Preliminary results analysis and "Adaptation of procedure for Orphacodes use in Spain"

REPORT

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1 - Introduction

During the early 2010s, the Research Institute for Rare Diseases (IIER) of the Carlos III Institute of Health (ISCIII) coordinated the Spanish Registry Network for Research for Rare Disorders (SpainRDR). Between 2012 and 2015, this network focused on setting the standards of procedures and regulations within regional governments to establish regional registries or information systems for rare diseases (RDs). As a result, a nationwide population-based RD registry was created to collect data from the regional registries. The Ministry of Health, with the collaboration of the regional governments, is the responsible of the National Registry of Rare Diseases (ReeR) that produces validation sheets for selected diseases. These documents include several coding systems (ICD-9-CM; ICD-10; ICD-10-ES; ICD-10-BPA; OMIM; ERA-EDTA; SNOMED-CT and Orphacode)* when the equivalences among them are available. The validation sheets are then circulated and established as references for the codification and communication of the cases diagnosed with such diseases within the national territory. Since 2016, the Spanish version of the 10th International Classification of Diseases (ICD-10-ES) has been used in Spain as the reference classification for clinical coding. Currently, most of the morbidity and mortality data are also collected using this classification and ICD-10.

The aim of this project is to promote the use of the Orphanet nomenclature for implementation into routine coding systems by establishing equivalences between ICD-10-ES and Orphacodes. This would enable a standardized and consistent level of information to be shared at Spanish and European level. In particular, for Spain, the goal was to pilot the implementation of Orphacodes according to the "Standard procedure and guide for the coding with Orphacodes" and the "Specification and implementation manual of the Master file" at the RD registries in a few selected regions in Spain. Six Autonomous Communities (AC) were enrolled from the beginning of the project to participate in a pilot phase consisting in the implementation of Orphacodes in their RD registries following the necessary Information Technology (IT) developments and according to the Procedure and the Master file developed in the frame of the RD-ACTION project. Expected results by M12 of the project included the achievement of significant progress towards the implementation of Orphacodes in 6 regional registries and to attain an Orphacode correspondence for at least 75% of all the RDs listed in the Master file.

*See List of Acronyms

2 - Materials and methods

Starting information

The «Standard procedure and guide for the coding with Orphacodes» and the «Specification and implementation manual of the Master file» both developed in the frame of the previous Joint Action on Rare Diseases RD-ACTION (2015-2018) have been used as reference for the implementation process. To promote the use of the Orphanet nomenclature for implementation into routine coding systems in Spain we started from the «Master file for statistical reporting with Orphacodes» also developed during RD-ACTION and two tables of correspondence from ICD-10-ES (Spanish version of ICD-10-CM) to Orphacodes, one developed in the Valencian Region and another one in the Basque Country. These three databases have been the starting point for the proposal of new and/or updated correspondences between the two coding systems within the present RD-CODE project.

The information provided by the Orphanet repository of RDs (e.g. disease description, links and ICD-10 correspondence) and the 2nd electronic edition of the ICD-10-ES provided by the Spanish Ministry of Health, Consumer Affairs and Social Welfare (eCIE-Maps - https://eciemaps.mscbs.gob.es/ecieMaps/browser/index_10_mc_old.html) were used on a daily-basis.

Standard procedures

The entries registered in the document «Master file for statistical reporting with Orphacodes» resulting from the RD-ACTION project were checked in the Orphanet repository of RDs in order to update the information about the Orphacodes. Once the existence of the code and its associated info was confirmed at the Orphanet server (https://www.orpha.net/consor/cgi-bin/index.php), we introduced the name; its synonyms or the ICD-10 code linked to the Orphacode (if any) at eCIE-Maps and then selected the ICD-10-ES associated when it was possible. The ICD-10-ES reached by this method was then compared to those proposed in the databases developed in the Valencian Region and in the Basque Country. The following decision-making criteria were applied:

- Choose the ICD-10-ES code that has an exact match for the name of the disease.
- When no match for the name or synonyms was found, prioritize the ICD-10 (from Orphanet) derived ICD-10-ES code.
- Send to the AC for revision of the equivalences that are unclear after applying these criteria.

3 - Regional registries starting point

Six regions have been involved in the implementation of Orphacodes for the RD registry: Castile and Leon, Catalonia, Murcia, Navarre, Basque Country and Valencian Region. These regions had previously established their regional registries for RDs and have experience retrieving and managing the data within their population registries.

General information

Castile and Leon

This registry was created in 2012 and is managed and maintained by the team of the Public Health Office. The software called ENRA runs on Java-JSF technology and the registry included at the beginning of the project 257,000 diagnoses for about 225,000 patients including 60,000 dead.

Catalonia

This registry was created in 2015. The software was developed by an external enterprise and is managed and maintained by the registry team of the Catalan Health Service. The registry included at the beginning of the project 2,681 clinically confirmed patients in Orphacode terms. In parallel, the Minimum Basic Data Set (CMBD) that collects information about hospital discharges detects ≈420,000 candidate patients (alive) from ICD codes.

Murcia

This registry was created in 2010 in collaboration between the "Rare Diseases Information System" (SIER) and the Informatics Unit of the Murcia Regional Health Department. The software is managed and maintained by the team at SIER and runs on Oracle-Java technology. The registry included before the beginning of the project data for around 78,000 RDs.

Navarre

The Population-based Rare Diseases Registry of Navarre (RERNA) was created in 2013. RERNA's software implementation finished in 2015 and it is managed and maintained by its team. The software is based on Angular web app, C# and sql 2012 technology.

Basque Country

This registry was created in 2017 by EJIE (Basque Government Informatics Society) which is also responsible for its maintenance. The software runs on Oracle technology and the registry included at the beginning of the project data for around 5,000 patients.

Valencian Region

This registry was created in 2012 and its software is maintained by an external enterprise. The software called VENT runs on Java technology and is managed by the team at SIER-CV. This software has loaded a list of ≈9,600 Orphacodes of the over 20,000 available at Orphanet for all entity levels.

The registry included at the beginning of the project, for the period 2000-2017, 18,278 cases validated and confirmed (excluding disease absence and presumable). From these 18 thousand, ≈11,800 come from the congenital anomalies registry, ≈300 from the renal diseases registry and ≈6000 that have been manually checked from other sources. The total of cases for this period corresponds to 10,076 patients that have been diagnosed with 446 different RDs. This registry manages in average (between 2016 and 2018) over 200,000 hospital discharges.

Information sources

Castile and Leon

The sources of information of this registry are the CMBD, the primary care electronic history, the orphan drugs registry, the mortality registry, the Castile and Leon renal diseases registry, the early-detection congenital diseases registry and the Rare Diseases Diagnosis Centre of Castile and Leon (DierCyL). The first two sources provide about 98% of the data.

Catalonia

The source of information of the Catalonian Rare Diseases Registry (Remin) are clinicians from selected units of clinical experience (UEC) networks, identified by thematic groups of diseases, deployed in line with European Reference Networks (ERN).

Murcia

This registry takes information from 49 different sources from which 14 are previously existing registries including but not limited to CMBD, disability, dependency, drug delivery, renal diseases, patient referral, and clinical history registries.

Navarre

The information sources of RERNA are the CMBD, the primary care services, the temporal disability (RITA), mortality, genetics, congenital anomalies, and drug registries.

Basque Country

This registry is nourished by direct declaration by physicians.

Valencian Region

The sources of information of this registry are the CMBD, the population-based congenital anomalies registry of the Valencian Region, the mortality registry, the neonatal screening program, and the renal diseases registry.

Coding systems in use

Castile and Leon

The coding systems in use at the beginning of the project were ICD-9 and ICD-10-ES but the software had the structure to implement the Orphacodes and their equivalences.

Catalonia

The rare diseases registry of Catalonia (Remin) was from the beginning fulfilled by clinical experts employing the ORPHA coding system. The system also includes the table of equivalences proposed at the Orphadata catalogue, as well as the mapping to ICD-9-CM standard, used to identify retrospective CMBD candidates.

Murcia

This registry was set to work with ICD-9-CM (until the end of 2015) and ICD-10-ES for all cases. Some cases are also coded with Snomed-CT and another slot to introduce the Orphacodes equivalence is in place but was of seldom use before the start of the RD-CODE project.

Navarre

RERNA worked with ICD-9-CM, ICD-10, ICD-10-ES and Snomed-CT, and all the validated cases had an Orphacode assigned.

Basque Country

This registry is based on the use of ICD-10 and ORPHA coding systems. Each one of the cases registered has an Orphacode associated.

Valencian Region

This registry can work with ICD-9-CM, ICD-10, ICD10-ES, ICD-10-BPA, ERA-EDTA, and is also developing the Snomed-CT database. The cases need to be associated to an Orphacode in order to be generated and promoted by the programme.

4 - Proposal of ICD-10-ES correspondences for Orphacodes

The Master file resulting from the RD-ACTION initiative was perused in order to propose the most accurate equivalences to ICD-10-ES for the Orphacodes reported on it. Starting with 5,775 different Orphacodes we have proposed ICD-10-ES codes to 5,232 of them. That means that we have proposed so far equivalences to ICD-10-ES for over 90% of the entries registered in the original Master file (Fig. 1). The number of different ICD-10-ES codes proposed is approximately 1/3 of the total equivalences (2,102/5,933) confirming the lack of enough specific independent codes for RDs in the ICD-10-ES coding system.

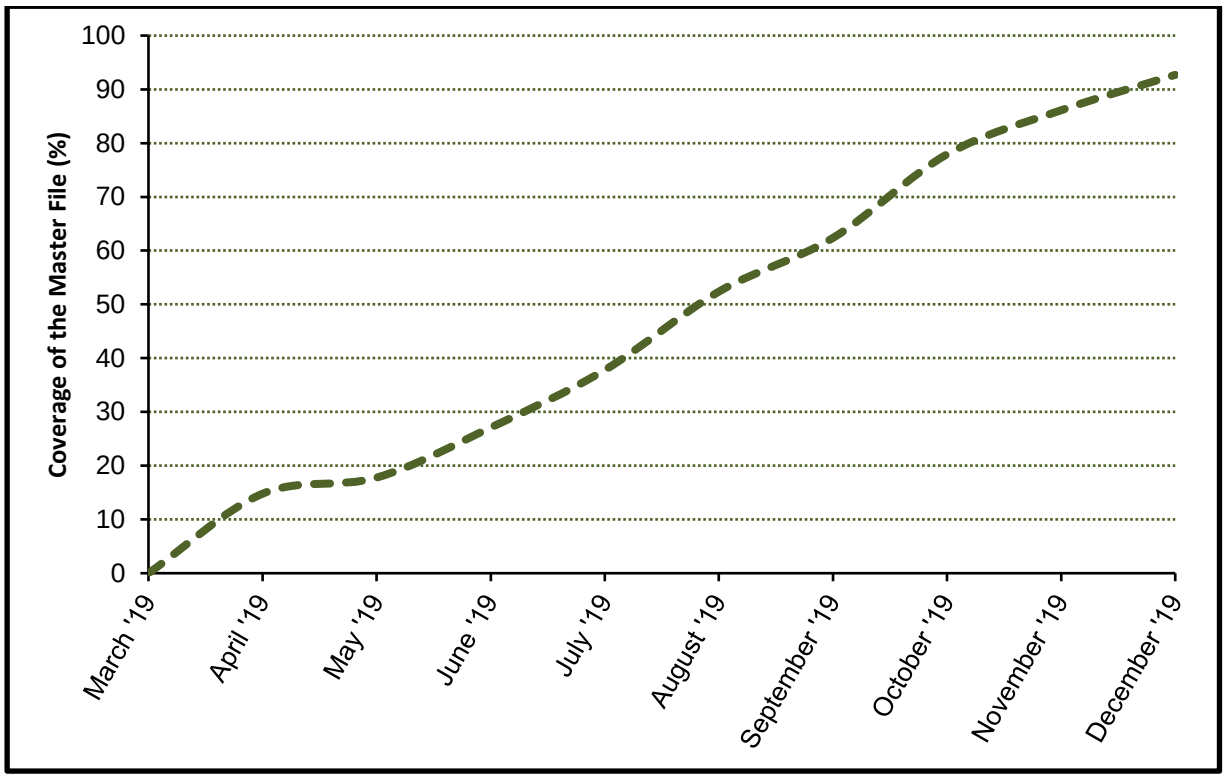

Figure 1. Evolution of the ORPHA and ICD-10 to ICD-10-ES mapping task during 2019.

5 - Coordination of regional registries efforts

FISABIO has centralized the efforts of the different regions involved in the pilot phase for the implementation of Orphacodes into their regional RD registries. Most of the equivalence proposal work was conducted at FISABIO in collaboration with the AC involved in the project.

Establishment of initial guidelines

In order to agree on the initial basis to establish equivalences to ICD-10-ES, we organized a face-to-face meeting with the coordinators of the work package 4 (WP4), representatives of the regional registries involved, public hospitals and the Ministry of Health, Consumer Affairs and Public Welfare in April 2019. After this meeting, a document specifying the agreements was circulated and approved by all AC involved. From this document, we adopted the standard procedures described in the methods section of the current document (Page 4).

Feedback on non-obvious correspondences

At the end of every month since the establishment of the standard procedures, the non-obvious correspondences found during that month were sent to the regional registries (Fig. 2). From April to September, 325 Orphacodes and their proposed equivalences to ICD-10-ES were distributed for their revision. Feedback on these equivalences was then retrieved and studied to select the most appropriate ICD-10-ES code matches.

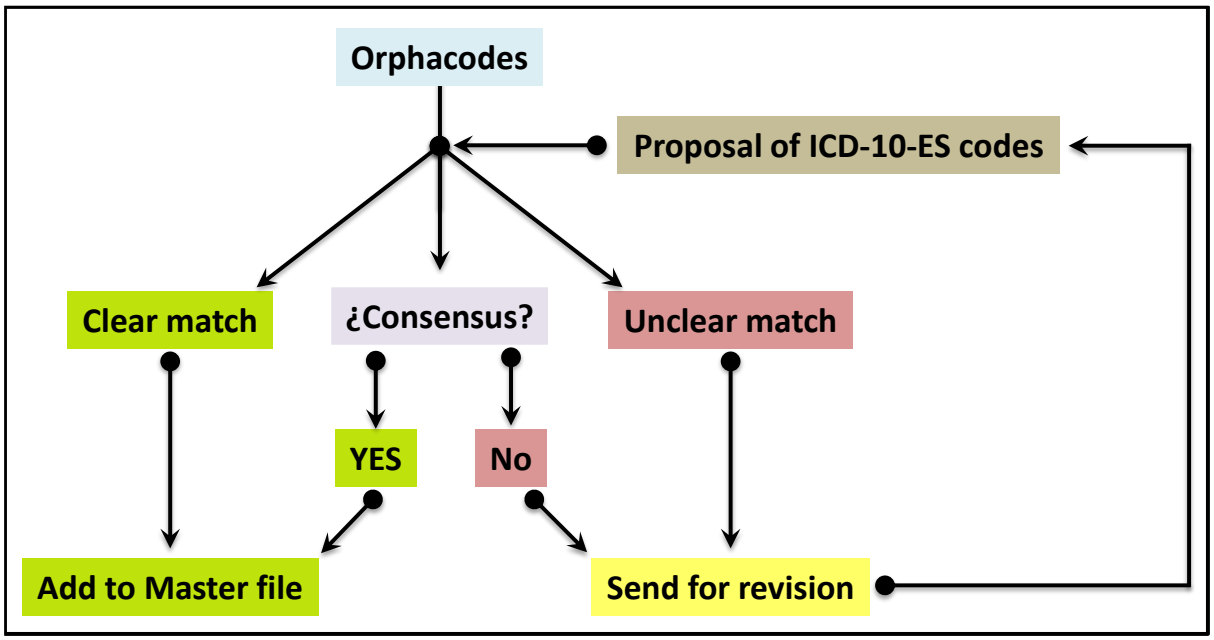

Figure 2. Steps undertaken to select matching ICD-10-ES codes for Orphacodes.

In parallel, a survey was created in order to expand the decision-making protocol. We gathered the more common situations that were faced during the proposal of ICD-10-ES equivalences and suggested at least two ways to act for each of them. The results of the survey were then registered and a new document with the survey-based way of solving conflicts was circulated and approved. The following criteria were chosen to be applied when the standard procedures were not enough (Fig. 3):

a) When the Orphacode corresponds to a syndrome or a multifaceted disease that is associated with a partially corresponding ICD-10:
   - Prioritize the ICD-10-ES derived from the ICD-10 associated in the Orphanet repository.
   - Keep sending for their revision the equivalences that are not convincing enough yet.

b) When the name of the disease and one or more of its synonyms are listed in ICD-10-ES under different codes. Also when more than one code seems to match a disease:
   - If the exact name of the disease is found at eCIE-Maps prioritize the ICD-10-ES code associated.
   - If not found, prioritize the ICD-10-ES derived from the ICD-10 associated in the Orphanet repository.
   - If the ICD-10-ES code clearly differs from that of the name assigned to the disease, send the equivalence for revision.

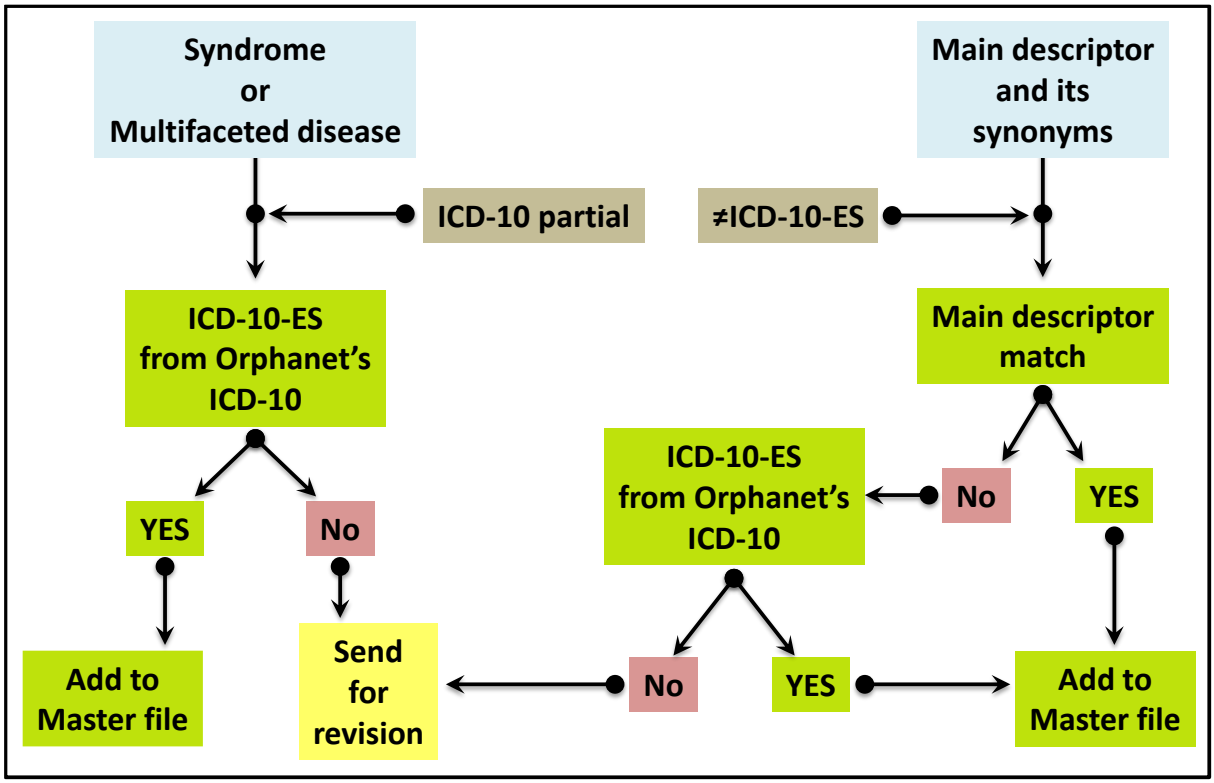

Figure 3. Decision making criteria established for specific non-obvious equivalences.

38 additional equivalences that could be solved neither by the initial guidelines nor with the extended procedures were sent for revision at the end of November after the first attempt to complete the Master file was fulfilled. Along with these new entries, 80 of the 325 entries previously sent were redistributed for a new round of revision due to lack of consensus in order to select the best match on the first round.

Equally, 425 of the Orphanet entries, from which 404 lack of proposal for ICD-10 code at its repository for RDs, were circulated to start a round of discussion about potential equivalences and/or strategies to solve their translation to ICD-10-ES.

First implementation attempt

During the first six months of the project we made a first trial to implement the Master file structure within the regional registries. We used a reduced sample of Orphacodes (≈1000) which equivalences were established in advance. This way, the regional registries would have a better idea of what to expect in the final document. After this trial period the registries sent back a report expressing the difficulties they found and might face during the subsequent pilot implementation phase.

The one-to-one relationship between Orphacodes and ICD-10-ES codes would be *a priori* easy to implement by all registries. Problems may come with the one-to-many and many-to-one relationships. In those cases where the ICD-10-ES system is more specific than the ORPHA classification, it is possible to implement Orphacodes even if some information is lost in the process. The big issue comes for most registries when there are many Orphacodes associated to the same ICD-10-ES code. Most of the inputs arrive as an ICD-10-ES code so if more than one Orphacode is possible for the code received it would be challenging to assign the right one in each case.

6 - Documents delivered for implementation at the regional registries

At the end of October 2019, an updated version of the Master file was distributed to the regional registries. The new version of the document contained 4,877 disorder level entities (≈85% coverage) with their Orphacodes and the equivalences to ICD-10-ES. This document was prepared for the final attempt of implementation of the pilot phase and the regional registries integrated it into their software in order to test the feasibility of its use. Together with this new Master file, the guidelines for their correct interpretation were circulated in order to facilitate their implementation.

7 - Implementation results

Castile and Leon

The main goals of this registry for the first year of the RD-CODE project were:

- To change the reference coding system from ICD-9 to ICD-10.
- To test the implementation options for the Orphacodes mapped to ICD-10-ES.

The work conducted throughout the year brought up the following outputs:

- Setup of the new version of ENRA software with compulsory ICD-10 codes for RDs:
  - Technicians and users can validate diagnoses, remove and modify entries in case of errors.
  - Successful uploads of data including ICD-10-ES as main diagnoses codification, upgrading data up to the year 2017.
- Characterization of the cases currently included at the software:
  - Most cases updated to have both ICD-9 and ICD-10 codes assigned.
  - New entries are assigned only an ICD-10 code.
  - There were a reduced number of ICD-9 codes mapped to ORPHA. Limited to those prioritized by the National Registry for Rare Diseases. From now on the codification will be based on ICD-10/ICD-10-ES and its equivalences to Orphacodes based on the Master file equivalences.
- Adaptation of the ENRA software data model:
  - Inclusion of the new variable in the application interface (Orphacodes) so it can be accessed by users.
  - First partial upload of Orphacodes with mapping to ICD-10-ES.
- Translation of current diagnoses to Orphacodes:
  - The cases where the ICD-10-ES maps to a unique Orphacode have been defined and debugged successfully.
  - The cases that have an ICD-10-ES associated with more than one Orphacode are being treated as follows:
    - Cases are grouped by ICD-10-ES and studied independently to propose the best matching Orphacode.
- Functionalities of the ENRA software:
  - Assign an Orphacode for each diagnosis corresponding to a RD starting from the previously included ICD-10/ICD-10-ES code.
  - For the cases where no direct relationship (1 to 1) between ICD-10-ES and Orphacodes is in place, description of the Orphacodes is attached to facilitate the choice and minimize errors. Before validation, the system assigns the more likely Orphacode automatically to avoid null values.
- Upload process update:
  - Modify database structure to accept different source coding systems as entry point.
  - Modify the uploading process from different information sources to consolidate the data.
  - Adapt the way to treat the received entries to include evaluation of the process.

- ENRA software supports both Orphacodes and their associated disease names.

Catalonia

The main goals of this registry for the first year of the RD-CODE project were:

- Creation of a working group integrated by professionals in clinical health documentation from all tertiary hospitals to contribute to the establishment of shared correspondences between Orphacodes and ICD-10-ES. This effort is particularly relevant in Catalonia, where the public hospitalization network (SISCAT) includes centers of (non for profit) different ownership, with different Health Information Systems (HIS).
- Promote the use of these correspondences in Catalonia to facilitate the retrieval of RD epidemiological data from routine sources.

The work conducted throughout the year brought up the following outputs:

- Inclusion at the Catalan Health Department terminological server of the Master file with the correspondences of ICD-10-ES to Orphacodes distributed from FISABIO.
- Inclusion at the Catalan Health Department terminological server of the complete Orphacodes database, along with all ICD-10-CM equivalences from all sources identified.
- Of the >850 Orphacodes listed in the Master file that are included in the registry:
    - 671 had total coincidence with the equivalences they've been working with
    - 64 had a different equivalence established in their registry
    - 138 had complementary equivalences in their registry

Murcia

The work conducted during the first year of the RD-CODE was focused on:

- Incorporate the Spanish translation of the disease name available in Orphadata for every Orphacode included in the Master file. At this webpage there is an access to "Cross-referencing of rare diseases" from where the list in Spanish was downloaded.
- Filtering the list of codes to exclude those not relevant for the registry.
- Incorporate and establish a correspondence between the Orphacodes selected from the Master file and the list of ICD-10-ES codes of the registry.
- Test the functionality in trial environment and its upload to production process.

To perform the analysis of the functionality, five hundred target cases from the SIER were randomly selected to check whether an Orphacode from the Master file could be associated to each of them. After this process the following results were obtained:

- ≈30% of the cases was validated as a rare disease.
- Seventy ICD-10-ES codes were associated to the 158 cases validated.

- >90% of these cases were linked to an Orphacode listed in the Master file. The rest of the cases weren't assigned an Orphacode from the Master file because of discrepancies of codes with the SIER. Examples of discrepancies found:
  - ICD-10-ES M32.9 → Orphacode 93552 = Pediatric systemic lupus erythematosus
    - Should include Orphacode 536 = Systemic lupus erythematosus
  - ICD-10-ES M34.1 → Orphacode 90291 = Systemic sclerosis
    - Should be Orphacode 90290 = CREST syndrome
- Some of the Orphacodes are less specific than the source ICD-10-ES code. Examples of loss of specificity:
  - ICD-10-ES Q60.0; Q60.1; Q60.2 → Orphacode 411709 = Renal agenesis
    - Q60.1 should map to Orphacode 1848 = Renal agenesis, bilateral
    - Q60.0 should map to Orphacode 93100 = Renal agenesis, unilateral
  - ICD-10-ES Q61.4 → Orphacode 93108 = Renal dysplasia
    - Include Orphacodes 93172 - unilateral and 93173 - bilateral
  - ICD-10-ES E70.0 → Orphacode 716 = Phenylketonuria
    - Should be Orphacode 79254 = Classic phenylketonuria

Navarre

RERNA is based on the ORPHA coding system since its establishment. An Orphacode must be eligible for every registered case, after its validation. The clinical history is always revised unless the case was directly notified from the specialist.

The only source of information that actually provides them cases with ICD-10-ES codes is CMBD but RERNA isn´t massively capturing CMBD data since the Spain-RDR network finished.

The main goals of RERNA for the first year of the RD-CODE project were:

- To create a working group integrated by professionals of healthcare information systems (HIS) to promote the use of Orphacodes in several Navarre's HIS.
- To implement in RERNA's software all the descriptors and synonyms for the complete list of Orphacodes.

The work conducted during the first year of the RD-CODE was focused on:

- Preparing the software to allocate the list of synonyms for all the implemented Orphacodes.
- Turning the Orphacodes collected in RERNA to ICD-10-ES. This may help in terms of communication from the registry towards other Health Services.
- Starting the contacts with Osasunbidea (Navarrese Health Service) to include the Master file equivalences within the clinical history management tool in order to enable clinicians to directly assign both codes in parallel (ICD-10-ES and Orphacode).
- Requesting the capture of potential RD cases from CMBD (2016-2018) using all the ICD-10-ES codes resulting from the Master File.

Basque Country

The Registry of Rare Diseases of the Basque Country (RER-CAE) is based on the ORPHA coding system since its establishment so an Orphacode must be eligible for every case registered.

The main goal of this registry for the first year of the RD-CODE project was:

- To develop the Master file establishing equivalences between ORPHA and ICD-10-ES coding systems as a useful tool for the Basque Country Health service – Osakidetza. The Master file has the potential to be implemented in the informatics systems to facilitate the communication of new cases.

The work conducted throughout the year brought up the following outputs:

- Active collaboration with FISABIO and the other regional registries to reach an agreement in the ICD-10-ES to ORPHA equivalences.
- The regional registry has started the contacts with Osakidetza (Basque Health Department) to include the Master file equivalences within the clinical history management tool.

Valencian Region

The main goals of this registry for the first year of the RD-CODE project were:

- Integrate the equivalences ICD-10-ES to Orphacodes of the Master file into the VENT software.
- Automate Orphacodes assignment for new entries.

The work conducted throughout the year brought up the following outputs:

- Development of implementation strategies:
    - Differentiate input mapping from ICD-10-ES to Orphacodes from output mapping from Orphacodes to ICD-10-ES.
        - Input mapping implemented to solve automatically the cases that have a one-to-one ICD-10-ES to Orphacode equivalence.
        - Output mapping implemented to be used in the cases in which more than one ICD-10-ES code correlates to the same Orphacode. Both the Orphacode and the most precise ICD-10-ES are used to solve the case.
            - The original ICD-10-ES declared is kept to avoid information loss.
    - Establishment of hierarchical Orphacodes to solve the cases where the Orphacode is more specific than its equivalent ICD-10-ES code.
- Applying these strategies we can get the following results:
    - Cases in which a unique ICD-10-ES code is assigned to several to many Orphacodes.
        - Initially the case is resolved with an Orphacode selected by the previously established hierarchy.

        - The case is then revised to check if the Orphacode automatically assigned is correct. On contrary, the Orphacode is changed manually and the descriptor corresponding to its associated condition is linked to the ICD-10-ES for this case. This way we don´t lose the gained specificity in the output mapping.
            - Preferential input mapping (Q78.1 → 93276 - Polyostotic fibrous dysplasia)
                - Output mappings:
                    - 93726 → Q78.1 (Polyostotic fibrous dysplasia)
                    - 562 → Q78.1 (McCune-Albright syndrome)
    - Cases in which the Orphacodes linked to a specific disease are associated to non-specific ICD-10-ES.
        - The creation of virtual non-specific Orphacodes equivalent to the non-specific input ICD-10-ES helps to establish the case before its validation.
            - Input mapping (E75.29 → #-E75.29 - Other sphingolipidosis)
                - Output mappings:
                    - 585 → E75.29 (Multiple sulfatase deficiency)
                    - 333 → E75.29 (Farber disease)
    - Cases in which the Orphacode is linked to a multifactorial disease or syndrome just partially described by the associated ICD-10-ES.
        - This scenario rests unresolved because of the need to sum up two or more ICD-10-ES codes to complete what the Orphacode represents.
    - Cases in which multiple ICD-10-ES codes match the same Orphacode.
        - For the input mapping, whatever the ICD-10-ES from the set received, the same Orphacode is given.
            - Q87.40 → 558 (Marfan syndrome)
            - Q87.41 → 558 (Marfan syndrome)
            - Q87.410 → 558 (Marfan syndrome)
            - Q87.418 → 558 (Marfan syndrome)
            - Q87.42 → 558 (Marfan syndrome)
            - Q87.43 → 558 (Marfan syndrome)
                - The ICD-10-ES code is kept to avoid loss of specificity.
- Every time the ICD-10-ES codes are less specific than their associated Orphacodes plenty of false positives are generated.

Results summary

The Master file circulated among regional RD registries contained 4,877 disorder level entities with their ICD-10-ES equivalence covering around 85% of the starting RD-Action Master file. The Master file was later updated to include 5,232 disorder level entities with ICD-10-ES equivalence meaning around 90% coverage to be used in a future attempt of implementation.

Three of the regional registries had manually curated the assignation of Orphacodes to validated cases either directly received from the clinicians or assigned when the case is revised by each registry team. In these cases, the Master file has been useful to complement the information the registries collected previously and to facilitate communication with other health departments. For the remaining three of the regional registries, the equivalences from ICD-10-ES to Orphacodes listed in the Master file have been of direct use to convert the input code they get to an Orphacode especially when a one-to-one correspondence was found. Some other circumstances need to be manually revised in order to validate and assign a final Orphacode to the cases. To sum up, all six regional registries have adapted to code RDs using Orphacodes by applying different strategies either in an automated manner or by manual revision of the non-obvious equivalences.

According to the objectives (4.4.1) of the pilot implementation phase all six regional registries had to adapt their servers towards the use of Orphacodes as the reference codification system. All of them have made advances in this direction during the first twelve months of the project. Four of them had to actually implement the Orphacodes as a coding system for the registration of RD cases and 5 out of 6 are now able to do this in different ways depending on the structure and software in use. The goal to have 75% of the cases with an Orphacode was fulfilled because all the RDs submitted to the national registry have now a matching Orphacode. In addition, with 90% coverage of the Master file the tool to translate the ICD-10-ES codes collected by the regional registries to the ORPHA classification is engaged to facilitate and homogenize the selection of Orphacodes.

8 - Conclusions and considerations

Implementation of Orphacodes as the reference system for classification of RDs within regional and national registries has been proven possible in Spain. However, a number of variables slow down the process:

First of all, each population registry has intrinsic working features that make them different from the others. The situations can be roughly divided in two groups:

- The registries that receive the notification of the cases from the clinicians, either with an Orphacode or with a descriptor that needs revision to validate and assign an Orphacode.
    - The impact of direct translation from ICD-10 to ICD-10-ES to ORPHA, although important, it is indirect.
    - While the Master file allows facilitating the communication with other health services using ICD-10 based systems rather than Orphacodes, it doesn't make or makes little impact over the assignment of Orphacodes to the registered RD cases.
- The registries that retrieve the cases from information sources with different coding systems and translate them to Orphacodes.
    - This type of registries is highly benefited by the establishment of a shared list of ICD-10-ES to Orphacode equivalences.
    - This list known as Master file facilitates the assignment of an Orphacode (automatically or manually) to the retrieved cases.
    - The Master file also helps to unify the criteria to choose the same Orphacode for the same disease in different registries so they can easily communicate their data in the same format at least in terms of Orphacodes.

The other main circumstance that hinders the total homogenization of the registries is the fact that there is a lack of direct and unique equivalences of Orphacodes to ICD-10-ES, which is the coding system mainly used by the information sources. This means that:

- Although there are a number of Orphacodes that can be directly translated from ICD-10-ES, just 2,102 different ICD-10-ES codes are available to establish 5,933 equivalences to Orphacodes.
    - Moreover, 484 of the Orphacodes listed in the original Master file lack of associated ICD-10 from Orphanet which difficults ICD-10-ES proposal leaving 404 of those remaining without any equivalence so far.
- Many of these ICD-10-ES codes have been then used more than once for different diseases which have a specific Orphacode associated.
- Even in a scenario were we could manage to manually curate the assignment of the right Orphacode from the bulk list of them hanging from the same ICD-10-ES code, it would be difficult to keep the homogeneity among services.

The fact that all the AC involved in the project report their RD cases to the National Registry of Rare diseases associated to an Orphacode helps filtering discrepancies of criteria. Nonetheless, several improvements including the homogenization of the regional RD registries' procedures and their information sources remain necessary. In addition, new specific codes for RD must be included in the coding system used as reference at national level (currently ICD-10-ES) and future versions of it and ideally implemented at all information sources. This would actually allow to make a direct translation to ORPHA and to standardize the way RDs are registered at regional and national level.

In summary, adaptation to Orphacodes although possible, is limited by the current codification tools. Efforts towards the establishment of equivalences allow us not only to approach the target of systematically report RDs but also help us realize which are the assets of currently employed systems and, moreover, their flaws and lacks.

9 - List of Acronyms

AC – Autonomous Community / Autonomous Communities

CMBD – Minimum Basic Data Set

ERA-EDTA – European Renal Association-European Dialysis and Transplant Association

ICD-9-CM – International Classification of Diseases 9th revision – Clinical Modification

ICD-10 – International Classification of Diseases 10th revision

ICD-10-CM – International Classification of Diseases 10th revision – Clinical Modification

ICD-10-ES – Spanish International Classification of Diseases 10th revision – Clinical Modification

ISCIII – Carlos III Institute of Health

OMIM – Online Mendelian Inheritance in Man

Orphacode – Orphanet nomenclature of rare diseases

RD – Rare disease

SNOMED-CT – Systematized Nomenclature of Medicine Clinical Terms

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