RB-Del. 4.3

Collection and evaluation of existing guidelines and research recommendations #2

Platform for sharing best practices for management of rare diseases

(*RARE-Bestpractices*)

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1. Guideline collection 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

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.

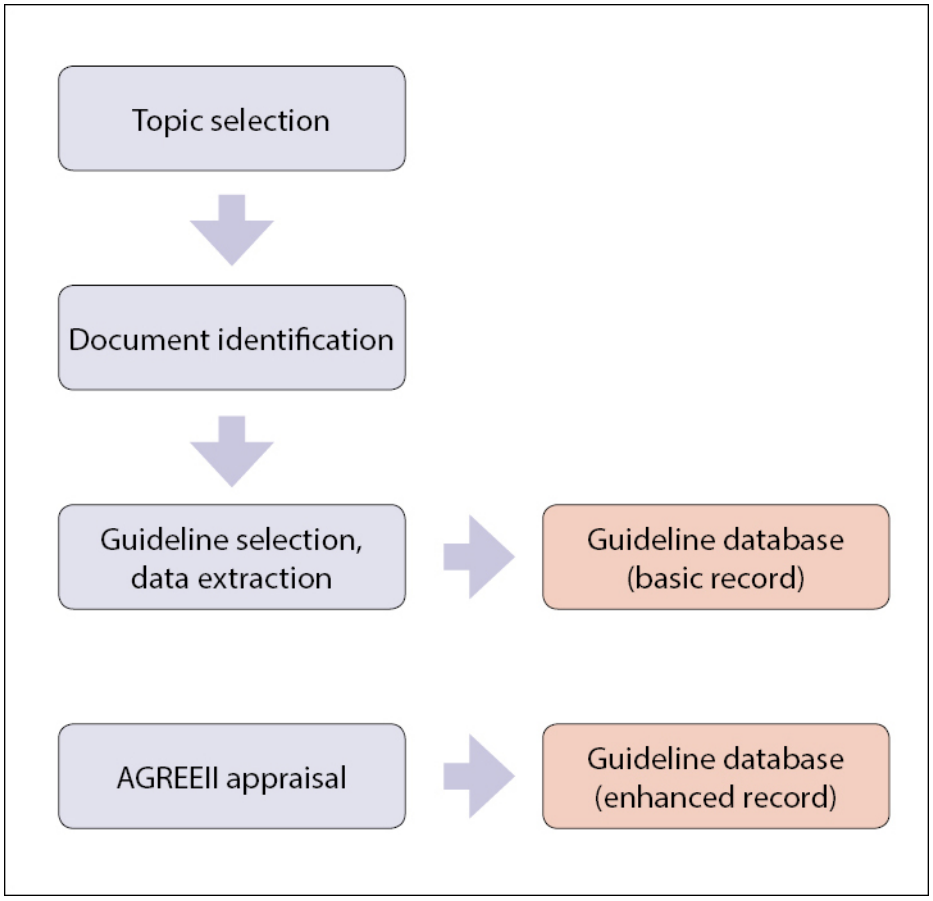

Fig 1 Guideline collection development process

1.1 Topic selection

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) 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 identified 20 rare diseases 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.

Individual participant areas of interests
Subsequent training courses run as part of WP6 have resulted in additional conditions being included in the model collection as a result of individual participant areas of interest.

Deliverable 4.1 presents the procedure manual for collection of guidelines and research recommendations.

1.2 Database development

Concurrent with the development of the collection (i.e., identifying and appraising documents for inclusion in the database) has been the database infrastructure development. The HIS team has provided feedback to the database developer on the usability of the administrator interface as the documents have been lodged within the database. The team has also provided feedback on the look and feel of the database from a user perspective. Details will be provided in Deliverables 2.2. and 2.3 when these are available.

The use of a taxonomy for management of the records has been explored but no existing classification method has yet been agreed upon. Meantime, guidelines will be listed on the basis of the condition of interest only and not grouped with other diseases.

1.3 Progress with collection building at December 2015

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.

To date searches have been conducted to identify guidelines in 24 rare diseases (marked * in Table 1). Work is ongoing with partners across the consortium to quality appraise each of these prior to their submission to the online collection which now has 11 rare diseases represented:

Addison's disease	Herpes simplex encephalitis
Alstom Disease*	Klinefelter's syndrome*
Anal atresia	Joint hypermobility syndrome
Aniridia*	Huntington's disease
Bardet Biedl Disease*	Long QT syndrome
Biliary atresia	Lichen sclerosus
Brucellosis (human)	Hirschsprung's disease
Carcinoid syndrome	Lyme disease*
Catastrophic antiphospholipid syndrome*	Mitochondrial disease (multiple disorder)*
Coarctation of the aorta in the newborn*	Multiple myeloma
Congenital anaemias*	Myasthenia gravis*
Congenital cataract	Noonan syndrome
Congenital myasthenias*	Osteosarcoma*
Costello syndrome*	Paroxysmal nocturnal haemoglobinuria
Cushing's syndrome	Phaeochromocytoma
Cushing's disease	Phenylketonuria*
Cystic fibrosis*	Porphyrias*
Duchenne Muscular Dystrophy*	Progressive Subnuclear Palsy
Epidermolysis bullosa*	Spinal muscular atrophy*
Gaucher's disease*	Turner syndrome*
Giant cell arteritis	Waldenström Macroglobulinemia*
Hereditary Spastic Paraplegia (Strümpell-Lorrain disease)*	Wolfram Disease*

*Table 1. List of topics identified for initial inclusion. Topic searched for at December 2015 marked **

1.4 Example of guideline presentation

The following screenshots (Figs 2-10) provide examples of how a guideline for a condition can be accessed and the information viewed within the database.

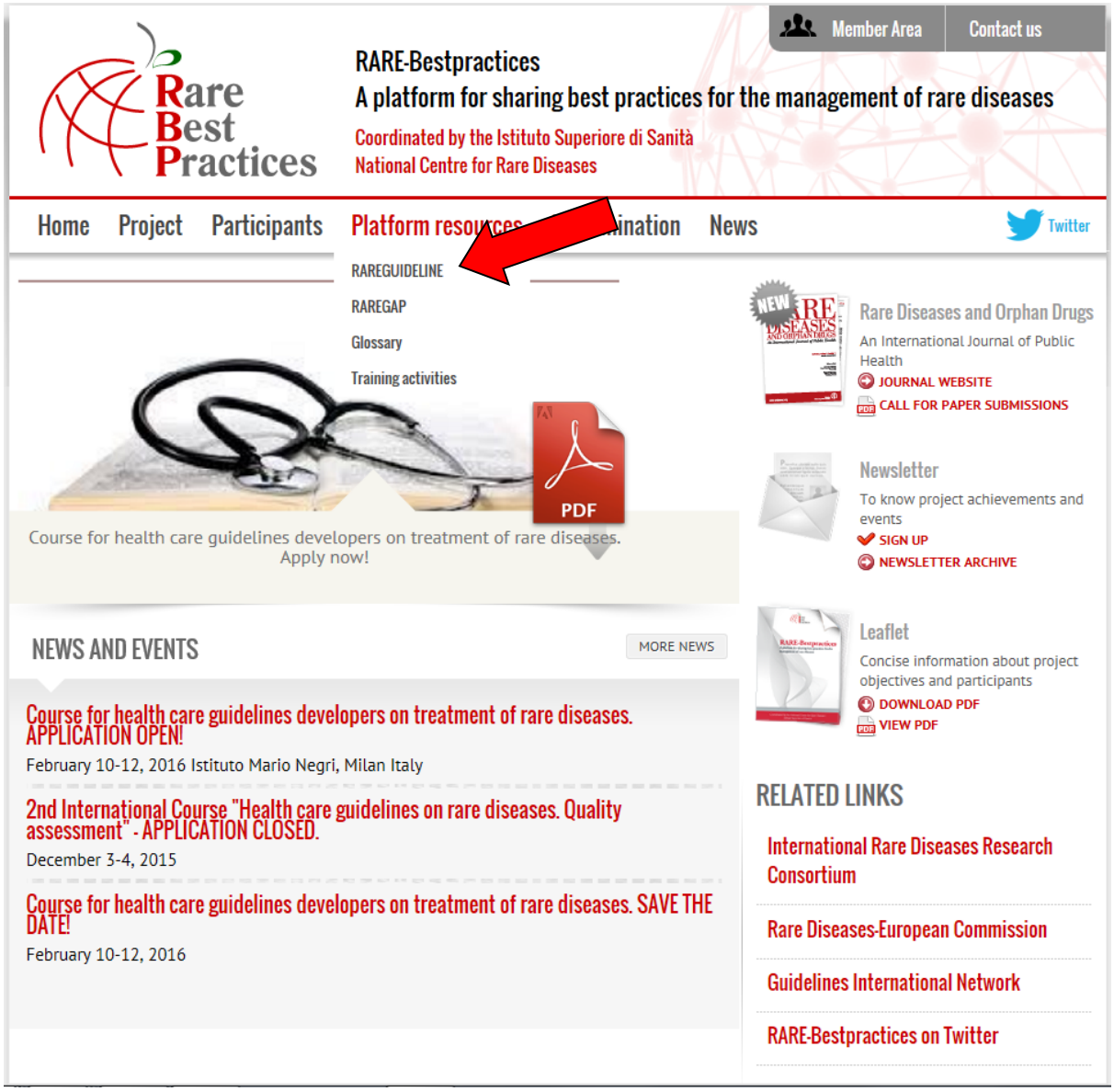

Fig 2 Screenshot of access to the database via the RARE-Bestpractices website homepage

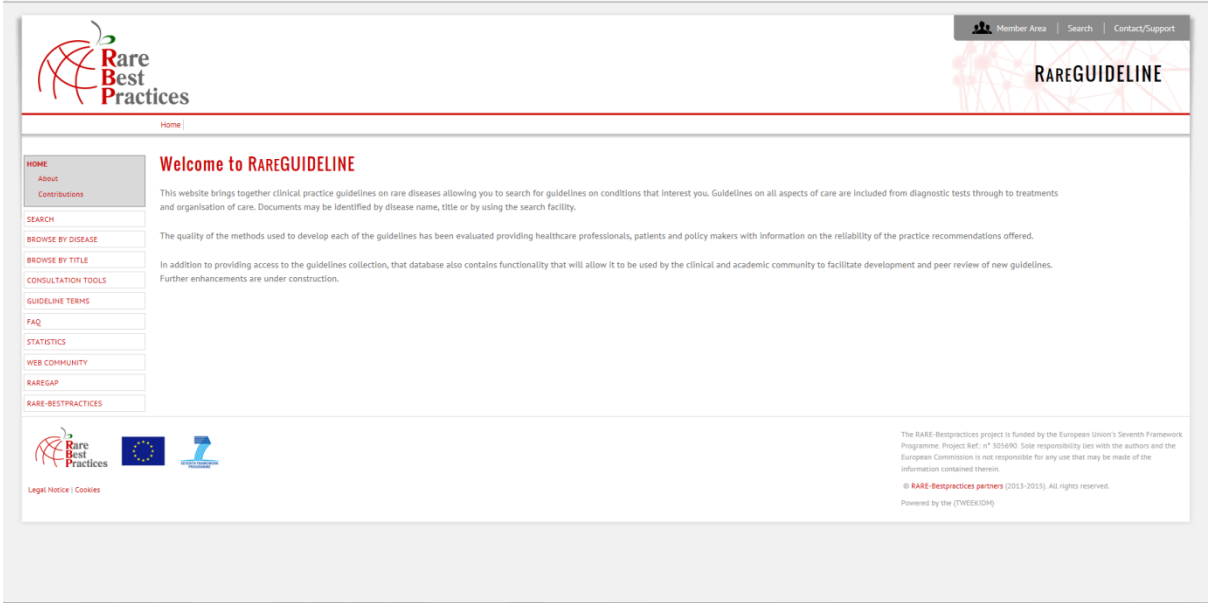

Fig 3 Screenshot of RAREGUIDELINE homepage

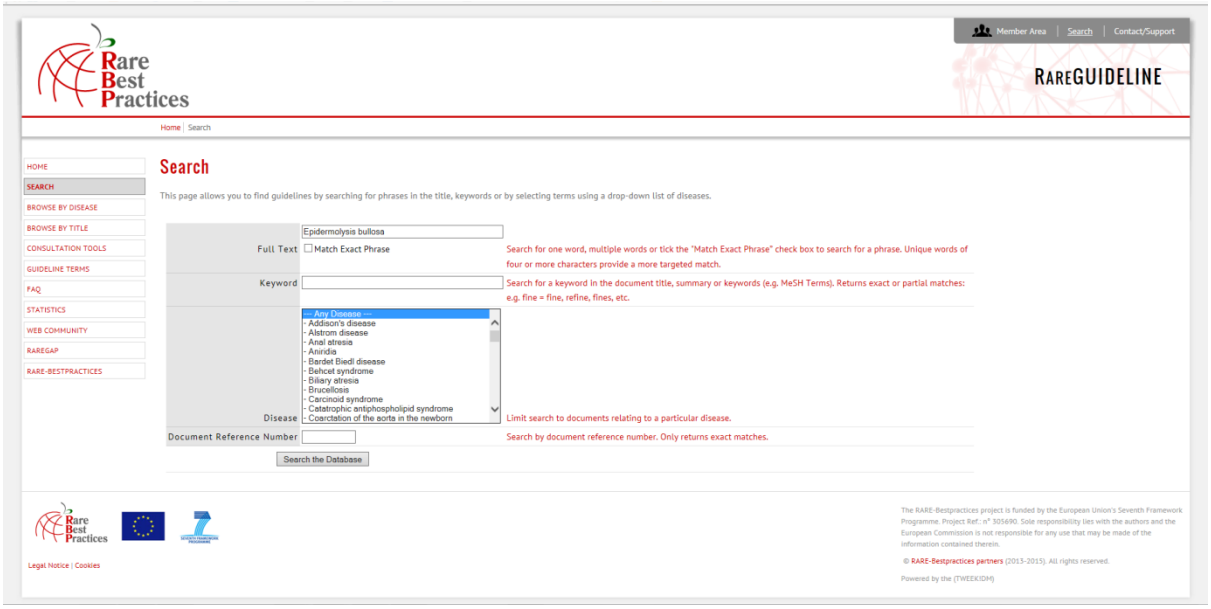

Fig 4 Screenshot of Search page

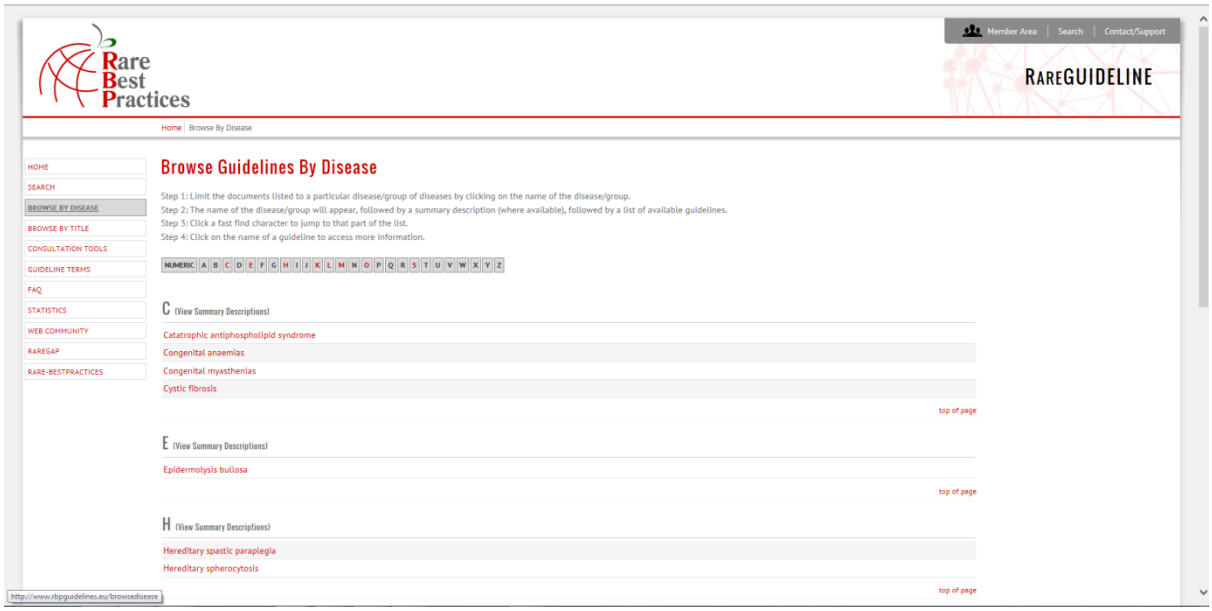

Fig 5 Screenshot of Browse by Disease page

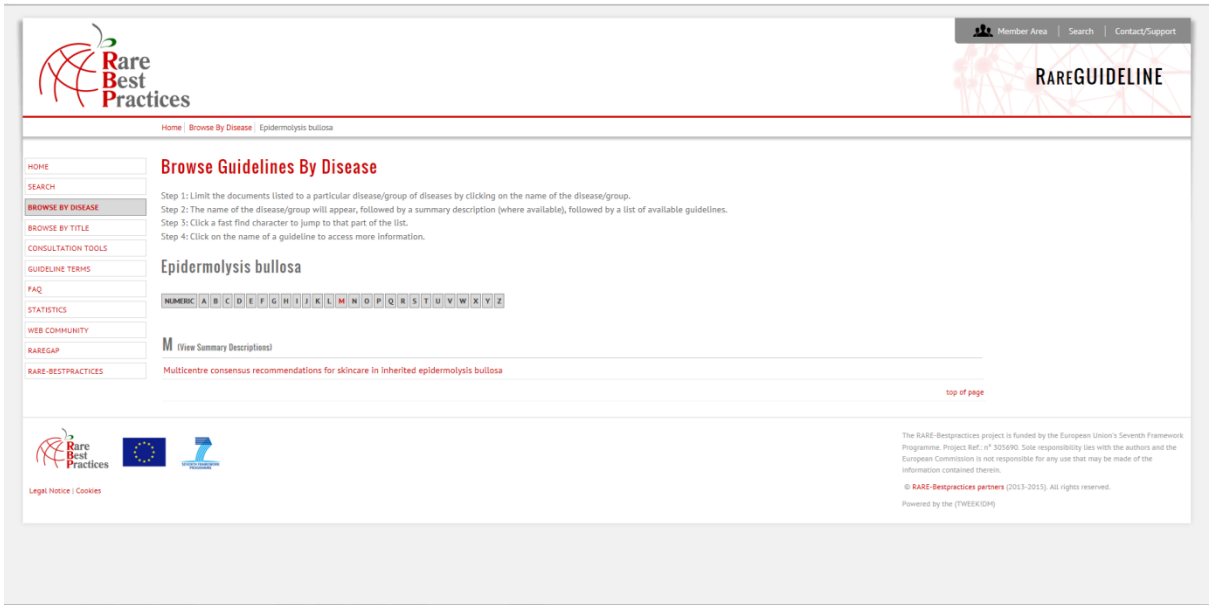

Fig 6 Screenshot of Epidermolysis bullosa disease page

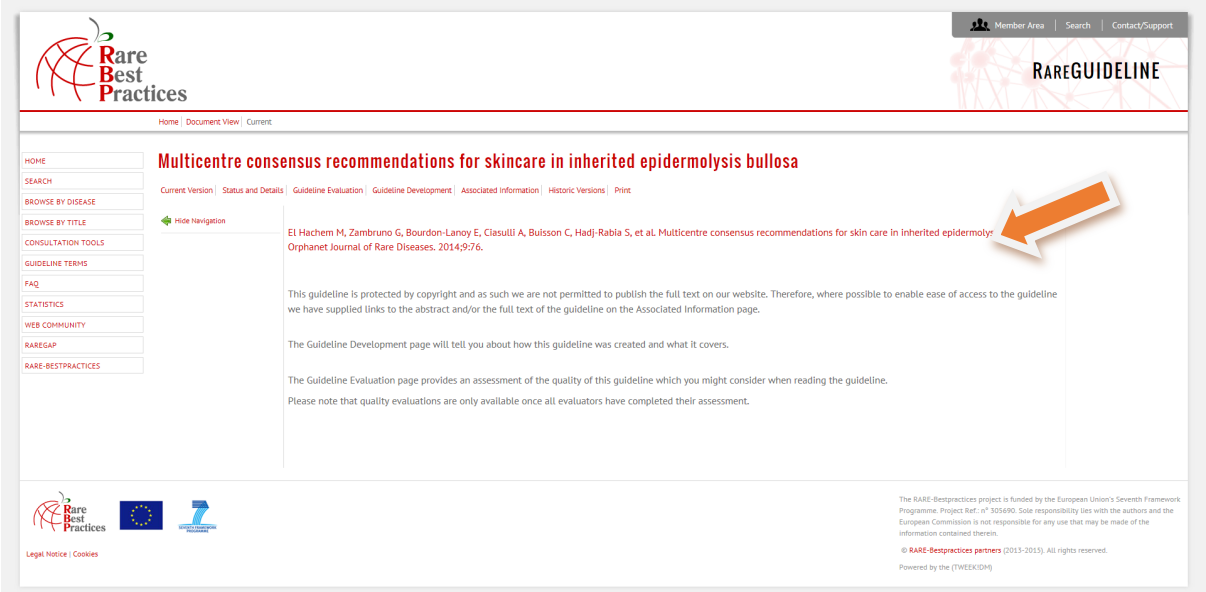

Fig 7 Screenshot of guideline record with link to full text highlighted

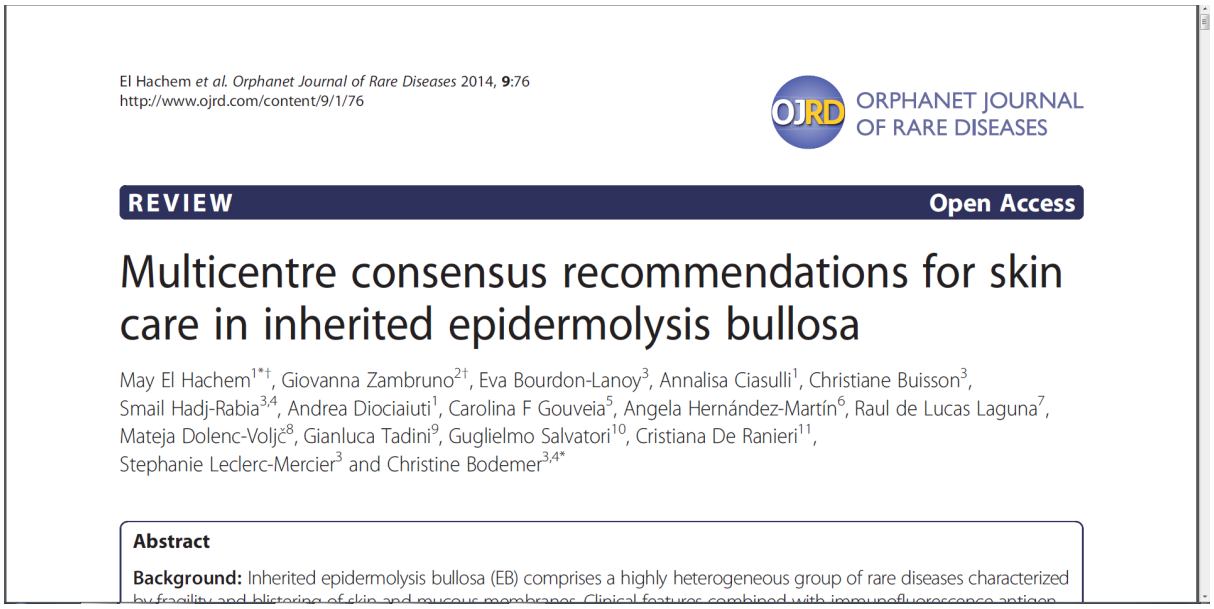

Fig 8 Screenshot pdf of full text guideline

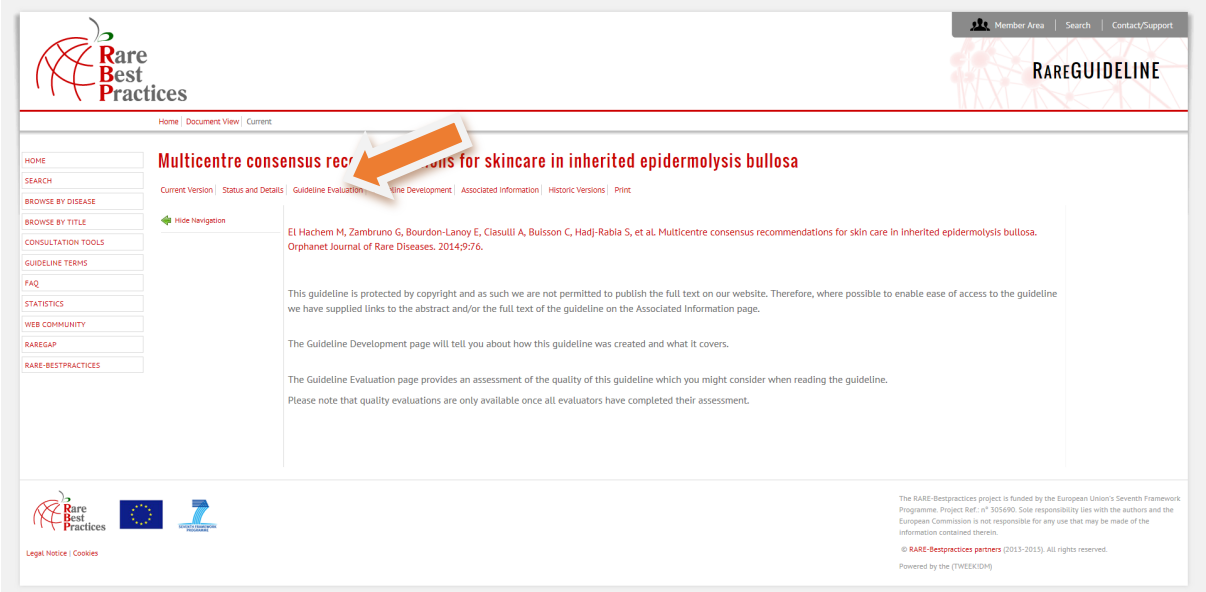

Fig 9 Screenshot of guideline record with link to guideline evaluation highlighted

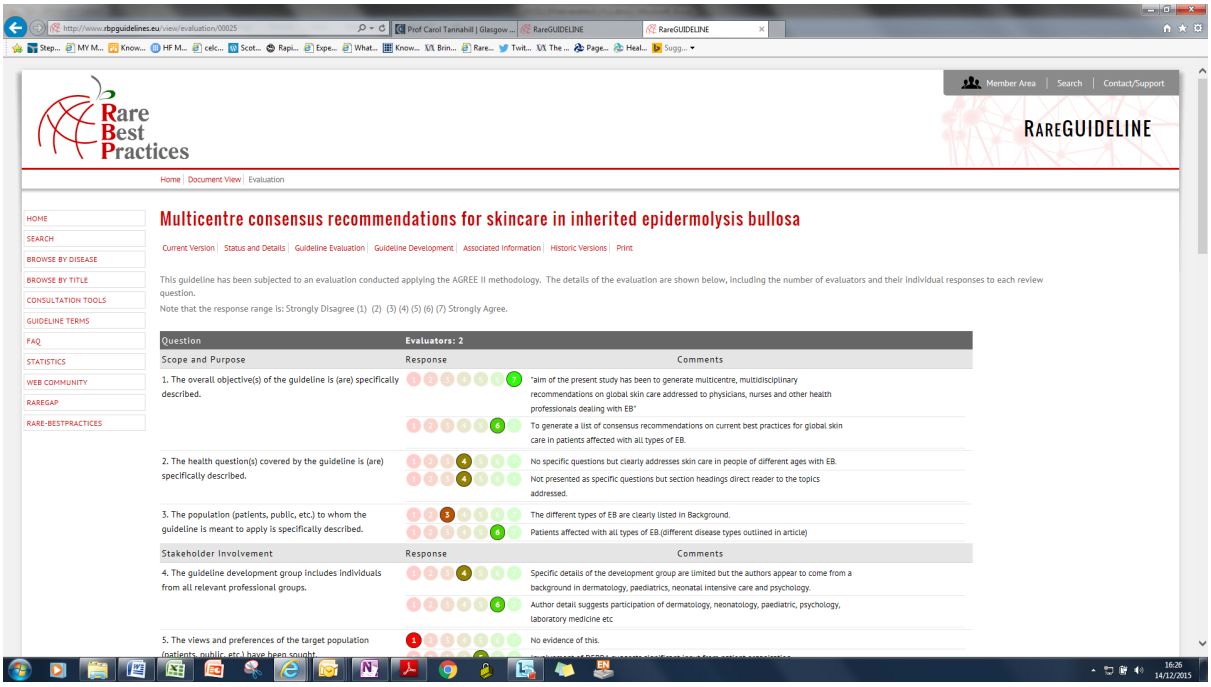

Fig 10 Screenshot of guideline evaluation page

2. Research Recommendations Database

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

Following agreement with the Cochrane Collaboration, searches of the Cochrane Library have 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 1.1). 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-methodsmanual/nice-data-users-profilefolders-fwilkie-desktop-nhs-evidence-process-andmethods-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. Full details of the rationale and process are provided in Deliverable 4.1

2.1 Structure of the research recommendations database

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, therefore the reporting of RRs follows the EPICOT format as described in Deliverable 4.1

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).

2.2 Research recommendations collection

To date 38 research recommendations have been identified from Cochrane systematic reviews and submitted to the RAREGAP data base.

Table 2 shows the disease areas for which research recommendations were identified and the number of research recommendations for each of these disease areas.

Disease	Number of recommendations
Behcet syndrome	2
Congenital toxoplasmosis	1
Cystic fibrosis	3
Dravet syndrome	1

Duchenne Muscular Dystrophy	1
Gaucher's disease	1
Guillain-Barre syndrome	1
Hodgkin Lymphoma	2
Homocystinuria	1
Hunter syndrome	1
Hyperthyroidism (in pregnancy)	1
Kleine-Levin syndrome	1
Lymphoma	1
Multifocal motor neurpathy	1
Multiple sclerosis	9
Myasthenia gravis	1
Myasthenias	1
Neuroblastoma	1
Ovarian carcinoma	1
Paget disease	1
Paroxysmal haemoglobinuria	1
Phenylketonuria	3
Primary nervous system lymphoma	1
Thymoma	1

Table 2 Research recommendations submitted to the RAREGap database

2.3 Example of Research Recommendation presentation

The following screenshots (Figs 11-15) provide examples of how research recommendations can be accessed and the information viewed within the database.

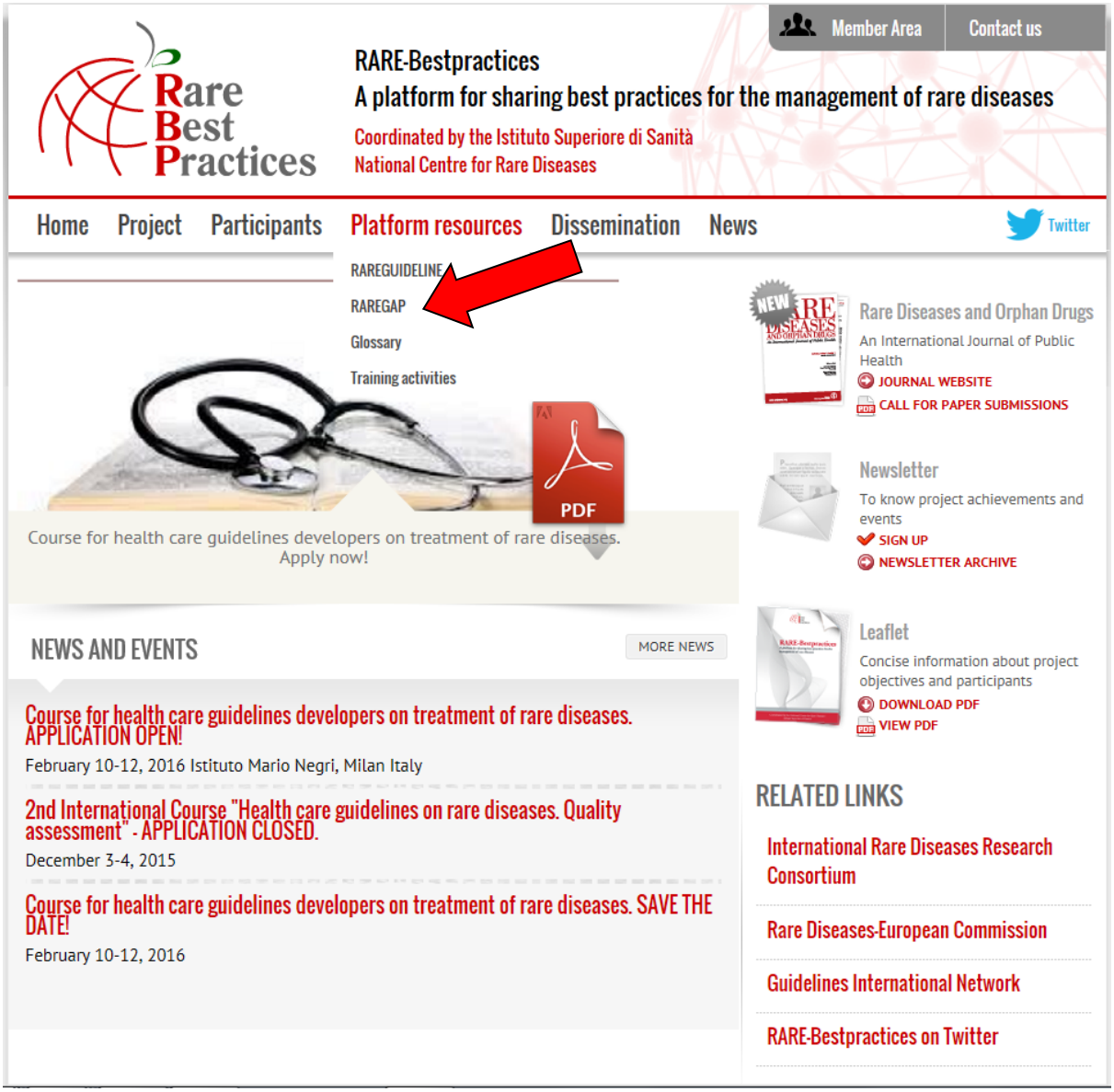

Fig 11 Screenshot of access to the database via the RARE-Bestpractices website homepage

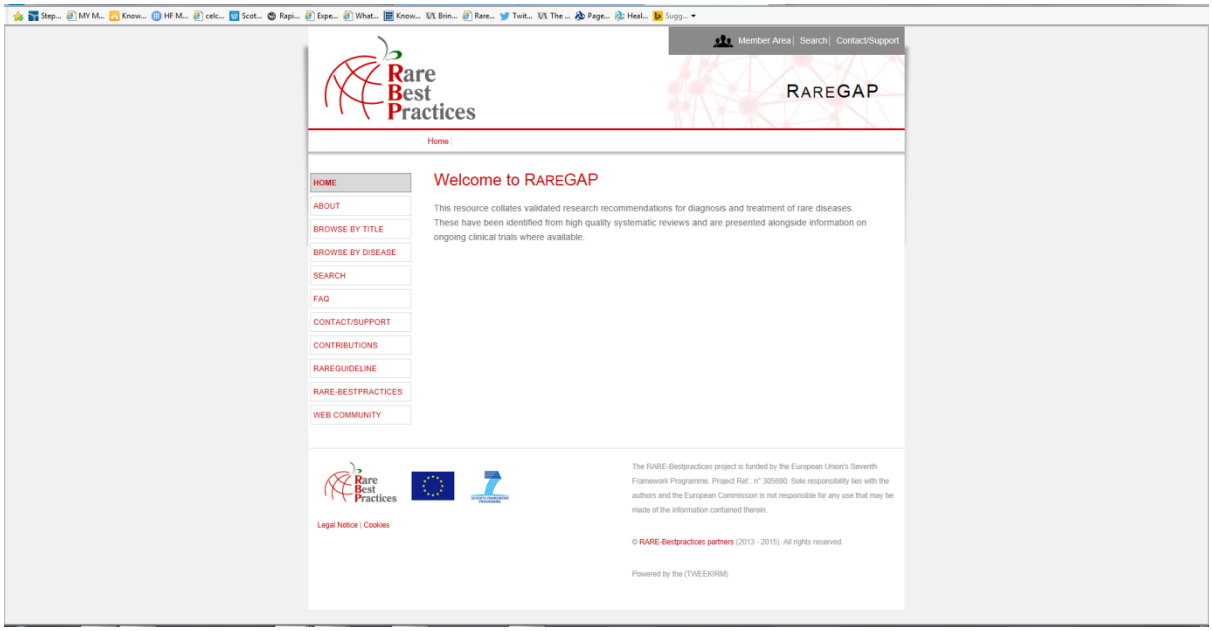

Fig 12 Screenshot of RAREGAP homepage

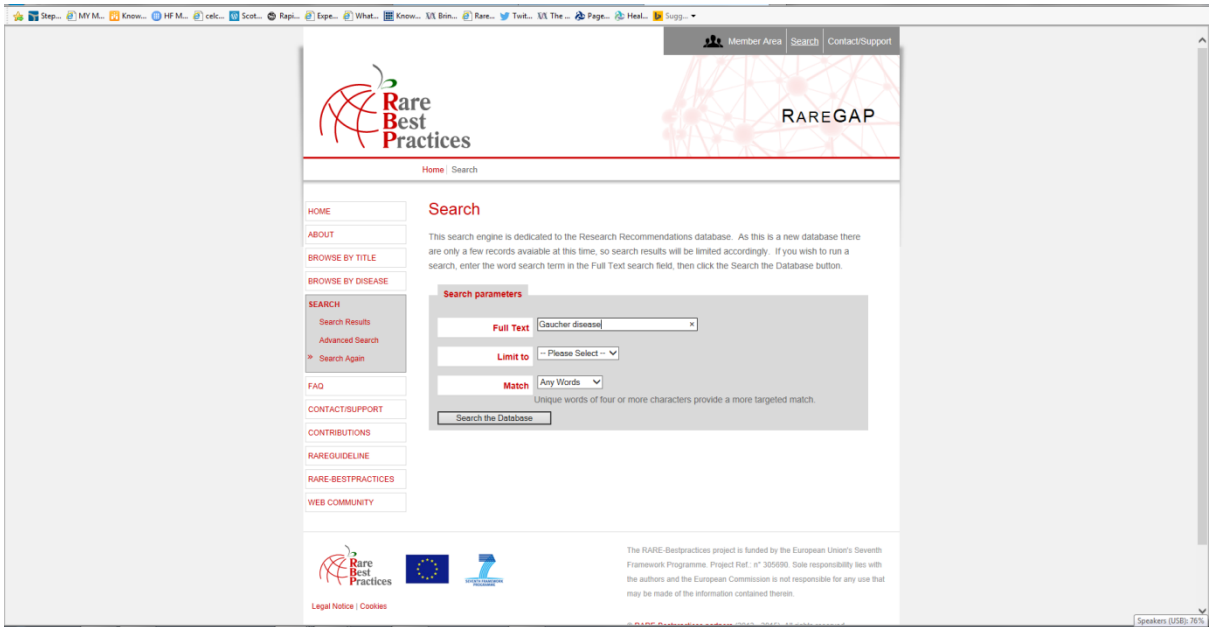

Fig 13 Screenshot of RAREGAP search page

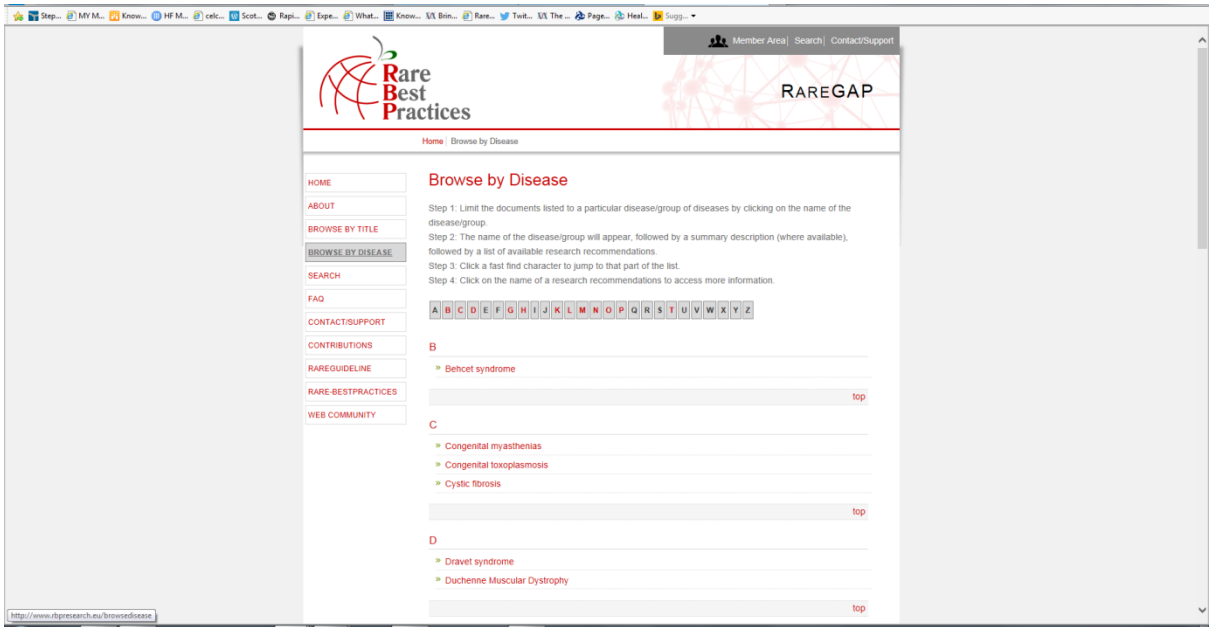

Fig 14 Screenshot of Browse by Disease page

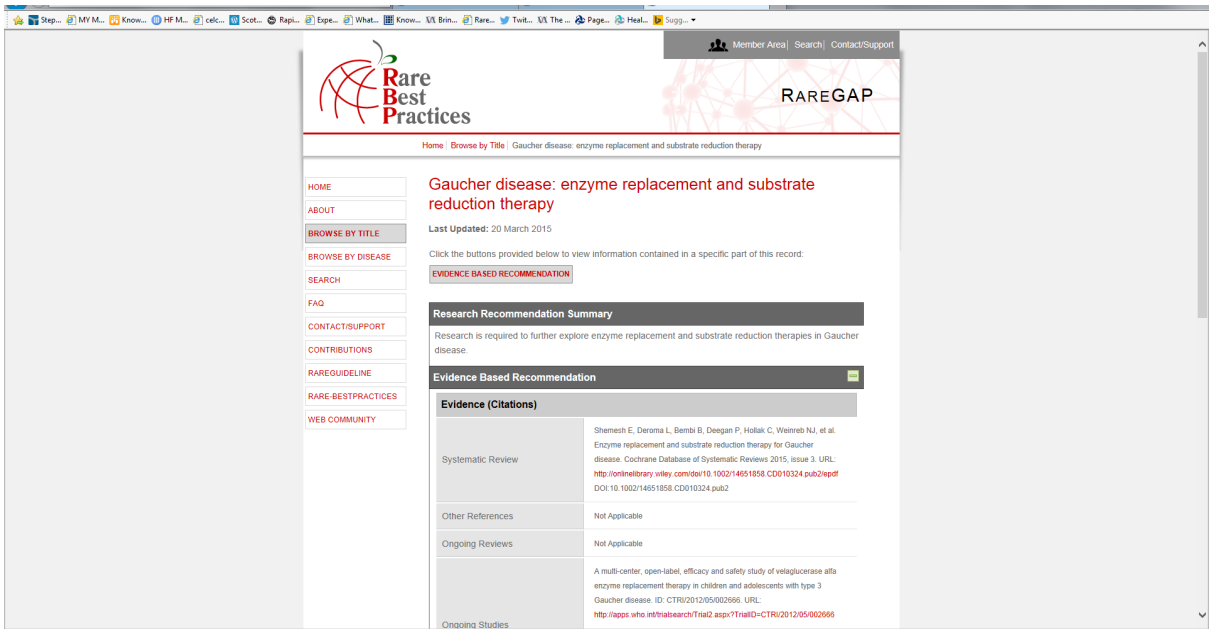

Fig 15 Screenshot of research recommendation