



Work Package 5

Deliverable 5.1

REVIEW DOCUMENT OF EXISTING TECHNICAL IMPLEMENTATIONS FOR RARE DISEASE CODING

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



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It has been produced by the co-leaders of the Work Package 5 and is part of the Task 5.1: To define and set the necessary strategy and tools to implement the Orpha codes in the European countries (Task Leader: Remy Choquet [BNDMR, APHP, France] - Contributors: all WP5 contributors). It constitutes the Deliverable 5.1: Review existing technical implementations for RD coding.

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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Summary

Identifying rare disease patients within health information systems is a key requirement to accelerate patient recruitment for clinical trials or observational and longitudinal data collections such as registries for research and public health purposes. A better RD coding and, consequently, an increased visibility of RD patients in health information systems can also inform health authorities about patients' care pathways and their use of health services, a necessary step in the care planning process.

Whilst the integration of specific codes within generic health information systems appears to be a key step to achieve these goals, each member state may proceed following different methodologies and pursuing different objectives.

Some European Union (EU) Member States (MS) have already started the work of introducing the means to identify rare diseases patients within their health system through the use of the Orphanet proposed nomenclature in their national (and/or regional) registries or national (and/or regional) health information systems, and others have expressed their interest in using it. Different approaches have already been implemented and start producing results, raising problems and bringing solutions that are of interest for all MS. As stated in the proposal of the RD-ACTION Joint Action, a coding nomenclature alone is not enough to guarantee that the patient data will be comparable from a Member State to another. Along with the complete and quality assessed nomenclature of rare diseases (Orphanet), it is required to provide the coders (with heterogeneous profiles) with the right code sets and instructions as well as clear objectives but also, to eventually set the necessary regulatory and/or financial incentives. Besides, given the nature of the rare diseases field and the celerity of new discoveries, it might be required to handle some uncertainty in diagnoses, undiagnosed patients (despite all investigations done) as well as a strong and standardized management of the nomenclature update process since the knowledge in the rare diseases field is evolving quickly.

The D5.1 deliverable aims at better depicting the actual situation in Europe with regards to current national implementation of rare disease coding and identifying current situations in countries with regards to actual morbidity coding and possible European exploitation of generated data that could be made.

First, we issued a survey to representative designated members of the Joint Action that raised interest into that specific topic. The result of this survey is presented (*although it may not represent the actual MS situation*). Secondly, we technically described in this deliverable in more detail the current implementation or situation in experience carried out by 3 MS that have implemented a codification mechanism for rare diseases using the Orphanet nomenclature. The outcome of this detailed description together with the survey results helped us to define a set of criteria to be met by MS to achieve successful implementation of RD coding and to guarantee qualitative and comparable data at EU level when similar implementation objectives are pursued. This will guide the work for

the next steps in the WP 5 to provide the necessary resources for easy implementation of the Orphanet nomenclature in varying settings of the different EU countries

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I. General definitions and considerations

Through this document, some technical terms may be used. A definition is proposed in this section.

Orphanet nomenclature: it designates the Orphanet list of rare disorders (i.e. diseases, syndromes, anomalies and conditions), groups of disorders, categories, and sub-types of disorders (designated as entities associated with Orpha numbers) as it can be downloaded from Orphadata (www.orphadata.org).

Orphadata¹: The mission of Orphadata is to provide the scientific community with a comprehensive, high-quality and freely-accessible dataset related to rare diseases and orphan drugs, in a reusable format. The dataset is a partial extraction of the data stored in Orphanet and is freely-accessible available in seven languages.

Orphanet classifications: Nosological classifications grouping within tree structures items from the Orphanet nomenclature as proposed by Orphanet on Orphadata. Orphanet classifications are numerous and pre-defined. Their main purpose is to group entities within major rare diseases groups (Rare metabolic disorders, Rare kidney disorders, etc.) following a nosological pattern. They were not built to be used as a statistical tool for grouping patients coded with underlying entities nor to be used as a diagnostic tool that would follow steps to be followed within the diagnostic procedure.

Orpha number: Unique identifying number assigned by Orphanet to a given disorder. (disease, group of disorders, subtype). The number assigned to each entity within the Orphanet nomenclature. It is unique and permanent.

OrphaCode: the Orpha number (extracted from the complete nomenclature) that can be used to be assigned to a patient within an information system.

Diagnosis: Is the best hypothesis a medical specialist can make given the actual observations (clinical or biological) on a patient. A diagnosis can be represented by a Disease, a condition or both associated.

Disease²: A disposition to undergo pathological processes that exists in an organism because of one or more disorders in that organism.

Clinical phenotype²: A (combination of) bodily feature(s) of an organism determined by the interaction of its genetic make-up and environment.

Phenotype²: A (combination of) bodily feature(s) of an organism determined by the interaction of its genetic make-up and environment.

¹ <http://www.orphadata.org/cgi-bin/inc/about.inc.php>

² <http://www.ncbi.nlm.nih.gov/pubmed/21347182>

Genotype³: Genotype is one of three factors that determine phenotype the other two being inherited [epigenetic](#) factors, and non-inherited environmental factors.

Morbidity⁴: Refers to having a disease or a symptom of disease, or to the amount of disease within a population. Morbidity also refers to medical problems caused by a treatment.

Patient Registry⁵: A patient registry is an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and serves one or more predetermined scientific, clinical, or policy purposes.

Health information system⁶: The health information system provides the underpinnings for decision-making and has four key functions: data generation, compilation, analysis and synthesis, and communication and use. The health information system collects data from the health sector and other relevant sectors, analyses the data and ensures their overall quality, relevance and timeliness, and converts data into information for health-related decision-making.

Electronic health record⁷: An electronic health record (EHR) is a digital version of a patient's paper chart. EHRs are real-time, patient-centred records that make information available instantly and securely to authorized users. While an EHR does contain the medical and treatment histories of patients, an EHR system is built to go beyond standard clinical data collected in a provider's office and can be inclusive of a broader view of a patient's care. EHRs can:

- Contain a patient's medical history, diagnoses, medications, treatment plans, immunization dates, allergies, radiology images, and laboratory and test results
- Allow access to evidence-based tools that providers can use to make decisions about a patient's care
- Automate and streamline provider workflow

One of the key features of an EHR is that health information can be created and managed by authorized providers in a digital format capable of being shared with other providers across more than one health care organization. EHRs are built to share information with other health care providers and organizations – such as laboratories, specialists, medical imaging facilities, pharmacies, emergency facilities, and school and workplace clinics – so they contain information from all clinicians involved in a patient's care.

DRG system⁸: A Diagnosis-Related Group (DRG) is a statistical system to classify any inpatient stay into groups for the purposes of payment. Depending on the country internal system, the DRG

³ <https://en.wikipedia.org/wiki/Genotype>

⁴ <http://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=44514>

⁵ EUCERD Core Recommendations on Rare Disease Patient Registration and Data Collection

⁶ http://www.who.int/healthinfo/statistics/toolkit_hss/EN_PDF_Toolkit_HSS_InformationSystems.pdf

⁷ <https://www.healthit.gov/providers-professionals/faqs/what-electronic-health-record-ehr>

⁸ http://www.euro.who.int/__data/assets/pdf_file/0004/162265/e96538.pdf

classification system divides possible diagnoses into more than 20 major body systems and subdivides them into almost 500 groups for the purpose of reimbursement. Factors used to determine the DRG payment amount include the diagnosis involved as well as the hospital resources necessary to treat the condition.

Mortality information system⁹: A Mortality Database (or information system) is a compilation of mortality data by age, sex and cause of death, as reported annually by Member States from their civil registration systems.

Morbidity information system: A Morbidity information system contains hospital discharge data (or outpatient data) by detailed diagnosis (mainly ICD 10 in Europe). It is generally sometimes linked to a DRG system at national level but many other systems for data collection although data may be individual can also produce data which is collected in such information systems. European countries reports to the WHO through the European Hospital Morbidity Database¹⁰.

II. RD Action WP5 Survey

All MS use morbidity and mortality recording systems. Morbidity recording systems utilize, for the generality of diseases and for the majority of countries, ICD classification. Only in a few countries other systems like SNOMED CT¹¹ are used. The Orphanet nomenclature is specifically dedicated to rare diseases and is used only in few countries. Taking into account these ongoing experiences, the contexts, the prerequisites, the methods to implement specific monitoring systems of RD patients will be defined.

This survey has some limitations that should be taken into account when reading the following results. Given the specific knowledge required to answer the subject, responses should be reviewed by national official bodies dealing with national health information systems in order to limit the observed biases of the survey.

Objectives

This survey was designed to draw a more precise picture of existing coding situations at national level within the participating countries of the joint action and to facilitate the first year's work of the WP5 work package. It also aimed at better measure the potential of MS to implement a specific codification system for rare diseases patient identification.

It was also an opportunity to better identify which parts of the work program participating countries would like to participate in, and to which level of implication for the years to come in order to build a European roadmap for RD coding.

⁹ http://www.who.int/healthinfo/mortality_data/en/

¹⁰ <http://data.euro.who.int/hmdb/>

¹¹ <http://www.ihtsdo.org/snomed-ct>

Methodology

The Greater Paris Hospital institution (APHP, France), the German Institute of Medical Documentation and Information (DIMDI) and the Rare Disease Coordinating Center of the Veneto Region (Italy) worked together to identify key questions that needed to be answered regarding the coding systems in participating countries. It was divided in three main parts: morbidity, mortality and registries. A last section was about the contribution to the WP.

The survey was created on an online platform (Zoho Survey) that allowed several reviewers to the answers. The link to this online survey was sent before the kick off meeting of the RD-ACTION joint action to all the subscribers to the WP5 session. Countries that did not answer previously were contacted individually to ask them to participate in the survey.

Results were extracted from the online tool and analysed by the co-leading teams of the WP5.

Results

Note: complete results are available at: <http://www.rd-action.eu/wp-content/uploads/2016/01/framework-survey-interpretation.pdf>

The survey was responded by 20 country representatives (15 EU countries representatives). Respondent profiles were heterogeneous but mainly composed of experts from RD centres or Orphanet network members. Few information system specialists from countries were participating. The survey was decomposed to get information from countries about the use of a national morbidity coding system, a national mortality coding system, an existing policy for coding rare diseases, information about national registries programs for RDs and finally their participation objective within WP5.

National morbidity coding system

Repondants reported that most MS have a national coding system to record morbidity and it is generally connected to a DRG-like system. 12% (3) of respondents declared not to have a national system to record morbidity. Countries mainly use ICD-10 (with local extensions in some cases) and very few are starting projects to use SNOMED-CT.

In the case of SNOMED-CT, it is important to note that DRG-like data collection mechanisms need to be also compatible with SNOMED-CT. SNOMED-CT is often first use at hospital local level to better document patient electronic medical records. The country may have a national program to push the adoption of SNOMED-CT codes but not yet intended to be used within a DRG-like data collection.

With regards to the coverage of the morbidity coding at national level, half the countries have a full coverage (in-patient, out-patient and ambulatory care) for coding, where the other half, cannot cover all healthcare activities at national level (mainly in-patient care). Subjectively but generally, countries do not trust the morbidity coding system as a system that could produce qualitative data

for epidemiological studies. Besides, coding biases within the DRG-like systems due to financial use is well documented in the scientific literature and could represent a major problem when dealing with disease specific epidemiological study. The potential biases at a national level could however be acceptable and eventually corrected but no study has been published so far.

The presence of expert centres for RD has not been studied nor the capacity of the MS to identify expert centres coded patients as to evaluate the quality and potential misuses of RD codes. This needs to be clarified and listed as a parameter in the guide for implementation and as a potential consequence in terms of data quality.

National mortality recording system

MS usually have a national regulatory system to record mortality, using ICD-10. In 2/3rd of the participating countries there is a centralized management of the coding system for mortality. A specific software for browsing ICD10 codes is used by half the countries. Less than half of the participants confirmed there is a patient identifier available in their country, which is almost not linked to the patient ID for morbidity recording.

Mortality studies for rare diseases could profit from a linkage from morbidity systems although it is not the priority. For prevalence studies, the date of death of the RD patient is although required.

Specific RD policy for RD data coding or collection

MS do not generally have a national policy with regards to RD codification in general. Few countries (5) have an on-going process though. They will be described in section 2 of this deliverable. They mostly are connected to a national/regional program for RD patient registration. Only 2 countries have introduced it within the health information system framework (e.g. DRG-like). Half of the participants declare discussing a national policy to be built.

Existing RD registries

The biases amongst respondents prevented us to take conclusions, participants seem to have a poor knowledge (in general) of the existing RD registries in their respective countries. When they have, a lack of coding harmonization is perceived. Harmonization among registries through a national hub or integration program exist in 1/3 of MS, another third have a project to launch one and 1/3 do not have any project on this matter.

Participation in WP5

Finally, most MS are keen on participating to the WP5 at local level for helping in implementing the products of the work package. Meanwhile at the WP5 level, MS are willing to participate to mainly report about their situation at local level, then in designing the WP5 framework (guidelines, definition of the master file etc.), some in communication and long term roadmap definition and some in organizing an international workshop of RD coding.

This survey, even with its limitations and biases, provides a broad overview of MS readiness to implement a specific coding system to identify rare disease patients. It provides a view on possible opportunities to work as at today with some countries. It will help in a second stage (year 2 and 3) to define a roadmap with local MS responsible for implementation or regulation.

III. Existing technical implementations

As partly described in the previous work done in the extent of the EUCERD joint action, several countries have started implementing the Orphanet nomenclature at national or regional level. Since each country organization is different with regards to health data capture, the purpose of this section is to describe 3 different implementations in order to define a set of implementation parameters that could have an effect on future exploitation of the data. For example, the lack of legal incentive could have an effect on the effectiveness and the timeframe of the deployment of the Orphanet nomenclature, the lack of expert centres could limit the use of very specific codes for very rare diseases or codes could be misused, using DRG system mechanics could lead into biases due to the financial primary use of the system, only confirmed cases could be included, etc.

3.1. The French implementations of the Orphanet nomenclature

3.1.1. The French expert centres for rare diseases

Since 2005, two rare disease national plans were launched by the French authorities. The first plan (2005-2009) focused on the organization of the rare diseases care network. Medical units were labelled either RD centres of expertise (centres de référence) or centres of competences (centres de compétences) according to their proficiency in care and treatment of specific RD. The expert centres are organized within hospitals, as specialized units or as a specific care process within existing units. There are 133 reference centres for rare diseases authorized by the French ministry of health. They are organized as networks, working closely with more than 500 competency centres spread across the country.

3.1.2. CEMARA (2007 – 2016)

The integration of the Orphanet nomenclature in France has started in 2008 within the CEMARA RD generic health information system. This system was an autonomous system used in many situations when hospital health information systems were not yet implemented in France. The system was set after the RD expert centres were authorized by the French authorities. Back then, in 2005, it was considered that there was no epidemiological surveillance for rare diseases (RDs) in France. The implementation of such monitoring required taking into account the RDs specificities. Their diversity did not allow a complete monitoring of all RDs. The medical nomenclature was not suitable for epidemiological monitoring of RDs. The plurality of supply and the multiplicity of care for RDs (RDs centres of expertise, RDs centres of competences, non-specialized services, paediatricians, general practitioners...) make identifying RD patients difficult. Sources of data on RDs existed but were scarce, disseminated and not coordinated, without epidemiological exploitation.

The need for a better knowledge led to the objective of implementing between 2005 and 2008 a coherent policy for the epidemiological surveillance of RDs. A specific monitoring for some RDs was

expected, with a better definition of the incidence, prevalence, impact on mortality, morbidity, quality of life and support for patient circuits. This surveillance was done within CEMARA for half of the expert centres (2016 centre inclusion rate).

CEMARA system was set to help RD centres to follow their care RD activity and patient rare diagnosis. So it captures data from the moment the patient is entering the expert centre the first time, to the establishment of their diagnosis, the evolution of the diagnosis or the incapacity to provide the patient a diagnosis even if all tests were processed. And by doing that, the data capture is requesting specific data to help in building some specific public health studies (time to diagnose, mortality, co-morbidity studies, etc.). As of today, 320 000 RD patients are included in CEMARA. And because of the use of a fine-grained terminology system for RDs, it becomes easier to identify patients for clinical trials or specific research.

3.1.3. The integration of the Orphanet nomenclature within the French DRG system (2013)

In 2013, as part of the national plan for rare diseases 2, a regulation was issued by the French ministry of health to ask all hospitals hosting a RD expert centre to set a specific documentary code (picked from the Orphanet website) whenever an in-patient clinic event might occur. The regulation instructed to tag RD patients regardless of the reason for the event. The perimeter was not clear as to know if only confirmed diagnosed patients should be coded, how the nomenclature should be used and the nomenclature itself was never used for more than half the RD centres. The result in terms of acceptance and data quality was rated as poor. The methodology was then assessed and re-integrated within the BNDMR project.

3.1.4. The National Database for Rare Diseases (2012-2016)

The BNDMR project was introduced within the 2nd national plan for rare diseases. The first objective of the project (2012-2014) was to propose a common data set to be gathered for all rare diseases in France. To encourage a consensus at a national level to constitute a homogeneous data collection at the point of care for rare disease patients, 4 national expert groups were identified. The scientific literature for rare disease common data elements (DE) was reviewed in order to build the first version of the F-MDS-RD. The French rare disease expert centres validated the DEs. The resulting F-MDS-RD was reviewed and approved by the National Plan Strategic Committee. It was then represented in an HL7 electronic format to maximize interoperability with EHRs. The F-MDS-RD is composed of 58 data elements in 6 categories: patient, family history, encounter, condition, medication, and questionnaire. It is HL7 compatible and can use various ontologies for diagnosis or sign encoding. The F-MDS-RD was aligned with other CDE initiatives for rare diseases thus facilitating potential interconnections between RD registries.

In order to facilitate the integration on their daily routine data capture tools, the minimum data set is now being integrated within the national health information framework to enable national interoperability between more than 60 university hospitals and the national BNDMR.

3.1.5. Implementation of a national terminology service

Along with a consensual data collection set of items, medical terminologies were proposed as standards. One usual barrier to the implementation of new coding systems is the lack of consolidation of such information scattered in different nomenclatures (and classification systems) such as Orphanet, OMIM or HPO both from a technical and an end user point of view.

To help both EHR vendors and clinicians with this task, a specific coding application LORD (Linking Open data for Rare Diseases – <http://enlord.bndmr.fr>) was built with a backend semantic database acting as a terminology server and a web application to help clinicians find codes. The application offers an integrated view of 6000 rare diseases (disorders) entities linked to more than 14 500 signs and 3 270 genes. The application provides a browsing feature to navigate through the relationships between diseases, signs and genes, and some Application Programming Interfaces to help its integration in health information systems in routine.

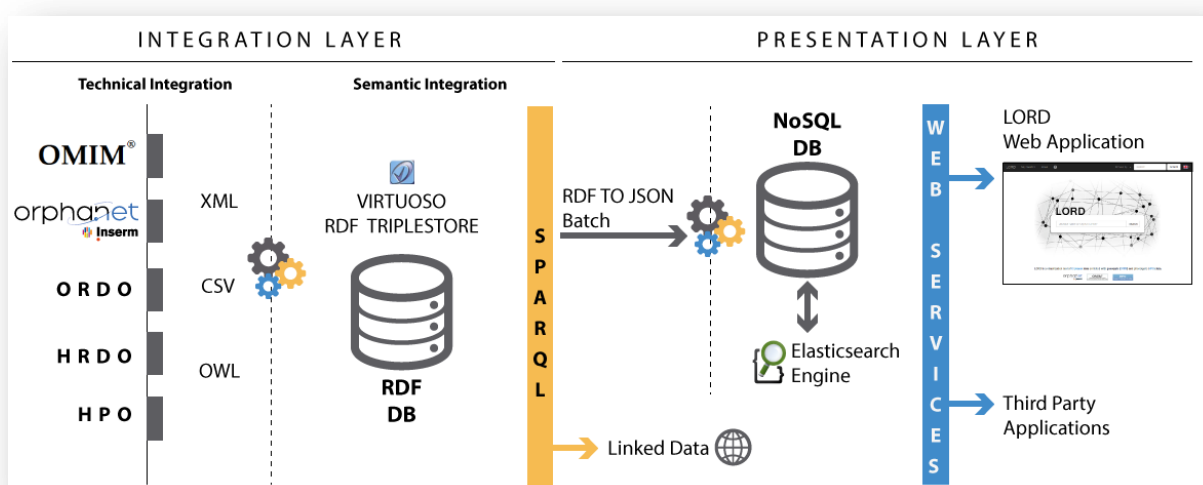


Figure 1 – The LORD overall biomedical data architecture of the terminology service developed

The integrated data can be browsed in an openly available web application for all expert centres. When users are navigating through diseases graphs, they can filter the displayed concepts. For example, while looking at *Cystinosis* information (<http://enlord.bndmr.fr/#disorders/213/97966>), the user can filter on Rare eye diseases (if the user is an Ophthalmologist) and then navigate through symptoms that are related to his medical expertise: *Unclassified maculopathy, metabolic disease with corneal opacity or metabolic disease with pigmentary retinosis*. The user then can have access to textual information from OMIM and HPO for a given disease and epidemiological information from Orphanet. As relations between data sources can be one to many (1 Orphanet disease for n OMIM entries) then we have developed an OMIM entry selector to help user navigation and data retrieval. From the web service standpoint, all data of all OMIM entries are gathered in the same JSON object for an individual Orphanet disease.

While the Orphanet nomenclature was used in CEMARA and recommended by the EU in 2014, the nomenclature is large and was recently reported to be not easy to manage and therefore to guarantee a homogeneous codification across the national expert centres. A dedicated expert group was then appointed by the French ministry of health in October 2014 to evaluate the fit of the proposed resource based on the CEMARA experience and medical experts' needs.

The conclusions of the group were delivered to the French ministry of health. The main recommendations consisted in phasing the validation and the rollout of the nomenclature together with expert centres that will define the appropriate granularity and lists of codes, the coding instructions and propose an exploitation plan for their data in the BNDMR. It was also foreseen by experts in RD centres that double-coding (together with ICD) is a blocking task to implement any other terminology within their care setting. In addition, terminologies that are describing genetic based diseases are evolving rapidly nowadays. Since the rare disease should be only coded once, the burden of double-coding is reduced. Also, to reduce that burden, the national college of medical information physicians is offering to propose transcodes from validated OrphaCodes to ICD at a national level.

Current works in France regarding the coding are the following:

- Assessment with national networks for RD of the proposed Orphanet leafs (aka OrphaCodes) existing to code identified patients
- Review of classifications to be used as statistical groups for national epidemiology per network
- Review of transcodes between selected OrphaCodes and ICD10 for DRG coding

3.1.6. National identifier

A national identifier availability, or at least a mechanism required to avoid duplication of cases is a requirement to generate statistics at nationwide level. In this area, we generally divide data collection in the healthcare domain within 4 following objectives: care, care reimbursement/planning, epidemiology/public health, and research. Depending on the objective, regulatory constraints are different as well as patient identifier requirements and/or availability.

In France, within the **care** domain, in the context of a local hospital, a strong patient identifier - which is generally linked to directly nominative information - is required to make a patient electronic medical record flow from a medical unit to the other. Hospitals do implement local identifiers for this task (PPI – permanent patient identifier) that tend to be permanent but locally generated. Hospitals are allowed by law to organize their own information system for care, implementing their local patient identifier to do so. Sharing this identifier is not allowed without proper authorization, justification and security mechanisms. Recently, to enable the rollout of the national DMP (personal medical file), French authorities proposed the national health identifier (INS) project to improve the fluidity of exchanging and sharing health data within a secure framework. The INS is assigned to each beneficiary of health insurance, and is recorded in the chip of his/her card. To meet short-term needs and in order to not penalize the deployment of shared health information systems the INS-C will be

used (“C” stands for calculated). The INS-C is generated from the social security number and other identifying information by recognized anonymization techniques. It is not available for children. The 2015 Health law has recently allowed the use of the NIR as a national health identifier in the care field to overcome this limitation.

In the **care reimbursement** field, the national social security number (NIR) is directly used. This number is generated at birth and is managed by the national identification directory for the identification of natural persons (RNIPP). This identification number is unique to the individual and is composed of 13 numeric characters.

For care **activity planning** and **cost analysis** of national care services, the NIR is indirectly used. The social security number, coupled to other nominative information, is locally hashed at the hospital level following a published methodology to make the individual data de-identified. It is then hashed a second time at the national level (6). The data is then sent and linked to the SNIIRAM database (health reimbursement services for outpatient clinics and laboratory procedures). The SNIIRAM database could also be used to perform studies for **epidemiological and public health** purposes upon specific authorization.

For **research** purposes, the authorized general mechanism is to build a specific identifier limited to the study, the correspondence table between this identifier and the nominative data items (name) should be kept separately from the database. It is authorized by two national independent organizations the Comité Consultatif sur le Traitement de l’Information dans le domaine de la Recherche en Santé (CCTIRS) and the CNIL.

Since no existing patient identifier meets those constraints, the chosen approach in France (within the evolving regulations) is to generate a national identifier for rare diseases patients from existing nominative data. The patient identifier to be used in the French Rare Disease Registry has to be a non-meaningful identifier. No personal information has to occur since the national registry has to be a de-identified database. Every patient will be attributed a unique and perennial identifier regardless of his path and movements through the healthcare institutions. Besides, children and even foetuses, which represent an important proportion of rare disease patients, must have their proper identifiers. In fact, about 80% of rare diseases are genetic ones and usually appear during the childhood (1). Foetuses represent a non-negligible proportion of rare disease patients since the genetic screening is done more and more early.

This patient identifier will be especially used for identity federation purposes in an epidemiological and statistical context, which is less stringent than a care context where an error of identification threatens patient’s safety. The new identifier for the French rare disease registry relies on nominative data (i.e. person identity), which are, to date, the most spread and most reliable available source of information.

This identifier will help in making data linkage between historical registries and the national BNDMR for retrospective data (enhancing the epidemiological studies), and linkage between the national NIR number for prospective data collections.

3.1.7. Implementation of the coding mechanism within applications

The second phase of the project aimed at modernizing the data collection methods as it was proposed in CEMARA. The modernization consists in favouring interoperability between Hospital Information Systems and the BNDMR. It is done through the use of an interoperable application (BaMaRa) that can get data from local EHRs when it is made compatible. The French national agency for shared health information systems (ASIP Santé) is now incorporating within the national health interoperability framework the minimum data set in order to ease data flows between proprietary applications and the BNDMR. Applications that are willing to be compatible with the BNDMR should then implement means to capture and/or generate the required data. With regards to the medical coding, CEMARA implementation was integrating several coding systems/schemes (Orphanet nomenclature, phenotypes from the London Dysmorphia, a chromosomal anomaly descriptor), the current proposed implementation within BaMaRa aims at giving a methodology to capture patient information from the initial investigation stage to confirmed diagnosis or undiagnosed cases. It also supports non rare disease patient recording but only for activity reporting purpose (parents during genetic investigations). The medical characterization should also support several uses depending on RD network objectives in terms of data exploitation, for instance: genotype-phenotype correlation, epidemiology, activity reporting, patient characterization for future inclusions, time to diagnose study, undiagnosed studies, etc. Therefore, several sets of medical terminologies are used conjointly:

- OrphaCodes (when the diagnosed is suspected or confirmed) representing the rare disease coding,
- Orphanet generic codes for nonspecific confirmed rare diseases,
- HPO codes (Human Phenotype Ontology) used to specify the phenotype of the patient, comorbidities, phenotype-genotype investigations through the use of Matchmaker Exchange Network,
- A possibility to use OMIM codes with suggested transcode to OrphaCodes,
- ICD10 codes for comorbidities or temporary coding until a rare disease can be suspected or confirmed,
- A chromosomal anomaly descriptor used when nonspecific rare disease can be confirmed,
- Gene(s) localization(s) and mutation(s).

The only mandatory description is the OrphaCode when the diagnosis is suspected or confirmed. The method for confirmation is then specified in order to differentiate clinical diagnosis and genetic diagnosis.

+
Diagnostic #1
Diagnostic #2

Statut actuel du diagnostic *

En cours
Probable
Confirmé
Indéterminé

Mode(s) de confirmation du diagnostic *

Maladie rare (Orphanet)

Cystathioninurie
×
▼

Description clinique

× Nécrose hépatocellulaire
× Hépatosplénomégalie
× Anasarque
▼

Signes atypiques

× Acanthamoebiose
× Anomalie inflammatoire de l'oeil
▼

Informations génétiques complémentaires (optionnel)
+

Figure 2 – The medical codification panel in BAMARA

3.1.8. Incentives: regulation and financial

Since the creation of expert centres for rare diseases within the first national plan (2005-2008), epidemiologic surveillance was set as a mandatory objective of expert centres. In 2012, the French ministry of health issued a national regulation as to enforce the coding of RD within the national DRG system. The regulation has been withdrawn since then. In 2016, a new regulation, refining the missions of the expert centres for rare diseases was issued. This regulation states the requirement for expert centres to capture epidemiological data within the national bank for rare diseases (BNDMR). The specific funding received by the expert centres might be modified depending on the participation of the centre to the epidemiological surveillance.

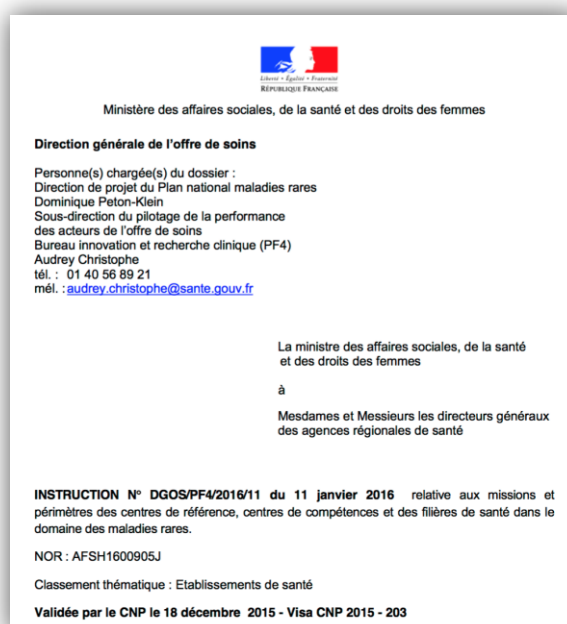


Figure 3 – The French national regulation for RD centres issued in January 2016 (http://circulaire.legifrance.gouv.fr/pdf/2016/01/cir_40460.pdf)

3.1.9. Data exploitation plans

The first phase of the project was to validate a minimum data set at national level with identified exploitation plans or to be support of the following study types:

- Descriptive epidemiology: prevalence, incidence of disease(s)
- Care provision assessment
- Expert centre care activity measurements
- Undiagnosed or time to diagnose
- Co-morbidities
- Phenotype to genotype through matchmaker exchange platform supported by IRDIRC

The second phase of the project aimed at modernizing the data collection methods as it was proposed in CEMARA. The modernization consists in favouring interoperability between Hospital Information Systems and the BNDMR. It is done through the use of an interoperable application (BaMaRa) that can get data from local EHRs when it is made compatible. The French national agency for shared health information systems (ASIP Santé) is now incorporating within the national health interoperability framework the minimum data set in order to ease data flows between proprietary applications and the BNDMR. The BNDMR anonymized data could then be linked with other national data bases in France to expand exploitations capabilities.

3.1.10. Synthesis

Implementation criteria's	Response
Diagnostic spectrum recording	From initial investigations to confirmed diagnosis and non-diagnosed patients
Terminology systems	OrphaCodes / ORPHA nonspecific entities / OMIM / ICD10 / HPO / Genetic descriptors
DRG integration	No (yes with national identifier at a second stage)
National identifier	Calculated specific for RD National number for health care (2016)
Interoperability framework	Yes, national
National data repository	BNDMR record linked with other national databases (phase 2)
RD expert centre	131 RD expert centres fully identified nationally
Coding guidelines	Being built through national networks or rare diseases expert centres
National Regulation	As of Jan 2016, the BNDMR is mandatory
Financial incentive	Specific national funding linked to the regulation

3.2. The Italian implementations of the Orphanet nomenclature

3.2.1. The Veneto Region RD care networks

Rare diseases have been recognized as a priority public health issue in Italy for the first time in the National Health Plan 1998-2000. In 2001 a Ministerial Decree (n. 279/2001)¹² was issued in order to establish a specific care network for RD patients within the national health system. As the Italian health system has a decentralized organization, Regions have the responsibility for the delivery of health services. Two agreements between the Government and the Regions were issued in 2002 and 2007 in order to assure the implementation of the Ministerial Decree. Within this framework, at regional or interregional level, a network of formally labelled Centres with recognised expertise on RD was set up. At the moment, there are 199 centres for RD recognized at national level.

Since 2002, Veneto region, in the northeast of Italy (4.9 million inhabitants), officially identified Centres dedicated to rare diseases patients' diagnosis and care. The RD Centres have been officially labelled on the basis of indicators and criteria established by the Regional Health Authority and are subject to continuous monitoring. In particular, their identification at the beginning of this process has been performed on the basis of activity data derived from health information systems (i.e. hospital discharge records, rehabilitation data flow, etc.) and combined with documented data referred to the candidate Centres (i.e. facilities and services provide to RD patients, research activities, relation with patients' associations, etc.). After the establishment of a dedicated RD registry, also data coming from this data source have been taken into account in the monitoring of existing Centres' activity. Since their identification, Centres of expertise work in strict cooperation with the territorial network of services, which provide primary and specialised care, as well as non-medical services to rare diseases patients. In 2004 a formal collaboration agreement between four neighbouring regions and provinces, located in the north-east of Italy, including Veneto region, lead to the identification of a common inter-regional network of labelled Centres, of expertise for specific groups of rare diseases (for instance for rare haematological conditions, rare neurological disorders, etc.). The established care network has undergone through a revision process in 2007 and in 2015. One or more clinical units, either within the same hospital or in different hospitals, compose RD centres. Rehabilitation services are fully part of the care network. All the health care providers involved in rare diseases patients' care use a common information system (IS), which enables the sharing of clinical data and supports the provision of benefits and services to patients. At the same time, the system is the basis for the establishment of an area-based registry recording data on rare diseases' patients. The RD Coordinating Centre of the Veneto Region manages the Registry. At the moment, the IS is adopted by other 7 Italian regions, corresponding to a monitored population of nearly 24 million inhabitants.

¹² Italian Ministry of Health: Ministerial Decree 18th May 2001 No 279. Regolamento di istituzione della rete nazionale delle malattie rare e di esenzione dalla partecipazione al costo delle relative prestazioni sanitarie, ai sensi dell'articolo 5, comma 1, lettera b), del decreto legislativo 29 aprile 1998, n. 124, Volume 160. Gazzetta Ufficiale; 2001:180. Available at : <http://www.trovanorme.salute.gov.it/norme/dettaglioAtto?id=17169>

3.2.2. The RD Italian list

A list of rare diseases annexed to the Ministerial Decree defines which patients can receive benefits and facilities in access to care. The list contains 331 names of diseases or groups of disorders, divided into 14 nosological categories, according to the ICD9-CM classification. For groups, only some examples of included diseases are provided in the Ministerial Decree. A preliminary work was carried out by the medical team of the RD Coordinating Centre in order to properly identify, according to medical literature and databases, all the diseases actually included, whose affected patients are eligible to benefits and should be monitored by the RD Registry. This work dealt also with the management of synonyms and eponyms. This list is subject to continuous updating, as new forms are described and new classifications enter in use. Corresponding codes used in international classifications (i.e. ICD9-CM, ICD-10, OMIM and OrphaCodes) are assigned to each disease entity. Considering diseases included into groups and sub-types of diseases, nearly 3,000 names of diseases have been identified. Nevertheless, some diseases or group of diseases that qualify as rare, are not currently covered by the list annexed to the Ministerial Decree. The process of revision of the list, implying the inclusion of other RD entities, is ongoing at national level, but not concluded yet. Excluding rare cancers, whose cases are recorded by regional cancer registries, the rare diseases entities monitored, considering diseases included into groups, represent nearly the 58% of all the rare diseases entities included in the Orphanet list.

3.2.3. The Veneto Region RD Registry

The RD Ministerial Decree n. 279/2001 envisaged the establishment of a national RD Registry at the National Institute of Health, with the aim of providing epidemiologic data on RD. Due to the decentralized health system organization, the set-up of regional or interregional registries was in charge to Regions. The two above mentioned agreements between the Government and the Regional Authorities, in 2002 and 2007, defined the modalities of data communication between the regional registries and the national one as well as a minimum data set of variables collected by regional registries that have to be communicated to the national level. Regions have set up regional registries according to different modalities, within regional health information systems.

Veneto Region developed since 2002 a dedicated RD information system, intended not only as a RD registry, but also as a system fully supporting the RD patients' care pathways and the provision of services to them. The information system connects through a protected network (Regional Health Network Intranet) the labelled Centres for rare diseases, located at hospital level, all the local health authorities, the territorial services and all the pharmaceutical services, both local and hospital ones, of the Veneto region. The computerized system is a complex platform based on a web-browser Java application, which populates a unique central Oracle database with a three-level architecture, able to collect and manage large amounts of data. L-DAP has been implemented to manage encrypted users' accesses according to personal different profiles. The system collects a core-set of information on socio-demographic data of patients, such as name, date and place of birth, sex, fiscal code, residence, and, in case, place and date of death. The basis of the Information System are the RD diagnoses, included in a list which is common for all users and periodically updated, as described above. Specific modules have been progressively developed starting from the diagnosis module. The IS allows the online prescriptions of treatments (i.e. drugs, para-pharmaceuticals, galenicals, dietetic products, etc. as well as medical devices) and the reporting of possible related adverse events.

Information on clinical data, specific per group of RD, is collected in the IS according to a hierarchical logic. 4,957 signs, 294 symptoms, 13,861 co-morbidities, 278 impairments and 18,201 localizations constitute the thesaurus at the basis of the clinical record within the IS. The IS has been adopted, with different levels of module implementation, in other 7 Italian Regions, (Trentino-Alto Adige, Emilia-Romagna, Liguria, Campania, Apulia, Umbria and Sardinia) with at the moment more than 130,000 recorded patients in the whole area. In the whole area more than 6,072 users access the system, of whom 3,081 are clinicians working in RD Centres.

The system has been developed to support Centres in the management of RD patients. According to the national legislation, a patient with a clinical suspicion of a rare disease has to be referred to a specific Centre of the RD network in order to have a complete assessment. Only if performed in an officially labelled RD Centre, this assessment is free of charge for the patient. Diagnosis' recording implies the issue of a certificate of diagnosis by the clinician working in the Centre of expertise and, at the same time, the issue of an exemption by the local health authority of residence of the patient. In this way, the patient can receive the benefits he/she is legally entitled to, such as specific drugs or medical devices listed in the therapeutic plan, defined by the Centre of expertise. All this information is recorded in the IS and shared among authorized users, avoiding time due to administrative procedures that generally take place between the moment of prescription and the actual access to treatment for the patient. A patient-centred approach has been followed also in the design of the IS. Clinicians working in RD Centre can access the information they have recorded in the IS. Patients are the owners of their recorded clinical information. They are given a personal code (assigned by the RD regional Coordinating Centre) in order to allow other clinicians working in labelled RD Centres of a wide interregional area to access their personal clinical information. In this way, followed patients can move freely within the RD care network.

Health data are collected and stored separately from other data in the IS. The possibility of linking the two components is guaranteed by the assignment of an ID, on the basis of a random number algorithm. This represents a non-meaningful identifier. This identifier is used when epidemiologic or clinical research has to be performed starting from registry data. Authorized users have access to personal identifiable data, when the IS is used for care purposes, i.e. to provide patients with benefits and other services.

At national level, the fiscal code represents the univocal identification key of each citizen. It is attributed by the National Revenue Agency and reported in the personal health card issued by the same Agency. The fiscal code is generated from nominative data. At national level there is an evolving situation regarding the regulation dealing with health information systems in general. It is planned in the near future the use at national level, starting from health discharge records, of another code, instead of the fiscal code, called CUNI (not invertible univocal code). Data will be transmitted from the local level to the national one using this new code, obtained applying an asymmetric algorithm to the original identification code.

3.2.4. The use of OrphaCodes within the RD Registry of the Veneto Region

The traceability of RD in health information systems has been recognized as an important issue in the National RD Plan 2013-2016. In particular, the Plan suggested the experimental use of the orpha-

OrphaCodes in addition to the ICD ones, in some health information systems, particularly at regional level¹³.

The use of OrphaCodes has been introduced in the Veneto Region RD Registry since 2006. The specific identification of RD entities monitored by the RD Registry has been a necessity since, as explained above, the Italian RD list includes single RD entities as well as groups of rare diseases. Some of these groups can include more than 200 different entities, although they do not appear explicitly in the national list. The necessity to adopt a system able to identify each RD entity responds to two necessities in the context of the development of the IS. First, to produce reliable epidemiological data the identification of a RD entity must be as precise as possible. From a health-planning point of view, not only it is important to know the contribution of different nosological groups to the global epidemiological datum referred to RD as a whole. It is essential to know which is the specific contribution of single RD entities, in order to plan appropriate and tailored interventions. As an example, at regional level specific benefits have been recognized to RD patients, in addition to the so-called essential levels of care established at national level. The provision of these benefits (i.e. off-label drugs, medical foods, drugs available in the market abroad, medical devices, etc.) is guaranteed only if the therapeutic plan is recorded in the IS by a clinician working in a labelled RD Centre. The authorization is disease-specific, is part of official regional acts, and comes after a process of consensus among RD Centres, based on the analysis of the available literature performed according to evidence-based criteria. This relationship, linking very specific RD entities to treatments that can be prescribed potentially free of charge for the patient, is managed automatically through the IS.

In the IS, the process of OrphaCodes recording is part of the diagnosis module. As explained above, a RD diagnosis is recorded in the IS only if performed by clinicians working in RD Centres, officially labelled for that rare disease or for a specific group of RD. A link to an external DB providing a description for each entity in Italian is available within the IS, at disposal of the clinicians in this phase. When the clinician selects the diagnosis, codes (ICD, OMIM and Orpha) corresponding to that diagnosis are automatically recorded as well. In this way, the ICD code can be integrated with the different branches of the Orphanet classification to which the RD entity results to belong. The user can select the branches together with the RD entity, accordingly to the clinical profile of the patient. In this way it is possible to automatically record the ICD code, the OrphaCode (identifying the RD entity) and a series of intermediate OrphaCodes, identifying the “upper” branches. In this way, a specific pathway of codes is recorded and the multidimensionality of the classification is preserved, describing phenotypic variability and health care needs, that is the additional value of the Orphanet classification, compared to the ICD one. This tool has been already tested in 2.750.000 hospital discharge records. Out of these, 96.000, contained RD diagnoses referred to nearly 66.000 patients. The use of this hybrid-integrated system has increased of the 85% the identification of rare diseases patients, compared to the mere use of ICD.

References

¹³ Piano Nazionale Malattie rare [Italian National

1. Italian Ministry of Health: Ministerial Decree 18th May 2001 No 279. Regolamento di istituzione della rete nazionale delle malattie rare e di esenzione dalla partecipazione al costo delle relative prestazioni sanitarie, ai sensi dell'articolo 5, comma 1, lettera b), del decreto legislativo 29 aprile 1998, n. 124, Volume 160. Gazzetta Ufficiale; 2001:180. Available at : <http://www.trovanorme.salute.gov.it/norme/dettaglioAtto?id=17169>
2. Piano Nazionale Malattie rare [Italian National
3. RD Plan]. Available at: http://www.salute.gov.it/imgs/C_17_pubblicazioni_2153_allegato.pdf

3.3. The German implementations of the Orphanet nomenclature

The use of the Orphanet nomenclature to code Rare Diseases has not been established so far in Germany. During the last 6 years many efforts have been undertaken in the Rare Diseases field in order to improve the life situation and the visibility of these patients in the German Health System.

3.3.1. Background

In 2010, the German Federal Ministry of Health (BMG), together with the German Federal Ministry of Education and Research (BMBF) and the Alliance for Chronic Rare Diseases (Allianz Chronisch Seltener Erkrankungen, ACHSE e.V.), founded the National Action League for People with Rare Diseases (Nationales Aktionsbündnis für Menschen mit Seltenen Erkrankungen, NAMSE). NAMSE's goal is to improve the life situation of each and every individual with a rare disease through a concerted effort. At the end of a three-year co-ordination process, which required the commitment of all of those involved in the healthcare sector, a total of 52 proposals for action were compiled and included in a National Plan of Action for People with Rare Diseases¹⁴. With the development of this action plan Germany aims to fulfil the recommendation of the European Union for an Action in the Field of Rare Diseases of 8th June 2009. The policy proposals are based on a broad consensus among the participants and reflect a wide spectrum of tasks to be executed. They include concrete recommendations for action on information management, possible paths to diagnosis, care-giving structures and on the conduct of research into rare diseases (see NAMSE, National Plan of Action for People with Rare Diseases, Bonn, 2013).

Until the ICD-11 becomes available, NAMSE recommended developing low-resource solutions. The German project "Rare Diseases Coding" is the proposed action 19 of the National Plan of Action and should investigate the possibility of automatically linking or coupling the Alphabetical Index of the ICD-10-GM to the Orphanet nomenclature provided by Orphanet. The goal would be to have a clear and uniform codification of the rare diseases available at the Centres for Rare Diseases to be used in

¹⁴ <http://www.namse.de/images/stories/Dokumente/Aktionsplan/national%20plan%20of%20action.pdf> (access on 30.05.2016)

research and care activities. (see NAMSE, National Plan of Action for People with Rare Diseases, Bonn, 2013).

The International Statistical Classification Of Diseases And Related Health Problems, 10th revision, German Modification (ICD-10-GM) is the official classification for the encoding of diagnoses in in-patient and out-patient medical care in Germany. In order to code rare diseases routinely and specifically, the Orpha number should be used in addition to the compulsory ICD-10-GM code. So coders would need to use two coding systems. The specific objectives of the DIMDI project "Rare Diseases Coding" are to improve the coding of rare diseases and to simplify this "double" coding process without increasing the bureaucratic burden of the process. The project, which started in July 2013, has been set up for three years and is financed by the Federal Ministry of Health (BMG).

3.3.2. Method

The project initially reviews whether all rare diseases listed in Orphadata are included in the Alphabetical Index of ICD-10-GM. Diagnostic terms that are not included there are added and assigned to an ICD-10-GM code. ICD-10 codes that are already assigned to a diagnostic term included in the Orphadata are reviewed. Any coding differences that are recognized in this review-process are reported and discussed with Orphanet. When a rare disease is added to the software version of the Alphabetical Index of ICD-10-GM, the entry is assigned to a specific identification number, called Alpha-ID. The produced database, called "Test file Alpha-ID-SE with Orpha numbers", includes the alignment of the Alphabetical Index of ICD-10-GM and the Orpha number and is published free of charge on an annual basis by DIMDI. This database is offered as electronic file in TXT (CSV) format in the download centre. The last published version of the database (October 2015) includes 2646 diagnostic terms for rare diseases¹⁵.

Two other proposed actions of the National Plan of Action have already implemented the database in their systems and built further functionalities based on it:

The Open-Source Registry System in the EU, OSSE¹⁶ (proposed action 29) is a free open source software for the development of registries. Osse aims at improving the quality of German registries and assuring their interoperability.

The proposed action 21, called Mapping of Health Care Providers for People with Rare Diseases, se-atlas¹⁷, is an interactive tool that aims to give Rare Disease users an overview of care providers in Germany.

Furthermore, the produced database is available to any user who strives to create a differentiated depiction of rare diseases. For example, the access to information from Orphanet regarding certain

¹⁵ <https://www.dimdi.de/dynamic/de/klasi/downloadcenter/alpha-id/seltene-erkrankungen/> (access on 30.05.2016)

¹⁶ <https://www.osse-register.de/de/> (access on 30.05.2016)

¹⁷ https://www.se-atlas.de/?ln=en_EN (access on 30.05.2016)

rare diseases can be simplified via the connection of ICD-10-GM codes and Orpha numbers by providing corresponding references to Orphanet for the user during the coding process in ICD-10-GM.

3.3.3. Results

On the Rare Disease Day, February 29th, 2016, DIMDI published an online survey as a part of the evaluation process of the project. DIMDI expected to recognize the status of the implementation of the published database in the clinical practice and possible issues that may occur. On the other hand, multiple ways to optimize the approach of the project should be described through this survey. Lastly, DIMDI wished to find out, if the produced database fulfils the needs and expectations of users.

The double coding of Rare Diseases by using both, Orpha numbers and ICD-10 codes, has a considerable acceptance between the responders. Most of them are planning to implement in the future the database produced in this project in their information systems in the future.

The database is only in a few cases currently used for routine coding or fully implemented in the information system of the users. No issues were reported regarding the implementation or structure of the database. The automatic coding was already tested. Neither of these tests reported any issues.

The completeness of the content of the database, this means the inclusion of all known Rare Diseases, was a major issue for the responders. Only few users are willing to implement a database that includes less than 75% of the known Rare Diseases. The database undergoes continuous development during the project period. The process has been prioritized based on the feedback of the users in order to reach a higher coverage. In the future it is planned to start with the inclusion of the missing diseases that are listed in the “Summary of disease expertise recorded via RD-ACTION Matchmaker under each Thematic Grouping and EURORDIS Members’ Thematic Grouping” (European Reference Networks ‘Matchmaker’) from the RD-Joint Action.

Finally, the responders showed a big interest on getting more training on the use of the database. Most of them were interested in online-tutorials or instruction booklets.

Furthermore, in the analysis of the results emerged some other fields of the German Health Care System where the use of the double coding of rare diseases is still unexplored and could be helpful. Some users mentioned as well the possibility of using other coding systems besides the Orphanet nomenclature and the ICD-10 to code rare diseases. These facts should be taken into account by the stakeholders in the development of further policies and actions on the Rare Disease field.

Regarding the work of matching two different classification systems that are produced and developed by different instances, DIMDI can conclude that:

Continuously exchange and the willingness to cooperate and learn from each other are key for a successful and precise result.

In order to maximize the chances of making a useful product and diminish the waste of time, the goals should be defined in a concise and careful way. Moreover a deep knowledge of the involved

classifications, and the carefully selection of the data to be matched, are major requirements for this exercise.

Given that the update-process of the database is for DIMDI one of the most resource consuming parts of the whole process. Through a transparent and standard update-process inconsistencies between the databases could be diminished, the whole process could be accelerated and the use of resources could be optimized.

The feedback of the involved parties is very useful for the further development of the involved classification systems.

IV. Conclusion and further work

Together with the survey results three (slightly) different methodologies are presented described in this document to implement the Orpha numbers at national/regional level, ideally connected to the local or national health information system. Whilst the French and Italian initiatives are sharing some commonalities (specific application to capture data from rare diseases expert centres connected to health information systems, regulatory and financial incentives), the German methodology provides a mechanism to include Orpha numbers alongside with the ICD-10-GM-codes that are mandatory for use in the existing DRG system as well as in outpatient settings that already implements information systems and proper channels to gather data at national level. The three implementations experiences although try to introduce the Orphanet nomenclature in correlation with extra already existing classifications or terminologies to better fit patient characterization and national regulations. All three experiences showed an important need for user training and support to use the proposed nomenclature. In every case, double coding is adding burden to the process if not assisted by proper tooling and joint classification allocation, especially when rare disease coding needs are added associated to already existing (mandatory) payment coding in ICD. Biases on implementation methods were not measured because of the lack of data to proceed within the first year of the Joint Action, this will be proposed within the best practices technical guide to implementation in year 2 of the JA.

Country reports from the survey as well as the detailed description from the three Work package countries showed that for an international approach to use unified coding systems the processes in each country should be respected and accepted. It is not feasible to change the overall coding process of routine data. Therefore on EU level it is only important to provide a unified coding resource for implementation in the existing systems of the countries in order to produce standardized data. Guidelines on how to implement the coding resource into existing systems should be provided.

In order to minimize confusion an agreed schedule and mechanism should be followed in the future to provide such resource in order to give countries long term stability and reliability. This will encourage countries to engage into the endeavor to implement the coding with parallel coding systems in their national IT infrastructure. This schedule should take into account that the rare

disease coding might need more flexibility as the routine coding with e.g. ICD-10 but should as well consider the burden of frequent changes on implementation processes and training needs. Therefore this schedule should consider not only national needs and needs of ICD-10 users but as well should be aligned with the needs of Orphanet development processes.

Learning from the survey and considering the three detailed descriptions from France, Italy and Germany such resource and guideline together with a proposed schedule will be developed in the next steps of this Work package.

For the coding resource it needs to be discussed further which detail is necessary for routine reporting on EU-level in order to leave enough room for countries to decide how detailed they will be willing and able to report on. The minimum detail necessary for international data collection should therefore be recommended for future reporting. As the implementation effort will be varying from country to country according to the already in place systems for routine reporting of health data, the provided resource should be as easy and flexible as possible to implement. The easier the resource for implementation will be the more likely it will be implemented and be used for reporting.

Informed by the lessons learned from this work the members of this Work package will be undertaking the next steps as outlined in the project plan of WP5.