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ACTA FACULTATIS PHARMACEUTICAE UNIVERSITATIS COMENIANAE

THE CREATION OF THE NATIONAL REGISTRY OF RARE DISEASES IN THE SLOVAK REPUBLIC

TVORBA NÁRODNÉHO REGISTRA ZRIEDKAVÝCH CHORÔB V SLOVENSKEJ REPUBLIKE

Original research article

Cisárik, F.✉, Baráková, A.[1]

Faculty Hospital and Clinic Žilina, Department of Medical Genetics and EUCERD Representative Slovakia, Expert of the Ministry of Health for Medical Genetics, [1]National Health Information Centre, Bratislava, Slovak Republic

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Fakultná nemocnica s poliklinikou Žilina, Oddelenie lekárskej genetiky, Slovenská republika Výbor expertov EÚ pre zriedkavé choroby [1]Národné centrum zdravotníckych informácií, Bratislava, Slovenská republika

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Abstract The creation of a registry of patients with rare diseases is a priority of the National Strategy for Rare Diseases as well as of the National Plan for Rare Diseases. Knowledge of the real number of patients with rare diseases would thus, in addition to basic clinical information, represent an important point in planning health and social care. The presented work introduces points of departure which constitute the basis of a new specific National Registry of Patients with Rare Diseases in the Slovak Republic.
Its creation builds on the existing registries as well as on the structure of health care in the Slovak Republic. With the protection of personal data in mind, the collection of data will be carried out by the National Centre of Health Information (NCHI), which will also use the existing tool in the process of creation. Thanks to the cooperation between NCHI and the Slovak Society of Medical Genetics, NCHI developed separate reporting forms on rare diseases according to OMIM (Online Mendelian Inheritance in Man) and ORPHANET rare disease coding (ORPHA codes of rare diseases), and the International classification of diseases code (ICD 10). The activities also include cooperation with the existing registries (part of which are rare diseases). For example National Registry of Congenital Developmental Heart Defects, national register of neuromuscular disorders, oncologic register or register of diabetes mellitus. Gathering the information from these registries we will extend the data about rare diseases in the Slovak republic. At the international level the participation in the European Surveillance of Congenital Anomalies (EUROCAT) is important.

Slovak abstract Prioritou Národnej stratégie pre zriedkavé choroby ako aj Národného plánu pre zriedkavé choroby je vytvorenie databázy pacientov pre zriedkavé choroby. Poznanie reálneho počtu pacientov so zriedkavými chorobami, by, okrem základných klinických informácií, bolo dôležitou informáciou pre návrh efektívnejšie fungujúcej zdravotnej a sociálnej starostlivosti. V prezentovanom príspevku prinášame východiskové body, ktoré vytvoria základ nového špecifického Národného registra pacientov so zriedkavými chorobami v Slovenskej republike.
Pri jeho tvorbe vychádzame z existujúcich registrov ako aj zo súčasného organizačného zabezpečenia zdravotnej starostlivosti v SR. Vzhľadom na ochranu osobných údajov, správcom zberu dát bude Národné centrum zdravotníckych informácií (NCZI), ktoré pri získaní údajov využije aj iné registre. Zástupcovia odbornej spoločnosti pre klinickú genetiku (ako hlavní iniciátori) v spolupráci s oddelením národných registrov NCZI vypracovali formulár: *Hlásenie vrodenej chyby -dedičné, genetické chyby a zriedkavé choroby**, v ktorom sa okrem Medzinárodnej klasifikácie chorôb (MKCH 10) zohľadňuje špecifikácia zriedkavých chorôb podľa OMIM (Online Mendelian Inheritance in Man) a ORPHANET (ORPHA kódy zriedkavých chorôb).
Súčasťou aktivít je aj spolupráca s inými existujúcimi registrami na národnej úrovni (ktorých súčasťou sú aj vybrané zriedkavé choroby). Napr. okrem registra vrodených chýb srdca ide najmä o národný register neuromuskulárnych ochorení, o onkologický register, register pacientov s diabetes mellitus (napr. novorodenenecký diabetes). Údajmi o zriedkavých chorobách z príslušných iných registrov budeme mať okrem údajov z *hlásenia vrodenej chyby (dedičné, genetické chyby a zriedkavé choroby)* k dispozícii doplňujúce údaje o ich výskyte v SR. V danej problematike je na medzinárodnej úrovni dôležité zastúpenie SR v rámci European surveillance of congenital anomalies (EUROCAT).

Keywords *rare diseases, national registries, OMIM code, ORPHA code, Registry of rare diseases.*

Kľúčové slová: *zriedkavé choroby, národné registre, OMIM kód, ORPHA kód, register zriedkavých chorôb*

INTRODUCTION

Rare disease registries and data collections aim to speed up the acquisition of knowledge and the development of clinical research. Nevertheless, the registries as well as data collections should be adaptable to serve regulatory purposes, when required. For these reasons, rare disease registries and data collections are one of the priorities of the European Commission in the field of rare diseases.

Thanks to the European Union Committee of Experts on Rare Diseases, Recommendations on Rare Disease Patient Registration and Data Collection were elaborated (Recommendations on Rare Disease Patient Registration and Data Collection, 2013). It supports the idea of rare disease registries and data collections as valuable instruments for increasing knowledge on rare diseases. Besides increasing knowledge, rare disease

* *cisgen@nspza.sk*

registries could serve as a support for fundamental, clinical and epidemiological research, as well as for post-marketing surveillance of orphan medicinal products and medicines used off-label. From the point of view of healthcare policy, this is crucial for the planning of healthcare services and expenditure allocations. The Recommendations call for the international operability of registries and databases and use of appropriate coding systems to enable the necessary data pooling for public health and research purposes. The Recommendations also give advice concerning the establishment of registries and data collection and highlight the various uses of patient data as well as the best way to share this information. A similar situation is in the Slovak Republic.

The targets of the initiatives to improve care for patients with rare diseases in EU include the creation of a specific national registry of rare diseases.

The resolution no. 578 of the Government of the SR from 24 October 2012 approved the National Strategy for the Development of Health Care for Patients with Rare Diseases and the preparation of the National Plan of Health Care for Patients with Rare Diseases is currently underway (National Strategy for the Development of Health Care for Patients with Rare Diseases for the Years 2012–2013. The creation of the Registry of Rare Diseases comprises a priority part of these activities.

Generally, a patient registry is an organised system that uses observational study methods to collect uniform data (demographical, clinical and/or other). It serves for the evaluation of specified outcomes in a population defined by a particular disease, condition or exposure. In this case, the common characteristic is the low prevalence of the disease – rare disease (not more than 5 in 10,000) (Regulation (EC) No. 141/2000 of the European parliament and of the council. The purposes of the registry are different. The registry might serve one or more predetermined scientific, clinical or policy purposes. A registry database is a file (or files) derived from the registry (Gliklich RE et al., 2010).

METHODS AND RESULTS

The National Centre of Health Care Information prepared the ground for the collection of data on patients with rare diseases. The preparation of the National Registry of Rare Diseases requires that these legislative standards be taken into account:

- European Union Committee of Experts on Rare Diseases: Recommendations on Rare Disease Patient Registration and Data Collection. 2013 Accessible at: http://www.eucerd.eu/wp-content/uploads/2013/06/EUCERD_Recommendations_RDRegistryDataCollection_adopted.pdf.
- SR. Act no.153/2013 on the National Health Information System and on Amendments and Additions to Certain Laws.
- SR. The Decree of the Ministry of Health Care of the Slovak Republic of 11 March 2014, which defines a list of reports to National Health Registries, their characteristics, details on the content of national health registries, procedures, methods, coverage of reporting units and time limits of reporting to national health registries.

The currently prepared Slovak registry is a population-based registry as it refers to a geographically defined population – people who live in Slovakia. It aims to register all cases of rare disease patients in the Slovak population (rare diseases of genetic origin as well as rare diseases from the category of congenital anomalies). It will serve mainly the policy purposes. The advantage of the registry is that it takes into account the European Union Committee of Experts on Rare Diseases (EUCERD) recommendation from June 2013, which recommends adaptation of the existing registries according to the changing environment in the European and international context. It takes into account the six core recommendations on the rare disease patient registration produced by EUCERD in June 2013:

- International interoperability in the collection as well as the exchangeability of data, thus allowing sufficient statistically significant numbers for clinical research and public health purposes.
- Applicability as information source, thus speeding up the knowledge and development of clinical research.
- Utilisability for health and research purposes.
- Adherence to good practice guidelines in the field.
- Adaptability for regulatory purposes.
- Sustainability.

RESULTS AND DISCUSSION

As 85% of rare diseases are genetic and a lot of congenital anomalies are genetically conditioned, we were looking for the possibilities of using the existing registries run by the National Centre of Health Information to create a virtual registry of rare diseases. In fact, the existing National Registry of Congenital Anomalies appears to be the closest in its nature.

This registry has had a long and successful history in Slovakia. The data have been published since 1965. This is to be credited to the diligent work of neonatologists and to their good cooperation with NCHI. Over these years, the registry has undergone more changes in the system of reporting as significant changes in discovering aetiological connection with congenital anomalies took place.

Congenital anomalies entered into the registry by paediatricians as well as neonatologists. Over these 2 years, the system has gradually become established.

According to Act No. 153/2013 on the National Health Information System and on Amendments and Additions to Certain Laws, since 2014, the National Registry of Patients with Congenital Anomalies consists of:

1. Registry of Congenital Anomalies (all congenital anomalies including inherited and genetic disorders and rare diseases).
2. Registry of Congenital Heart Defects (specific reporting).

Data for the „Registry of Rare Diseases" (diseases with incidence lower than 1:2000) will, in addition to the up-to-now used reporting form on congenital developmental disorders entitled „Report on Congenital Anomalies in Live Births and Stillbirths" (Figure 1), be obtained from two new reporting forms that will be filled in by clinical geneticists:

1. Report on Congenital Anomalies – Inherited Diseases, Genetic Disorders and Rare Diseases (Figure 2).
2. Report on Congenital Anomalies of the Foetus – Genetics (Figure 3).

The content of the collected and processed data is thus constituted by the information on all prenatally and/or postnatal diagnosed congenital anomalies (in the broad sense of the congenital anomalies – including inherited diseases, genetically conditioned developmental disorders and rare diseases with incidence lower than 1:2000). Out of these databases, diseases with the specification of rare diseases are selected by software means.

As of the 1 January 2014, it is obligatory to report selected genetic diseases and disorders to clinical geneticists as a part of the National Registry of Patients with Congenital Anomalies. Clinical geneticists will report inherited and genetic disorders, i.e. rare diseases in a separate reporting form: Report on Congenital Anomalies – Inherited Diseases, Genetic Disorders and Rare Diseases (Figure 2).

Clinical geneticists will report the detected chromosome abnormalities, significant monogenic diseases and clinical-genetic syndromes. They will thus build on the experience with the so-called "Genetic registry SR", which was run under the Slovak Society of Medical Genetics for more than 10 years. The extent of information as well as the obligations concerning reporting is summarized in Table 1.

The information source for the virtual "Registry of Rare Diseases" was extended to include also prenatally identified genetic defects (Report on Congenital Anomalies of the Foetus – genetics Figure 3).

NCHI keeps a separate registry of congenital heart disorders within the National Registry of Patients with Congenital Anomalies. Other registries of rare diseases of NCHI include:

- National Cancer Registry.
- National Registry of Patients with Diabetes Mellitus.
- National Neurological Disorders Registry.
- National Chronic Lung Disease Registry.

Out of these registries, we intend to select patients with rare diseases by software means and coding. This is only possible provided that correct rare disease coding is used, which means not only the use of ICD 10 codes but also the use of specific codes of genetic disorders OMIM (Online Mendelian Inheritance in Man) and codes of rare diseases according to ORPHANET (ORPHA codes of rare diseases).

Table 1. The List of reports to the National Registry of Congenital Anomalies and their characteristics and other details according to the Decree no. 74/2014 Coll. (Decree of the Ministry of Health of the Slovak Republic no. 74/2014)

DETAILS ON THE CONTENT ACCORDING TO ICD 10
1. Coagulation defects, purpura and other haemorrhagic conditions (D66–D68.2)
2. Thyroid disorder (E03.0–E03.1)
3. Congenital malformations of the nervous system (Q00.1–Q07.9)
4. Congenital malformations of eye, ear, face and neck (Q10.0–Q18.9)
5. Congenital malformations of the circulatory system (Q20.0–Q28.9)
6. Congenital malformations of the respiratory system (Q30.0–Q34.9)
7. Cleft lip and cleft palate (Q35.1–Q37.9)
8. Other congenital malformations of the digestive system (Q38.0–Q 45.9)
9. Congenital malformations of genital organs (Q50.0–Q56.4)
10. Congenital malformations of the urinary system (Q60.0–Q64.9)
11. Congenital malformations and deformations of the musculoskeletal system (Q65.0–Q79.9)
12. Other congenital malformations (Q80.0–Q89.9)
13. Chromosomal abnormalities, not elsewhere classified (Q90.0–Q98.9)
LIST OF REPORTS
1. Report on congenital developmental disorder in live births and stillbirths
2. Report on congenital developmental disorder in the foetus – genetics
3. Report on congenital developmental disorder – inherited, genetic disorders and rare diseases
4. Report on congenital heart defects
THE OBLIGATION TO REPORT APPLIES TO
A) Provider of constitutional health care the following departments:
1. Neonatology including the intensive care unit
2. Paediatric department including the intensive care unit
3. Neonatal resuscitation care unit
B) Provider of outpatient health care operating a clinic:
1. General paediatric care
2. Paediatric cardiology
3. Medical genetics

An important role in the process is assumed by paediatricians – general paediatricians, as they are obliged to record and report everything pertaining to rare diseases. What represents a problem is the registration of adult patients with rare diseases who are not registered at medical genetics clinics but in specialised centres, e.g. the Centre for Hereditary Hematologic Disorders. Possibilities of categorization of information from clinical sources will have to be dealt with gradually.

CONCLUSION

The creation of the registry of patients with rare diseases at the European and national levels represents a great challenge to health care and information systems. Gradual expansion of the content of the existing registries is, however, one of the promising conceptual approaches. Gradual approach guarantees easier implementation as well as future sustainability.

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National Registry of Patients with congenital developmental disorder
according to Act no. 153 / 2013 Coll. on the National Health Information System and on Amendments and Additions to Certain Laws

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Report on Congenital Disorder in Live Births and Stillbirths year 2014

Report by: a neonatologist (stillbirths, deaths after birth before hospital discharge and all children discharged from neonatal department). Reports on other children to the age of 15 with newly found or additionally diagnosed CD by general paediatrician.

Facility identification

Year of processing | Month of processing: | Date of reporting: day / month / year

HCP ID no.: | HCP Code:

Facility name:

Reporting doctor's name and surname:

Reporting doctor's code:

Child's details

SELECTED SPECIFICATION OF THE REPORTED CASE

1 - child from a rescue nest
2 - child of anonymous birth

(in these cases, identification data of the child /except for gender/ is not given)

BASIC IDENTIFICATION DATA OF THE CHILD

Surname: | Name:

Birth ID no.: /

Date of birth:

Sex: 1 - male 2 - female 0 - not found

BIRTH DATA

Birth weight (g)
Birth lenght (cm)
Gestation week

STATE OF THE CHILD

1 - stillbirths / death at birth
2 - died in 7 days after birth
3 - died between 7th day and 1st year
5 - died older than 1year
4 - alive

(no. 1-4 were retained due to code list in the original e-version)

If option 5 applies, how old was the child at the time of death?
(this concerns cases when CD is detected shortly before child's death)

Examinations

PRENATAL AND POSTNATAL EXAMINATIONS

Prenatal screening examination:

1 - positive
2 - negative
3 - exam. undergone, unknown finding
4 - examination not undergone
5 - no information available

Reasons for examinations beyond the scope of prenatal screening

Known reasons:
1 - pathological finding in ultrasound screening examination
2 - pathol. finding in biochemical screening examination
3 - mother's age <17y and > 37y at the time of conception
4 - family history
5 - other

Other circumstances
1 - examination undergone (data unknown)
2 - examinations not-indicated / information not available

Specific examination type (prenatal- or/and postnatal)

Reasons known:
1 - cytogenetic
2 - molecular genetic (DNA)
3 - biochemical
4 - imunological
5 - virological
6 - ultrasound
other (if postnatal CD diagnostics was determined only clinically, please indicate: e.g. cleft palate)

Other circumstances:
1 - examination undergone (data unknown)
2 - examinations not indicated / no information available

These examinations were carried out:
1 - only prenatally 2 - only postnatally 3 - both pre- and postnatally

CD detection and diagnosis

CONGENITAL DISORDER DETECTION

Prenatal:
1 - yes
2 - no
9 - data unknown/ not given / examination not taken

Gestation week when CD was detected:

Postnatal:
1 - to 7th day
2 - from 7th day to 1st year
3 - from 1y to 15y

Age of CD detection in children older than 1y (in years)

CD DIAGNOSIS ACCORDING TO ICD 10 AND THE FAMILY HISTORY OF CD

in words
in words
in words

Other dg. if missing in the offered ICD options or not possible to specify.

Did the child have a combined congenital disorder?
1 - yes 2 - no 9 - data unknown/not given

Incidence of congenital disease in child's relatives
1 - the same congenital disorder
2 - different congenital disorder
3 - no history of congenital disorder (family history)
9 - unknown/not given data

Was the genetic examination based on an indication?
1 - yes 2 - no 9 - unknown/not given data

CHILD'S PARENTS' DETAILS

Child's parents' details

Mother:
(with anonymous birth/child from a rescue nest, mother's details are not given, mother's birth ID no. is then 0050000000)

Name: | Surname:

Birth ID no.: /

Permanent address (St., House no.): | City:

Father:
Year of birth:

RF

Serious diseases and RF in mother's history:

before pregnancy (ICD options in the e-form) | If the disease/RF is not in ICD options or could not be specified (indicate) | negative PH:

during 1. trimester (ICD options in the e-form) | If the disease/RF is not in ICD options or could not be specified (indicate) | negative PH:

Medical history of risk pregnancy (the latest): 1 - yes 2 - no 9 - data unknown / not given

Medical report

Reports, other important information from the doctor reporting the case

Figure 1. Report on Congenital Anomalies in Live Births and Stillbirths.

National Registry of Patient with congenital developmental disorder
according to Act no. 153 / 2013 Coll. on the National Health Information
System and on Amendments and Additions to Certain Laws

Report on Congenital Disorder - Inherited, Genetic Disorders and Rare Diseases
year 2014

Facility identification

Year of processing | Month of processing: | Date of reporting

Facility name:

Reporting doctor's name and surname: | HCP ID:

Reporting doctor's code: | HCP Code:

Details on the proband / patient

MODULE: 1 Data on proband/ patient

CD report concerns:

1. proband
2. patient of known parentage
3. child from a rescue nest / of anonymous birth

(this concerns situations with no identif. data available)

MODULE 2: Basic proband's identification data

Surname:

Name:

Birth ID no.: /

Date of birth:

Sex: 1 - male 2 - female

Permanent address (St., House no.) | Nationality (please, write)

Place of permanent residence (choose from options)

Title (description) and classification of the diagnosis, DNA examination

MODULE 3: Title (Description) and classification of the diagnosis, DNA examination

Detailed diagnosis in words:

Monogenic disease (coded in all three codes: ICD10,OMIM,ORPHA)

Chromosome abnormality (described according to standards, coded in all three codes if identifiable)

Clinical-genetic syndrome (can be classified in all three coding systems)

Diagnosis classification

Diagnosis according to ICD10 | Diagnosis according to McKusick (OMIM)

ORPHA code

Caryotype (symbol)

Result of DNA analysis:

1 - DNA not taken
2 - DNA taken

DNA result:

Additional information on the proband

Date of reporting: | Filled in by: (doctor) | Docktor's signature:

Figure 2. Report on Congenital Anomalies – Inherited Diseases, Genetic Disorders and Rare Diseases.

National Registry of Patients with Congenital Developmental Disorder
according to Act no. 153 / 2013 Coll. on the National Health Information
System and on Amendments and Additions to Certain Laws

ZR_VCH_plod

Report on Congenital Disorder in Foetus - Genetics
Year 2014

Reported by clinical geneticist

Facility identification

Year of processing | Month of processing: | Date of reporting: day / month / year

HCP ID: | HCP code:

Facility name:

Reporting doctor's name and surname:

Reporting doctor's code:

Prenatal examinations

PRENATAL EXAMINATIONS

Prenatal screening / risk

1 - Screening positive for Down syndrome	O
2 - Screening positive for NTD	O
3 - Screening positive for Edward's syndrome	O
4 - Abnormality screening (extreme markers)	O
5 - Positive ultrasound screening (NT, minor markers)	O
6 - Sonographically detected CD	O
7 - IUGR	O
8 - Mother over 40	O
9 - Genetic risk	O
10 - Negative screening	O

Prenatal diagnostics

Examination		Results (detailed record + evaluation of finding's seriousness)
1 - cytogenetic / molec.-cytogen.	O	Record: / Finding: 1 - serious 2 - not serious 3 - effect on phenotype unclear
2 - ultrasonographic	O	Record: / Finding: 1 - serious 2 - not serious 3 - unclear finding
3 - molecular genetics	O	Record: / Finding: 1 - serious 2 - not serious 3 - unclear finding
4 - biochemical	O	Record: / Finding: 1 - serious 2 - not serious 3 - unclear finding
5 - other laboratory diagnostics	O	Description of foetus, if CD is detected
if 5, specify:		

Detection

Detection of CD

Which gestation week was the diagnosis made in?

Genealogy

Chromosome abnormality in a parent	O	
Chromosome abnormality in the family	O	Other, specify::
Familial risk of monogenic disease	O	
Other risk	O	

Diagnosis

DIAGNOSIS ACCORDING TO ICD 10, OMIM and ORPHA

A. according to ICD-10:

1.
2.
3.

choose from the options in case of e-reporting

B. according to OMIM (McKusick)

C. according to ORPHA

Parents' details

CHILD'S PARENTS' DETAILS

Mother

Name: | Surname: | Age of mother(calculated automatically in online version)

Birth ID no.: /

Permanent address (address, house number): | City:

Father:

Year of Birth: | Age of father (if known):

Serious diseases and RF in mother's personal history

before pregnancy

choose from ICD in the e-form

If the disease/RF is not in ICD options or could not be specified (indicate)

negative PH:

during pregnancy (present)

choose from ICD in the e-form

If the disease/RF is not in ICD options or could not be specified (indicate)

negative PH:

Medical report

Reports, other important information from the doctor reporting the case

Figure 3. Report on Congenital of the Foetus – Genetics.