Work Package 5

Deliverable 5.5

Recommendation for routine maintenance of codification resources for rare diseases

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by the WP5 members of the RD-ACTION European Joint Action

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It has been reviewed by WP5 participating countries within an open for comments phase.

The RD-ACTION Joint Action was launched in June 2015 for a 36 months period.

More information on the activities of the RD-ACTION Joint Action can be found at www.rd-action.eu.

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1. Background

The recognition of the fact that underrepresentation of specific entities for rare diseases (RD) in coding systems prevents visibility of rare disease patients in healthcare systems, thus precluding the exploitation of sound epidemiological data.

As the need of evidence supporting public health measures lead to the inclusion of the codification issue as one of the key elements of the Council Recommendation in 2009: “An appropriate classification and codification of all rare diseases is necessary in order to give them the necessary visibility and recognition in national health systems”. In its 2014 recommendation, the Commission expert group for rare diseases (CEGRD) promoted the adoption of the Orphanet nomenclature of rare diseases for codification purposes in European member states. It gave rise to a specific work package in the 2015-2018 Joint Action for rare diseases, RD-ACTION.

RD-ACTION Codification WP has issued a series of documents in order to provide recommendation and tools with the aim of enable Orphacodes implementation in health information systems: these documents and tools are briefly described here, and appropriate links are also provided (section 1.1)

The use of the Orphanet nomenclature for coding rare diseases (RD) in a standardized way should improve the visibility of rare disease patients on Member State (MS) and European level. This leads to comparable data with which the European and national health authorities can plan their following steps in the field of rare diseases accordingly.

The current document complements this series by providing recommendations on the way the codification resource should be maintained and distributed, and on the way it should be maintained at the end-user level. This recommendation is based on the work of RD-ACTION codification work package and in particular on the development and testing of codification and exploitation resources.

1.1. Current resources for rare diseases coding implementation

The Orphanet nomenclature aims at providing a comprehensive reference of all rare diseases. Rare diseases are numerous, often complex, at the frontier of several medical specialties. This complexity is depicted in the Orphanet classification of rare diseases, a clinical nosology gathering rare diseases in groups but also offering a variety of subtypes if relevant. Orphanet defines a rare disease as a recognizable and homogeneous clinical presentation, whatever the cause, and has developed a multi-hierarchical terminology including unique identifiers – Orphacodes – to provide accurate classification of all rare diseases. Entities in the Orphanet classification system (and their unique identifiers) are organized in categories, groups of disorders, disorders, and subtypes. The whole Orphanet nomenclature and its classification

system are made available by Orphanet at www.orphadata.org together with the alignments with their terminological resources.

Due to the complexity of the Orphanet classification, it might be difficult for unexperienced coders to identify the appropriate code in the multi-hierarchical classification.

In the framework of the RD-Action, a reduced list of Orphacodes has been agreed in order to allow data sharing and statistical analysis at EU-level. This list, based on the disorder level excluding categories, groups and subtypes, is used to produce the so far named "Master file" (MF). A specification and implementation manual of the Master file has been conjointly provided.

In MS, coding may be performed in different settings and can be linked to national coding systems or be a standalone coding system for specific settings. As a result of a survey and on a face-to-face discussion of the Codification WP members (see Annex 1 for list of countries) in October 2016, a European approach was catered to fit all kinds of different settings. In order to allow data sharing at European level, generation of the statistical data for international use, and to facilitate implementation of reference files, a set of guidelines "Standard procedure and guide for coding with Orphacodes" was developed and included in the testing process. The first testing phase explored retrospectively two complementary aspects related to the real-world Orphacodes' use: the comparability between monitored RD entities, in terms of which OC are actually used to describe existing patients, and the comparability of patients' distribution, as described by OC. The second testing phase adopted a prospective approach. The test was based on web-based tool allowing the direct correspondence between names of diseases coded in RD patients and the corresponding OC.

Whatever the chosen implementation method, it is desirable that countries report data for statistical purposes in a consistent way, thus using the same, agreed level of granularity. With this aim, the Master file list of Orphacodes and the coding guidelines should be used.

The six guidelines to be considered for statistical reporting with Orphacodes are reminded here:

Guideline 1 - Several tools and strategies could be set at MS level to produce data or statistics for RD, nevertheless each country should set this strategy accordingly to a standard principle of maximizing exhaustiveness as well as possible re-use of existing data collections.

Guideline 2 - Code the data in a way that the reporting can compile to the granularity of the international recommended list of Orphacodes (MF-granularity). If no further national needs for reporting are necessary, use the codes from the MF directly.

Guideline 3 - Whenever possible capture the information of the diagnostic assertion for all RD cases. Use the Options “Suspected rare disease”, “Confirmed rare disease” and “Undetermined diagnosis”. Additional options might be helpful.

Guideline 4 – Although rare disease registries (disease, population or patient based) should promote the use of data standards to increase interoperability of their data, they should not be the only instruments upon which the EU strategy to produce health statistics for RD at population level relies.

Guideline 5 - Update your coding resource according to the internationally agreed cycle in order to have the most recent coding file and to ensure comparability.

Guideline 6 - If Orphacodes are used together with another national coding system for morbidity coding, the two systems should be linked in a standardized way to ensure that code combinations are standardized and the coding effort for the user is minimized.

1.2. Lessons learnt from the Joint Action

In the work of the RD-Action period different settings and coding scenarios were discussed and the Orphanet nomenclature was investigated for its routine use in MS and for international reporting.

One challenge shared by users of the Orphanet nomenclature is to identify the more suitable Orphacodes to the patient’s situation at the time of coding. Due to the complexity of the Orphanet classification, it might be difficult for unexperienced coders to identify the appropriate code in the multi-hierarchical classification. To facilitate this process, the “Master file” has been developed and was tested in different settings and coding scenarios in order to reduce the burden of an extremely detailed classification, if not absolutely necessary. Limiting the Orphacodes to the ones included in the “Master file” restrains the diagnosis process and follow-up.

Notably, a high proportion of patients are undiagnosed or can be attributed a “generic” diagnosis, while the diagnosis process is still ongoing. Using the Orphacodes from the “Master file” alone does not allow to capture these cases. An option to overcome this problem is to use the groups of disorders until a definitive diagnosis is achieved. Recording this data is strategic to assess the delay in diagnosis and diagnostic pathway. Still, for statistical purposes this approach need to be further specified and described.

In the other extreme of the spectrum, genetically established diagnosis can be reflected by coding with a sub-type of a disorder, which is by definition excluded from the “Master file”. Using the whole Orphanet nomenclature enables to carry out every coding situation however the resulting heterogeneity is not compatible with internationally agreed and standardized way that allows uniform statistical reporting. Due to the complexity of the Orphanet nomenclature and its organisation in a multi-hierarchical classification, having a correspondence between all Orphacodes and the “Master file” is essential to ensure that the aggregated level is reached whenever

possible. Ideally, visualizing the classification would help coders to find this correspondence and more generally to find the right granularity level for coding with the nomenclature.

Another challenge for the user is the availability of the Orphanet nomenclature on different formats and web interfaces (orpha.net, orphadata.org and Orphanet Ontology of Rare Diseases –ORDO-). These media have different purposes and for this reason different update cycles. The resulting discrepancies could be confusing for coders. Having a dedicated entry point to the Orphanet nomenclature maintained exclusively for coding purposes would reduce the coding burden. This entry point should centralize the nomenclature and tools developed to help in the coding process.

Knowledge about rare diseases is evolving rapidly and so is the Orphanet nomenclature. To be able to maintain the coding process overtime and to update patient files, a steady update cycle, including versioning and differentials between versions, is mandatory.

Finally, as coding with the Orphanet nomenclature is a complex process potentially time-consuming, having self-intelligible names to the resources will also help users. In the first RD-Action documents, a distinction in the use of the terms “Orphacode” and “Orphanumber” has been made, the first one being a subset of the second for the particular case of coding a patient in a health information system. However, as a result of the testing activities it was experienced that potentially every clinical entities within the Orphanet nomenclature (i.e. Groups of disorders, disorders or subtypes of disorders) are likely to be assigned to a patient during the diagnosis process. Accordingly, “Orphacode” and “Orphanumber” should be used equivalently, and designates every entity in the Orphanet nomenclature.

Equally, the reduced list of Orphacodes that has been agreed in order to allow data sharing and statistical analysis at EU-level, so far named “Master file” will be renamed to “Master file for statistical reporting with Orphacodes” (MF) to clearly indicate its intended purpose.

2. Recommendations

In the context of the aforementioned topics of the use of the Orphanet nomenclature for coding rare diseases and the routine maintenance of the used resources, the RD-ACTION Codification WP proposes the following 10 recommendations for the routine maintenance and use of codification resources for rare diseases:

2.1. Recommendations for the distribution of codification resources for rare diseases:

Coders and software developers need to have easy access to the materials needed for the implementation and as a reference for further use. Therefore the material needed for this enterprise should be handled separately from other resources provided by the Orphanet:

1. It is recommended to provide a server dedicated to the resources needed for coding rare diseases with the Orphanet Nomenclature (including the most recent version of the “Standard procedure and guide for the coding with Orphacodes”). It should be stable over time to serve as the reference for the coders and implementers. It can as well be referenced for the analysis of standardized coded data.

For the coding and analysis a certain stability of the coding resources is necessary. If these resources change frequently and in varying intervals, the comparability of the data will be impeded. Still, the changes in the medical knowledge on rare diseases are rapid and should be reflected. A solution to cater to both requirements is proposed as follows:

2. It is recommended to release the Orphanet nomenclature and the “Master file for statistical reporting with Orphacodes” in an annual cycle (e.g. each September 1st) and keep the files of previous years available to allow analysis over time.

In order to show the users what changes have been made between two versions a list of changes is necessary. This list of changes can help as well in comparison of data over time and to explain shifts in coded data.

3. It is recommended to provide list of changes between consecutive versions of the Orphanet nomenclature and consecutive versions of the “Master file for statistical reporting with Orphacodes”. The list of changes should indicate at least all new Orphacodes, all deleted Orphacodes and all changes to existing disease names of the included Orphacodes.

Using the “Master file for statistical reporting with Orphacodes” will be one way of coding. But other ways might be sought by the users as well including more granularity of Orphacodes (e.g. including all subtypes of diseases). Therefor it is

necessary to provide tools to align the different uses to be able to report according to the level of granularity of the “Master file for statistical reporting with Orphacodes”.

4. It is recommended to develop tools provided with the Orphanet nomenclature, including a mapping tool to enable countries to map their data, of different levels of granularity, to the “Master file for statistical reporting with Orphacodes” and a browser of the Orphanet classification of rare diseases.

2.2. Recommendations for the correct use of codification resources for rare diseases:

The following recommendations aim at guiding the user. They are important for the collection of standardized data as the comparability will be impeded by different uses of the Orphacodes.

Even though in some cases a reporting on a less granular level of Orphacodes might seem sufficient, it is still better for secondary use of data (e.g. research) if a minimum of alignment is followed. The Orphacodes included in the “Master file for statistical reporting with Orphacodes” are the result of analysis and testing and seem to be fit for different purposes. If used together with the “Standard procedure and guide for the coding with Orphacodes” not only the Orphacodes are standardized but as well their application:

5. It is recommended to use the Orphanet nomenclature at least on the level of the “Master file for statistical reporting with Orphacodes” without compromising the quality or the precision of coding and to use the “Standard procedure and guide for the coding with Orphacodes” for the implementation and coding process.

Orphanet provides a huge variety of resources and information. Due to its richness, the Orphanet website provides multiple ways to access the Orphacodes. But, due to the different requirements of the information platform sections, it cannot be guaranteed that all ways will direct the user to the Orphacode as presented in the “Master file for statistical reporting with Orphacodes”. Some sections might be updated more frequently due to the specific requirements and this might lead to inconsistencies in data collection.

6. It is recommended for the purpose of coding to use exclusively the Orphanet nomenclature and adjoining tools from the dedicated server, once available.

As mentioned above with recommendation No. 2, the development of the Orpha nomenclature encompasses frequent updates. For the purpose of coding an annual cycle is proposed in recommendation No. 2. For the user this implies as well, that the coding tools in use need to be updated in an annual cycle. For a national implementation with a mapping to a national coding system this implies to follow the annual cycle and update the national coding resource accordingly. The same applies for international tools that make use of these resources. As the changes in the

“Master file for statistical reporting with Orphacodes” can be substantial the process needs to be considered and planned carefully:

7. It is recommended to update all implementations of the Orphanet nomenclature and the “Master file for statistical reporting with Orphacodes” in an annual cycle. This includes implementations within national or other coding systems.

Moving to a new version in the annual cycle can be burdensome if not guided by respective tools and documentation. A file to document the changes is described in recommendation No. 3. For a user this file can be an easy way to address the changes between two versions and to focus the work on primarily implementing these changes. If a national coding system has included the “Master file for statistical reporting with Orphacodes” the list of changes can direct the maintenance organisation to implement the changes with a minimum amount of burden.

8. It is recommended to make use of the list of changes between consecutive versions, once available, to alleviate the burden of updates.

2.3. Open Issues to be followed up upon after the end of the RD-Action

The problem how to internationally standardize the coding of patients with undiagnosed but suspected rare diseases was not addressed in total. It was discussed to some extend and some initial thoughts are given in the “Standard procedure and guide for the coding with Orphacodes”. Still, more discussion is needed and an international consensus should be reached to address the problem of undiagnosed and partly diagnosed patients in a uniform way in coded data. As well, some discussion should follow on how to represent this in aggregated data in order to guide public health decisions in a well-informed way.

9. It is recommended to follow up on finding international agreement on how to code patients with undiagnosed or partially diagnosed rare diseases in order to achieve greater comparability of international data. This should be addressed together with the Orphanet team, the group to maintain the “Standard procedure and guide for the coding with Orphacodes” and the “Master file for statistical reporting with Orphacodes” and together with experts on rare diseases and on international standardization.

The Orphanet structure of the classification responds to the need for multihierarchy. According to this design, the same disease entity can appear in multiple places in the classification and in the hierarchy. As the “Master file for statistical reporting with Orphacodes” is produced as an output of this work, further analyses based on the extended use of Orphacodes in different settings are needed to enhance the “Standard procedure and guide for the coding with Orphacodes”. This process should not only regard the use of Orphacodes to record RD patients but also consider how to consistently aggregate and elaborate data to ensure comparability.

As well, the use of the “Master file for statistical reporting with Orphacodes” and the “Standard procedure and guide for the coding with Orphacodes” was limited to the RD-Action. This limited work has to widen after the end of the RD-Action to encompass all kind of applications and settings in which Orphacodes can be used. An example amongst others is the use within applications of the European Reference Networks on Rare Diseases where initial discussions have started.

10. It is recommended that the recommendations should be distributed widely amongst all kind of EU-projects that work on standardizing semantic content and to engage in discussions on how to use these resources as best as possible over all EU projects and in routine coding settings.

Annex 1: List of participating countries at the WP5 face-to-face meeting in October 2017, Paris

1) Austria
2) Belgium
3) Bulgaria
4) Cyprus
5) Czech Republic
6) Estonia
7) Estonia
8) Finland
9) France
10) Germany
11) Great Britain
12) Hungary
13) Iceland
14) Ireland
15) Italy
16) Lithuania
17) Luxembourg
18) Malta
19) Netherlands
20) Norway
21) Poland
22) Portugal
23) Slowenia
24) Spain
25) Sweden
26) Switzerland
27) Turkey