appear to be inconsistent and so further searching will be

carried out for each research recommendation database entry as part of the RBP process.

Multiple resources are available to identify ongoing clinical studies and research. For example, The Cochrane Handbook provides a list of over 20 potential trial registries (Handbook pt2 section 6.2.3.1 http://handbook.cochrane.org/) and the University of York 'Searching for Clinical Trials' website sign posts over 30 trial, registry and research resources (https://sites.google.com/a/york.ac.uk/yhectrialsregisters/home).

In order to keep the process manageable, only the two largest sources of registered trials shall be searched to identify ongoing studies for the database:

- World Health Organization International Clinical Trials Registry Platform (WHOICTRP)
- ClinicalTrials.gov

WHOICTP is a central database holding records from multiple individual trail registries from around the world; a full list of included resources can be found on the WHOICTP webpage http://apps.who.int/trialsearch/Default.aspx

ClinicalTrials.gov is an international registry which invites researchers to register their work. The site receives over 300 new submissions per week (Zarin et al http://www.ncbi.nlm.nih.gov/pubmed/21366476). Although ClinicalTrials.gov is listed as contributing resource for the WHOICTP, it is recognised that the search functionalities in each database mean that search results can differ; so both resources should be searched.

Ongoing studies which replicate the inclusion criteria of studies in each Cochrane review will be identified and listed in the research recommendation database record entry.

11 Format of research recommendations and database records.

As noted above, research recommendations are a product of translating uncertainties into proposals for future research. In order to avoid vague or general research recommendations which may be difficult to implement, it is suggested that the reporting of RRs follows the EPICOT format (9)

E What comprises the Evidence?

P What is the Population of interest?

I What are the Interventions of interest?

C What are the Comparisons of interest?

O What are the Outcomes of interest?

T Time stamp (date of recommendations).

Table 5 below describes in detail the fields to be captured in each record of the RR database. The information specified fully captures all elements of the EPICOT research recommendation format.HIS will continue to work with Jamarau to develop the database format in order to incorporate this information.

Specific information	How it will be used	Associated information
Record title	To provide a title for the record that will appear in search results or browsing lists To allow users to search by keyword To allow users to quickly judge the relevance of the record to their information need	This is a short title for the description of the research recommendation. For example: 'Duration of physiotherapy for cystic fibrosis'; 'Effectiveness of gluten-free diet for 9p deletion syndrome'
Citation and URL of source of research recommendation (if publication)	To allow users to view the source information directly within its original context	
Citation of systematic review which verifies the uncertainty	To demonstrate that the uncertainty stems from a systematic review of the literature	Citation needs to be given in Vancouver style and include the Digital Object Identifier (DOI) or database identifier (PMID) where possible.
Citation to protocol of any ongoing systematic review which may resolve the uncertainty	To assist the updating of the uncertainty	Citation needs to be given in Vancouver style and include the Digital Object Identifier (DOI) or database identifier (PMID) where possible.

Citation to any ongoing primary studies which might address the uncertainty	To assist the updating of the uncertainty To allow clinicians and patients to identify ongoing trials	Give the title of the study and either clinical trials.gov reference id or ISRCTN reference number, or website URL.
Disease topic / Health care condition	To allow searching and browsing of uncertainties	To list the relevant health care condition (broader category and specific disease name) from the controlled vocabulary lists
Intervention	To promote structured reporting of uncertainties To facilitate design of studies that would resolve the uncertainty	To list the intervention to be investigated against using the controlled vocabulary list. It should be possible to see a list of possible matches while inputting text into the field, and to add new terms to the list from the input field.
Comparator	To promote structured reporting of uncertainties To facilitate design of studies that would resolve the uncertainty	To list the comparator the intervention should be compared against using the controlled vocabulary list. It should be possible to see a list of possible matches while inputting text into the field, and to add new terms to the list from the input field.
Outcome(s)	To promote structured reporting of uncertainties To facilitate design of studies that would resolve the uncertainty	List the outcome(s) of interest for the research question.
Age group of population	To promote structured reporting of uncertainties To facilitate design of studies	Identify the age of patients/population from the controlled vocabulary list.

	that would resolve the uncertainty	
Date of last update	To ensure clarity on the current status of the uncertainty	Enter the last date on which searches were conducted for systematic reviews and primary studies that could resolve the uncertainty.

Table 5 Proposed fields for research recommendations database

References

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