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Procedural document: Creation and Update of Disease Summary Texts in English for the Orphanet Encyclopedia for Professionals

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I. Introduction

1. Purpose/objectives

For patients affected by a rare disease, obtaining a timely and accurate diagnosis is key to accessing the appropriate medical expertise. Textual information, primarily intended for healthcare professionals, is provided for the disorders in the Orphanet encyclopedia for professionals. The information provided is clinically orientated, impartial and objective, and is reviewed either by an expert reviewer (abstracts) or a medical doctor (definitions).
This document aims to outline the Orphanet procedure for the creation or update of disease summary texts.

2. Disclaimer

- This publication is part of the project ORPHANETWORK DIRECT GRANT which has received funding from the European Union's Health Program (2014-2020).
- The content of this publication represents the views of the author only and is his/her sole responsibility; it cannot be considered to reflect the views of the European Commission and/or the Consumers, Health, Agriculture and Food Executive Agency or any other body of the European Union. The European Commission and the Agency do not accept any responsibility for use that may be made of the information it contains.
- The information provided by Orphanet in the disease summary texts is based on published scientific articles, but may not apply to specific cases due to the extensive variability of disease expression. Given the rarity of these diseases, the treatments outlined in the abstracts are not always evidence based. The provided information is not intended to replace existing local, regional or country specific recommendations and guidelines. Certain information may be shocking to some readers. It is of the utmost importance to check if the provided information is relevant or not to a specific case.

- Information found on the Orphanet website is updated and translated on a regular basis. Where there is a delay in text translation, users are directed towards the most recent version in English. It may happen that new discoveries are made in between updates and these do not yet appear in the disease profile. The date of the last update of the disease summary text is always indicated. Professionals are always encouraged to consult the most recent publications before making any decisions based on the information provided.
- Orphanet cannot be held responsible for harmful, truncated or erroneous use of any information found in the Orphanet database.

3. Range of application

This procedure concerns all Orphanet team members and external parties, not least European Reference Networks (ERNs), involved in the creation and update of disease summary texts for the Orphanet Encyclopedia for Professionals. The present procedure applies to all disorder level entities of the Orphanet database.

4. References

Orphanet Standard Operating Procedures: Provides Orphanet teams with general information related to the Orphanet mission.
Rare disease nomenclature in English: Outlines the rules for establishing or changing disease nomenclature.
Procedural document: Translation of the Disease Summary Texts of the Orphanet Encyclopedia for Professionals: Outlines the Orphanet procedure for the translation of disease summary texts.
Epidemiology of rare diseases procedure: Describes the collection, analysis and validation of epidemiological data related to rare diseases integrated into the Orphanet database
Inventory of genes related to rare diseases: Describes how the Orphanet inventory of genes related to rare disorders is maintained and updated.
Pubmed – NCBI: Bibliographical research (content related)
GeneReviews®: reviews on genetic diseases
OMIM (Online Mendelian Inheritance in Man): Online Catalog of Human Genes and Genetic Disorders
RARECARE Net: Information on rare cancers
Neuromuscular Disease Center : Information on neuromuscular diseases
DermNet New Zealand : Information on dermatological diseases
UpToDate : Expert information on medical diseases
HGNC (HUGO Gene Nomenclature Committee): Gene nomenclature and locus information
UniProt : Protein nomenclature information
Human Phenotype Ontology (HPO): Clinical signs nomenclature

5. Definitions

Abstract: Texts composed of up to 10 of the following sections: disease definition, epidemiology, clinical description, aetiology, diagnostic methods, differential diagnosis, antenatal diagnosis (if relevant), genetic counselling (if relevant), management and treatment, and prognosis.

Disease definition: A short text stating the group of disorders that the clinical entity belongs to, and listing the major clinical characteristics (e.g. clinical, pathological, radiological, etc.) that define the entity and differentiate it from other entities classified within the same clinical group.

Data transfer agreement: Contract between the data provider and recipient institutions governing legal obligations and restrictions, as well as compliance with applicable laws and regulations, related to the transfer of such data between the parties.

Editorial assistant (EA): Person responsible for the follow-up of exchanges between the Orphanet medical writers and the external expert reviewers as well as for the publication of the validated disease summary texts on the Orphanet website.

Editorial coordinator (EC): Person responsible for prioritizing the diseases summaries text to be written or updated as well as coordinating all editorial activities of the Orphanet medical writers and medical validators across the Orphanet countries.

European Reference Networks (ERNs): Virtual networks involving healthcare providers across

Europe that aim to tackle complex or rare diseases and conditions that require highly specialised treatment and a concentration of knowledge and resources[1]

Expert (Expert reviewer, ExR): A medical doctor or researcher with prominent clinical experience in a rare disease or a group of rare diseases, and identified by Orphanet based on published articles (particularly reviews and guidelines), involvement in expert centers, expert networks, and/or in dedicated research activities including clinical trials.

Historical entity: A clinical entity for which no new information has been published in the literature since the advent of the genetic era in the 1990s, but is considered as a distinct phenotype and is therefore kept in the nomenclature.

Information scientist: Member of the Orphanet team with a scientific and/or medical background in charge of collecting, producing and updating information provided in the Orphanet database.

Orphadata: A platform developed by Orphanet to provide the scientific community with comprehensive, high-quality and freely accessible datasets related to rare diseases and orphan drugs, in a reusable format.

Orphanet knowledge base (Orphanet database): Orphanet is the International Rare Diseases and Orphan Drugs knowledge base, an organised and dynamic collection of information about rare diseases and orphan drugs where data from multiple sources are archived, reviewed, distilled and manually annotated by experts and quality controlled according to published procedures.

Orphanet medical reviewer (OMR): Member of the Editorial team responsible for assuring and validating the editorial and medical consistency of the disease definitions.

Orphanet medical writer (MW): Information scientist, responsible for producing and/or curating, the disease summary texts.

Orphanet network national teams: An Orphanet team based in one of the member countries of the Orphanet Network as per the Orphanet Network Agreement, and responsible for the collection of data on national expert resources. Some of the national teams are also in charge of the translation of the Orphanet nomenclature and/or the Orphanet database.

Orphanet Rare Disease Ontology (ORDO): An open access, structured, and machine-readable vocabulary for rare diseases derived from the Orphanet database, capturing relationships between diseases, genes and other relevant features, and forming a useful resource for the computational analysis of rare diseases. ORDO was jointly developed by Orphanet and the European Bioinformatics Institute (EMBL-EBI).

6. Filing and updates

This procedure is updated by a medical writer as often as necessary and at least once per year.

[1] from European Reference Network handout, ISBN 978-92-79-65469-5

II. METHODOLOGY for the production of definitions

1. Flowchart

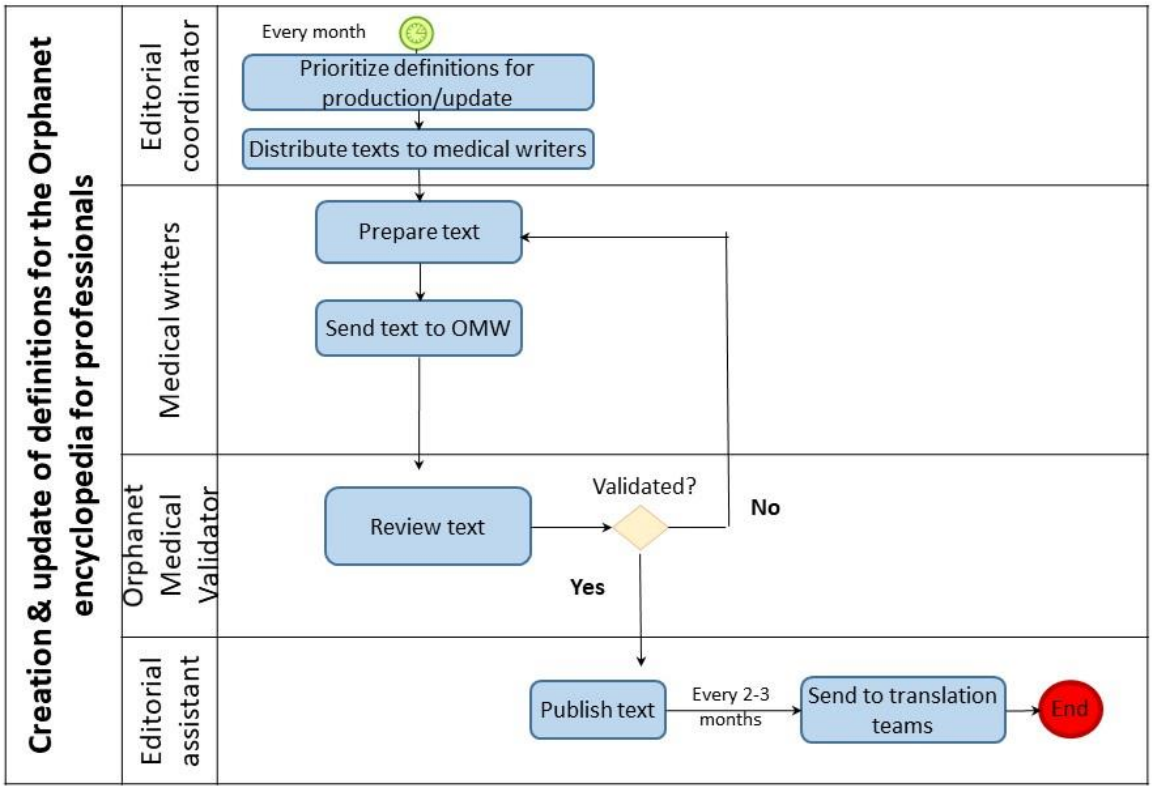

Figure 1. Workflow for the production of definitions.

2. Overview of the editorial process for definitions

a. Disease prioritization and distribution

Definitions are part of the Orphanet nomenclature, a clinically-oriented and multilingual coding system that assigns a unique and specific identifier (ORPHAcode) to each rare disease registered in Orphanet. Orphanet's aim is to produce a definition for every single rare disorder in the Orphanet database. As soon as a new disorder is created in Orphanet, the production of a definition is assigned to a MW, who begins the draft preparation of the text. Moreover, whenever a change in the perimeter of a disorder is identified (for instance via a classification or nomenclature update), the corresponding existing definition will be assigned to a MW to be updated.

b. Draft preparation and submission for review

All disease definitions are created and updated utilizing the most up-to-date scientific and medical

literature in order to accurately reflect the current knowledge and clinical practice. Definitions are prepared according to the specific characteristics listed in section IV. The MW also cross-checks the produced text with information registered in the Orphanet knowledge base (including nomenclature, synonyms, classification, epidemiology and genetics) and signals any incoherence to the responsible information scientist. Once the draft text is completed, it is submitted to the OMR in order to be validated before publication.

c. Medical validation

The OMR reviews the disease definitions for medical and editorial consistency. The OMR can ask the MW to make corrections to the text before the final validation. Once validated, the editorial assistant publishes the text on the Orphanet website.

d. Publication

Once published, definitions are accessible via the corresponding disease page on the Orphanet website. Moreover, all published definitions are contained in the Orphanet Nomenclature pack files on Orphadata.org and in the Orphanet Rare Disease ontology (ORDO).

e. Translation

Every 2-3 months, a list of the published definitions is sent to the Orphanet network national teams (ONT) for translation into their national language.

f. Quality control of disease definitions

In order to assure the quality of the textual information provided, definitions are periodically submitted to an appropriate expert reviewer for quality control, ensuring that the correct classification is used and the major clinical characteristics that define the disorder, and distinguish it from other entities in the same group, are described.

III. METHODOLOGY for the production of abstracts

1. Flowshart

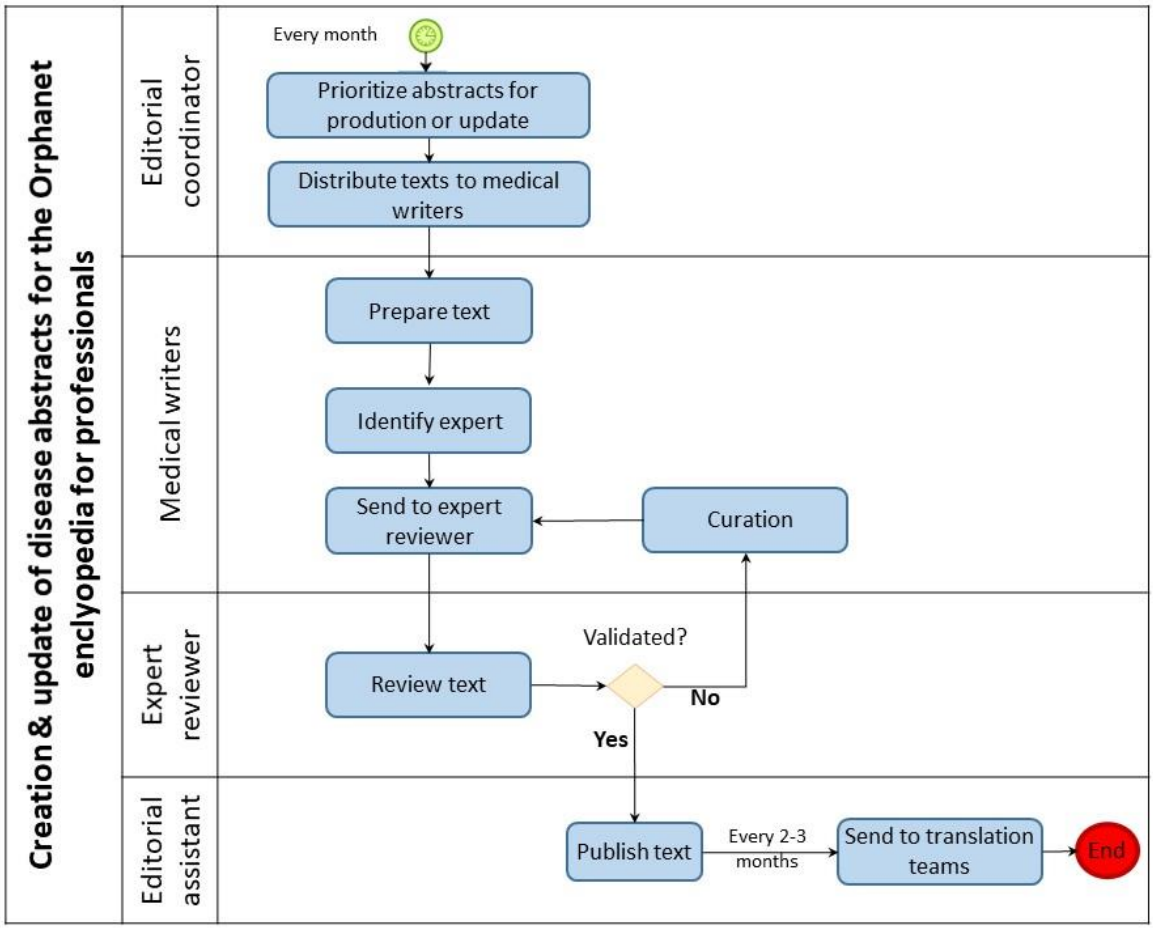

Figure 2. Workflow for the production of disease abstracts.

2. Overview of the editorial process for abstracts

a. Disease prioritization and distribution

Orphanet's aim is to produce textual information for every single rare disorder in the Orphanet database. However, due to the considerable number of entries present, disease prioritization is necessary in order to organize the production of these texts. Creation or update of disease summary texts are thus prioritized monthly based on the following criteria:

Criteria

- Texts that have not been updated in the last 3 years.
- Disorders that have no abstract.

- Disorders with a relatively high prevalence (>1/1,000,000).
- Disorders prioritized in the frame of an ongoing project or partnership.
- Diseases for which detailed and recent information has become available (e.g. published journal review articles or clinical practice guidelines).
- Disorders for which Orphanet users request a disease summary text. Indeed, Experts, patient organizations or other relevant bodies may contact Orphanet to request the creation or update for a specific disease or group of diseases.
- Disorders that have generated recent interest among the public and/or the medical community.
- Disorders that are not historical entities, for which a definition is preferred.
- Disorders that are not infectious diseases or cancers (for which Orphanet is not the leading source of information)

According to the above-mentioned priorities, the Editorial coordinator compiles a list of disorders for which a new or updated abstract is necessary. The disorders on this list are then distributed to the MWs, who subsequently begin preparing the draft text.

b. Draft preparation and submission for review

All disease summary texts are created or updated utilizing the most up-to-date scientific and medical literature, knowledge and/or external expert reviewer advice, with preference given to the most recent reviews and guidelines. Texts are prepared according to specific characteristics for each section of the disease summary texts, as defined in section IV. Once the draft text is completed it is submitted to a suitable expert reviewer.

In certain circumstances, the abstract may be submitted directly to an external expert reviewer for production or update.

c. Invitation of an external expert reviewer

The Orphanet MW invites an expert to review a disease abstract based on the criteria below. Criteria are intended to prove that the expert reviewer has a specific, undisputable, clinical expertise regarding the specific disease or group of diseases. The criteria include:

- Professional qualifications (e.g. medical doctors)
- Experience in relevant domain (as evidence by the number of published relevant clinically-orientated articles, reviews or clinical guidelines, or conduct of research or clinical trials related to the disease).
- Clinical experience of the relevant disease(s).
- Forms part of an expert center, patient organization advisory board, or learned society. Recommendation by a member of Orphanet, expert reviewer, scientific committee or ERN.

If the contacted external expert reviewer declines the invitation, the Orphanet MW repeats this step until a suitable external expert reviewer accepts the invitation.

d. Expert review

The invited external expert reviewer is invited to either review or produce a new abstract or update an existing abstract, making modifications where necessary. The expert also reviews the additional data associated with the disease (nomenclature, synonyms, natural history, inheritance, genes, and epidemiological indicators) and updates this information where necessary. If desired, the invited external expert reviewer may in turn invite additional colleagues to contribute.

e. Curation of disease summary texts

Following external review, the Orphanet MW implements the changes made to the disease summary text as well as any additional information provided. If necessary, the modifications are discussed between the relevant parties. In addition, the disease summary texts are cross-checked against information registered in the Orphanet database (including nomenclature, synonyms, classification, epidemiology and genetics), and where any discrepancies are identified the relevant Orphanet information scientist for the corresponding data is contacted in order to resolve the issue.

f. Final validation

Once the curation of the disease summary text has been finalized and any discrepancies resolved, the text is sent to the external reviewer to obtain the final validation before publication on the Orphanet website.

g. Publication

The disease summary texts are published by the Editorial assistant and are subsequently accessible via the corresponding disease page on the Orphanet website. The complete abstract collection is available via Orphadata via signature of a Data Transfer Agreement (for academia) or via signature of a service contract (for for-profit).

h. Translation

Every 2-3 months, a list of the published disease summary texts is sent to the Orphanet network countries for translation into their national language.

IV. Characteristics of the disease summary texts

General guidelines for the disease summary texts

Texts are written in American English, and contain a maximum of 3500 characters for abstracts or 3-4 sentences for disease definitions. Whilst scientific and medical publications are used to produce the disease summary texts, references are not provided on the Orphanet website.

1. Disease definition: This section details the group to which the disease belongs to and the principle clinical characteristics that distinguish the disease from other entries in the same group. Variable features (occurring in less than 50% of affected individuals) may also be included in the definition if they are considered to characterize the disease. The age of onset, mode of inheritance, gene or etiology are not included in the disease definition unless they are defining features.

2. Epidemiology: This section describes the known disease frequency (either point prevalence, prevalence at birth, incidence or number of cases/families) along with the geographical area concerned. The geographical distribution is described with preference for worldwide data when available. If unavailable, the applicable geographical regions or affected ethnicity is specified. Where there is very limited epidemiological data, a single country may be cited. Where there is a sex predominance, the male:female ratio is stated.

3. Clinical description: This section includes information about the age of onset of the disease, as well as a detailed description of the clinical presentation of the disease. Clinical manifestations are typically described in order of their frequency (i.e. most frequent to less frequent). However, if the disease is a polymalformative syndrome, the presenting signs and symptoms are described in a descending manner (i.e. head to feet). For progressive diseases, the signs and symptoms are arranged in chronological order, with clinical manifestations prioritized by frequency and then severity.
Clinical features are described using the Human Phenotype Ontology (HPO) terms whenever possible. In cases where the HPO term is lacking, the appropriate medical term is used.

4. Etiology: This section describes the etiology and/or the physiopathology of the disease where known. For genetic diseases, the causal gene and locus are always noted if the relationship has been established as disease-causing. For multifactorial diseases, the genetic background, when established, is explained. Where evidence is lacking on the etiology/physiopathology, the consensus from the scientific and medical community may be described.

5. Diagnostic methods: This section describes the principle tools used to establish and/or confirm a diagnosis, with a brief description of the key findings (e.g. laboratory results, imaging findings). For genetic diseases, genetic screening is mentioned if applicable.

6. Differential diagnosis: This section lists the main differential diagnoses of the disease, beginning with the most similar and continuing in descending order. Rare and non-rare diseases may be included in the differential diagnosis.

7. Antenatal diagnosis: This section is only completed when an antenatal diagnosis is possible. The text is impartial and objective, with focus on briefly describing the tools used to reach such a diagnosis. All positions on the ethics of antenatal diagnosis are not included.

8. Genetic counseling: This section is only completed for hereditary diseases. It describes the mode of transmission and the genetic counseling to be given to inform affected patients/families with respect to the genetic risk of transmission of the disease, citing variable penetrance where relevant.

9. Management and treatment: This section provides a brief description of the management and treatment options, including any available orphan drugs, if appropriate. Although not typically mentioned, unapproved medications that have shown objectively promising results in published clinical trials or included in clinical practice guidelines may be included at the discretion of Orphanet. Medications that are only in the pre-clinical phase of development are never described. Trade names are never included in Orphanet abstracts.

10. Prognosis: This section briefly describes the prognosis of the disease with regards to functional consequences, quality of life, life expectancy, and likelihood of recurrence after treatment.

For any questions or comments, please contact us: contact.orphanet@inserm.fr

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