

Contract number: 2010 22 04

Proposal title: EUROCAT : European Surveillance of Congenital Anomalies

Acronym: EUROCAT

Starting date: 01/01/2011

Duration of the project: 36 months

Reporting period: Months 13-24

Main partner: University of Ulster (UU)

Names of associated partners:

1. Forschungsverein zur Registrierung Steirischer Geburtsfehlbildungen (SFR)
2. Provinciaal Instituut voor Hygiene (PIH)
3. Institut de Recherche Scientifique en Pathologie et en Genetique (IRSPG)
4. Klinika za dječje bolesti Zagreb, Medicinski fakultet Sveucilista u Zagrebu (KDB)
5. Region Syddanmark (Hospital Lillebaelt)
6. National Institute for Welfare and Health
7. Paris Registry of Congenital Malformations, INSERM (French National Institute of Health and Medical Research), Unit 953 (INSERM U953)
8. Universite de Strasbourg (UDS)
9. University medical Centre of the Johannes Gutenberg University Mainz (UMC-Mainz)
10. Otto-von-Guericke University Magdeburg (OVGU)
11. National Centre for Healthcare Audit and Inspection (NCHAI)
12. Health Service Executive (HSE)
13. Azienda Ospedaliero Rilievo Nazionale "Gaetano Rummo" Benevento AO "G Rummo")
14. Azienda Ospedaliero Universitaria di Ferrara (IMER)
15. Istituto Superiore di Sanita (ISS)
16. Istituto di Fisiologica Clinica del consiglio Nazionale delle Ricerche (IFC-CNR)
17. Children's University Hospital (BKUS)
18. The National Health Service (NHS) formerly known as The Centre of Health Economics (VEC)
19. Malta Congenital Anomalies Register (MCAR DHIR)
20. Academisch Ziekenhuis Groningen (UMCG)
21. University of Groningen (RUG)
22. Norwegian Institute of Public Health (FHI)
23. Poznan University of Medical Sciences (PUMS)
24. Instituto Nacional de Saude Dr Ricardo Jorge (INSA)
25. University Medical Centre, Ljubljana (UMCL)
26. Agencia de Salut Publica de Barcelona (ASPB)
27. Fundacion Vasca de Innovacion e Investigacion Sanitarias (BIOEF)
28. Fundacio Centre de Recerca en Epidemiologia Ambiental (CREAL)
29. Asociacion Espanola para el Registro y Estudio de las Malformaciones Congenitas (ASEREMAC)
30. Centre Superior de Investigacion en Salud Publica (CSISP)
31. University of Leicester (ULEIC)
32. University of Newcastle upon Tyne (UNEW)
33. Queen Mary University of London (QMUL)
34. The Chancellor, Masters & Scholars of the University of Oxford (Oxford)
35. Public Health Wales (CARIS)
36. Southampton University Hospitals Trust (SUHT)

Names of Collaborating Partners

1. Belarus Research and Clinical Center “Mother and Child” (Minsk, Belarus)
2. Clinical Genetics Department, Pediatrics Department, Archbishop Makarios III Hospital (Nicosia, Cyprus)
3. Department of Medical Genetics - Thomayer University Hospital (Prague, Czech Republic)
4. Research Institute of Pediatrics and Child Surgery (Moscow, Russia)
5. Slovak Medical University in Bratislava (Slovakia)
6. University Clinical Centre Maribor (Maribor, Slovenia)
7. Service de Genetique Medicale, CHUV, Lausanne (Switzerland)
8. University of Glasgow (Scotland)
9. OMNI-NET Centre (Ukraine)

Total amount of the project: 3,360,210.89 EURO

EC Co-funding: 1,106,302 EURO

First pre-financing payment: 331,891 EURO

Second pre-financing request: 221,260 EURO

1. Executive summary

EUROCAT (European Surveillance of Congenital Anomalies), funded by the European Union as a Joint Action of the EU and Member States through the DG Sanco Public Health Programme, and in existence since 1979, is a network comprising almost all of the population-based congenital anomaly registries in Europe. It currently surveys more than 1.7 million births per year in Europe, covered by 37 registries in 21 countries. Cases of all major structural congenital and chromosomal anomalies among livebirths, stillbirths and terminations of pregnancy for fetal anomaly (TOPFA) following prenatal diagnosis, are registered using multiple sources of information. Using common software, each member registry transmits a standard dataset to a central database at EUROCAT Central Registry, where further quality validation is performed.

EUROCAT's general objective is to facilitate the reduction of the public health burden of congenital anomalies by epidemiological surveillance through the EUROCAT network.

The strategic relevance of the Joint Action is that congenital anomalies are a major group of mainly rare diseases where concerted action across Europe has been identified as a priority in the Council Recommendation of the 8th of June 2009 on an action in the field of rare diseases, and in the Communication from the Commission on Rare Diseases: Europe's challenges of November 2008. These recognise the need for registries and databases coordinated at European level, for pooling of expertise, improving the coding and classification of rare diseases, for comparable epidemiological data at EU level, and for identifying the possibilities for primary preventive measures. This Joint Action combines funding of the EU Member States in order to secure a sustainable, high quality and easily accessible information system on congenital anomalies for almost one third of the European birth population. Through the Joint Action EUROCAT expects to have an important impact on future Member State policy on prevention and surveillance of congenital anomalies, including via National Rare Diseases Plans.

This interim report outlines EUROCAT's activities in the second funding period of the current Joint Action contract: January to December 2012.

Workpackage progress

WP1: Coordination

- Registry Leaders Meeting held June 2012
- Election of new Steering Committee member and Association President in June 2012

WP2: Dissemination

- 18 peer reviewed collaborative publications and 30 conference presentations

WP3: Evaluation

- PMC agreed evaluation plan and website evaluation survey content to be implemented in 2013.

WP4: Registration, central database and surveillance

WP4 is responsible for the continued development and maintenance of a centralised database of congenital anomalies, data management, statistical monitoring and biannual update of prevalence information on congenital anomalies to the EUROCAT website. The Registry Advisory Service along with Central Registry staff provide support to new and existing

registries to enable successful transmission of anonymous data on congenital anomalies using a standardized coding system and data management program (EDMP).

- Data from registries updated and new prevalence tables uploaded to website.
 - Prevalence data for 31 registries updated to 2010
 - Prevalence data for 5 registries updated to 2009
 - Data on proportion of cases prenatally diagnosed transmitted by 26 registries
- Revisions to EDMP/ECD software made, including to statistical monitoring module
- Registry Advisory Service
 - held workshop at Registry Leader's Meeting
 - liaised with new and applicant registries (i.e. Slovenia and Latvia)
- Statistical monitoring for trends and clusters over time conducted to include year 2010

WP5: Coding and classification, and data quality

The main aim of WP5 is to improve the data quality of the EUROCAT Database. The methods developed for this are unambiguous data variables, written instructions for classification and coding of the congenital anomalies and use of data quality indicators (DQI) applied to the local registries. The longterm experience from EUROCAT on coding will also be used in the development of International Classification of Diseasev11 (ICD11).

- EUROCAT Coding and Classification Committee were active throughout the period improving quality of coding in EUROCAT registries
- Document commenting on ICD11 revision proposals was sent to Orphanet and ICD11 EUCERD meeting attended
- The revised DQI was applied to the 2010 data received at Central Registry in February 2012.
- The EUROCAT Data Management Program has been updated to include variables for the new Guide 1.4. The new version is now available for the local registries for birth data collected in 2013.

WP6: Investigation of trends, clusters and new exposures

The aim of WP6 is to investigate and respond to trends, clusters and new exposures of concern for congenital anomalies. This will be done through the preliminary investigation of those clusters and trends signalled by the statistical monitoring (WP4), through establishing a Task Force for the Evaluation of Clusters, through detailed investigations of trends in specific anomalies, and through the analysis of new exposures, including swine flu and environmental exposures.

- All trends and clusters identified in WP4 were subject to preliminary investigation by registries (with some involvement of the Taskforce for the Evaluation of Clusters), and included in Annual Statistical Monitoring Report.
- The swine flu systematic review, seasonality study, ecological time series analyses and case-malformed control analysis are ongoing.
- A data file has been formally requested for investigation of hypospadias.
- 2 papers have been submitted (1 published) relating to the prevalence and risk of congenital anomaly in multiple births.
- Analysis of the changing epidemiology of gastroschisis and of Hirschsprung's disease is ongoing.

- A paper on trends in congenital heart defects has been published
- A paper on the epidemiology of Atrioventricular Septal Defects has been published.
- A case-control study protocol has been resubmitted for funding.
- A literature review on air pollution and congenital anomalies has been published.
- A feasibility study, linking congenital anomaly data with environmental pollution maps has been completed in Barcelona.

WP7: Primary prevention of congenital anomalies

WP7 is focused on primary prevention of congenital anomalies. One focus will be on evaluation of progress in the prevention of neural tube defects by raising periconceptional folic acid status. The objective is also to assess other potential routes including management of chronic diseases, drugs in pregnancy, maternal infection and vaccination, environmental pollution, alcohol and smoking, and other maternal lifestyle issues. WP7 will assess the feasibility and process for considering risk factors for congenital anomalies in national plans of EU - MS for rare diseases, with the support of EUROPLAN. The overarching aim is to establish and agree a recommendation on primary prevention for congenital anomalies to be included in European countries' national plans for rare diseases.

- Recommendations on policies to be considered for the primary prevention of congenital anomalies in national plans and strategies on rare diseases were published
- A EUROCAT folic acid committee was established

WP8: Prenatal Screening, Down syndrome and genetic syndromes

WP8 aims to improve and provide more information on prenatal diagnosis that is occurring in Europe by providing more information on prenatal diagnosis for specific anomalies in tables and improved graphics on the website, incorporating data from a national Down syndrome register and investigating the effect of prenatal diagnosis on the prevalence of cardiac anomalies in babies born with Down syndrome. The epidemiology of specific single gene syndromes will also be investigated.

- A paper on prevalence of Down syndrome has been published in the European Journal of Human Genetics. Twenty-year trends in the prevalence of Down syndrome and other trisomies in Europe: impact of maternal age and prenatal screening, EJHG (2013) 21: 27–33.
- Website prevalence rates have been updated to 2010. National (England and Wales) Down Syndrome Cytogenetic Registry data incorporated in prenatal tables.

WP9: Medication during pregnancy

The main objective of WP 9 is to 1) establish the conditions for the development of case-control monitoring system for safety of medication use in pregnancy using data from birth defects registries, 2) improve the data on drug exposure in pregnancy and 3) enable more registries to provide data on maternal medication use in pregnancy.

- A new variable, “first trimester use in pregnancy”, was piloted in 5 EUROCAT registries.
- A study of SSRI exposure and congenital anomalies was completed (PhD Project).
- The fourth update of a study of lamotrigine exposure and congenital anomalies was completed.

2. Specification of the project:

2.1 General Objective of the project:

To facilitate the reduction of the public health burden of congenital anomalies by epidemiological surveillance through the EUROCAT network of population-based congenital anomaly registers.

Reduction of public health burden encompasses delivery of high quality diagnostics, treatment and counselling services prenatally and postnatally; promotion of health and reduction of teratogenic risks preconceptionally and in early pregnancy, on a population or individual basis; minimising inequalities in experience of prevention and care.

The Joint Action will contribute a statistical basis for the reduction in the number of Disability Adjusted Life Years due to congenital anomalies and for priming the community regarding the need for preventive measures.

The European population of pregnant women changes over time: higher maternal age, more chronic diseases and obesity, new infections, new pollutants, new medications and changing immigration. Thus, surveillance policy and prevention must follow these changes.

2.2 Specific objectives of the project

Number	Title	indicators	WP
1	<p>Prevalence information - To provide comprehensive epidemiologic information on prevalence of congenital anomalies in Europe. This is needed for public health planning and will be essential background information for several other objectives, in particular assessment of the impact of policies for prevention, prenatal diagnosis and care of newborns with congenital anomalies, and role of old and new (emerging) risk factors eg. swine flu.</p> <p>Members of the EUROCAT network are population-based registries using multiple sources of information for case ascertainment and diagnostic accuracy, registering cases among livebirths, stillbirths/late fetal deaths from 20 weeks gestation, and terminations of pregnancy following prenatal diagnosis. Coverage of a geographically defined resident populations means that prevalence and prenatal detection rates represent the experience of the entire population, not just tertiary centres with special expertise/high risk mothers. Information to be collected on each case and coding is standardised across registries. "Full member" registries (33) transmit a file of anonymised individual records of CA cases each year to the Central Database, to be updated to cases born 2009-2011. Prevalence rates are calculated per 10,000 births in the registry population. All full member registries use the EUROCAT Data Management Program (EDMP) for data input/import, validation, duplicate checking, and transmission. The EDMP allocates cases to the standard 95 EUROCAT congenital anomaly subgroups (specified in EUROCAT Guide 1.3) according to their International Classification of Diseases (ICD) codes. Web programming produces epidemiological tables according to user specification.</p>	<p>Process Indicators Successful annual data transmission to Central registry from all Associate Partner Registries.</p> <p>Output Indicators Prevalence tables for 95 anomaly subgroups on the EUROCAT website, updated each year.</p> <p>Outcome Indicators Citations of EUROCAT prevalence information.</p>	4, 5 and 6
2	<p>Network expansion and data quality improvement - To co-ordinate the establishment of new registries throughout Europe collecting comparable, standardised data. The integration of new registries and countries allows the sharing of knowledge</p>	<p>Process Indicators Integration of Latvia, Slovenia and Valencia as new Full Members of EUROCAT, with</p>	4 and 5

	<p>and expertise and a widening contribution to public health planning. Data quality monitoring and improvement is an essential prerequisite for use of the data for all other objectives, and for effective comparison between countries.</p> <p>A new Registry Advisory Service will be set up to help new registries become EUROCAT members. Data Quality Indicators are monitored. The Coding and Classification Committee agrees coding and classification guidelines, liaises with WHO ICD 11 revision, and reviews cases with multiple anomalies. A subcommittee will update the guidelines for coding of variables in the common dataset to keep up with clinical practice and public health developments.</p>	<p>successful data transmission.</p> <p>Submission of revised ICD11 proposal to WHO.</p> <p>Outcome Indicators Improvement in Data Quality Indicators in two thirds of Registries.</p>	
3	<p>Early warning - To co-ordinate the detection and response to trends and clusters and early warning of teratogenic exposures, to allow appropriate action to be taken regionally, nationally and at an EU level.</p> <p>The EDMP incorporates software for statistical monitoring for the detection of clusters and trends in time, including a “scan” moving window technique. Annual statistical results generated centrally are sent to registries for preliminary investigation, which identifies whether the cluster is due to changing diagnostic or reporting patterns, data quality issues, or possible environmental factors, and the spatial boundaries within/between regions. A new Task Force for Evaluation of Clusters will be established to facilitate rapid response to cluster, including self detected, and interaction with public health authorities. In depth database analyses of trends and risk factors for selected CA. A feasibility study will test linkage to spatial environmental pollution databases for future surveillance.</p>	<p>Process Indicators Improvement in number of Registries meeting earliest data transmission deadline.</p> <p>Output Indicators Annual Statistical Monitoring Reports.</p> <p>Five in-depth investigations, including one by TEC and one of swine-flu impact.</p> <p>Environmental data linkage feasibility report.</p> <p>Outcome Indicators Generation and preliminary investigation of clusters/trends in each registry.</p>	6
4	<p>Primary prevention policy - To make recommendations for the inclusion of primary prevention of CA in national rare disease plans and to evaluate the effectiveness of existing primary prevention measures. A focus will be folic acid but this objective will</p>	<p>Output Indicators Report on public health actions relevant to prevention of BD at EU MS level.</p>	7

	<p>also assess other potential routes including management of chronic diseases, drugs in pregnancy, maternal infection and vaccination, environmental pollution, alcohol and smoking, and socioeconomic and migrant issues.</p> <p>Policy surveys and consensus development to provide a framework for the incorporation of primary prevention of CA in national plans for rare diseases. In relation to folic acid, a policy survey and analysis of central database for neural tube defect trends will be carried out.</p>	<p>Report on actions to prevent NTD by raising folic acid status at EU MS level.</p> <p>Report on potential consensus approach toward inclusion of primary prevention actions in national plans on RD.</p>	
5	<p>Prenatal screening information - To assess the impact of developments in prenatal screening at a population level, with particular reference to Down Syndrome. Prenatal screening is continually evolving, and evolving differently in each country. EUROCAT will allow a common approach to monitoring of detection rates for individual anomalies and pregnancy outcomes in relation to policy and demographic characteristics eg. maternal age.</p> <p>Analysis of central database (enhanced with additional DS registry data) on genetic syndromes.</p>	<p>Process Indicators Integration of England and Wales NDSCR into central database.</p> <p>Output Indicators Expansion of prenatal diagnosis tables on EUROCAT website.</p> <p>Outcome Indicators Publication of 6 genetic syndrome papers.</p>	8
6	<p>Postmarketing drug surveillance - To develop EUROmediCAT as an effective postmarketing surveillance tool in relation to medication use in pregnancy and risk of CA. Despite concerns since the thalidomide epidemic, there is still no effective postmarketing surveillance of drug use in pregnancy. EUROCAT will continue to develop its role in this area by analysing a database of worldwide importance, and by exploiting new possibilities for linkage with prescription data.</p> <p>Analysis of medication exposure (ATC coded) in central database, prescription data linkage and protocol development.</p>	<p>Process Indicators 3 Workshops on quality of medication exposure data.</p> <p>Joint meeting with ISPE and ENTIS.</p> <p>Output Indicators 3 scientific papers.</p> <p>Outcome Indicators Protocol for early warning of drug-malformation associations.</p>	9

2.3 Overview of activities for the period covered in the interim report

WP	Activities	Outcomes/ deliverables	Date foreseen	Date of achievement	Level of achievement (measured by indicators)	Justification/ Problems encountered	Action to be taken to overcome the problem
1	Activity 1 - 27 th EUROCAT Registry Leader's Meeting (RLM)	Milestone 4 of WP1	Month 18	Month 18	Meeting took place in Budapest. Meeting minutes and presentations made available to network.		
	Activity 2 – Organisation of Project Management Committee Meetings		3 within reporting period	Months 15, 18, 24	3 meetings took place and meeting minutes were made available to network.		
	Activity 3 – Maintenance of EUROCAT website		Months 13-24	Months 13-24	Continuously reviewed and updated, currently relevant to the Joint Action with related improvements (i.e. new EUROCAT publication list for Associate Partners)		
	Activity 4 – Financial Management		Months 13-24	Months 13-24	Continued implementation of EUROCAT online Budget Management System (EBS) to report budget for 2 nd reporting period		
	Activity 5 – Reports to and liaison with Executive Agency and DGSanco	Milestone 2 of WP1 – 2 nd Interim Report	Months 24	Month 28	2 nd Interim Report submitted	Date of achievement was anticipated to be after date foreseen as we had to delay until after the reporting period had been completed.	
	Activity 6 – Administrative support to all work packages		Months 13-24	Months 13-24	Met the needs of all WPs in reporting period		
	Activity 7 – Overall project management and co-ordination tasks		Months 13-24	Months 13-24	Met the needs of all WPs in reporting period		
2	Activity 1 - Creation and co-ordination of a dissemination strategy including reports, publications and editorials in public health or clinical journals, presentations at scientific meetings and conferences, contacts with media, promotional leaflet, use of website and newsletters (WP leader in discussion with Project Management Group). At the first meeting, a new	Dissemination plan	Month 3	Month 3	Dissemination plan available and agreed by PMC.		
		Milestone 5 of WP2 (Promotional Leaflet)	Month 3	Month 3	Leaflet produced and disseminated		

	promotional leaflet will be finalised.						
	Activity 2 - Contributions on demand to DG SANCO newsletters, web- site or scientific or technical meetings, conferences or reports.						
	Activity 3 - Co-ordination of liaison with other networks, organisations and committees						
	Activity 4 - Facilitation of national EUROCAT Committees or equivalent						
	Activity 5 - Review of the EUROCAT website				Continuously reviewed and updated, currently relevant to the Joint Action with related improvements		
	Activity 6 - Editing three issues of the EUROCAT newsletter	Milestone 1 of WP2 – Newsletter 1	Month 12	Month 12	Disseminated in accordance with plan		
		Newsletter 2	Month 24	Month 24			
	Activity 7 - Organisation of European Symposium on Prevention of Congenital Anomalies - Antwerp 2011, Zagreb 2013	Milestone 4 of WP2 – 1 st European Symposium	Month 6	Month 6	Meeting took place and evaluation complete and available on meeting website		
3	Evaluation WP	Milestone 2 of WP3 – Last PMC meeting of 2013	Month 23	Month 24	Meeting took place, PMC agreed evaluation plan and website evaluation survey content to be implemented in 2013.	Tender for independent evaluation was not successful.	Alternative arrangement agreed with the Executive Agency involving independently acquired consultancy.
4	Activity 1 - Database related activities	Milestone 1 of WP4 – website epidemiological tables updated to 2009	Month 4	Month 4	Process indicator – successful annual data transmission to Central Registry from Associate Partner registries		
		Milestone 3 of WP4 – website epidemiological tables updated to 2010	Month 16	Month 16	Output indicator - Prevalence tables for 95 anomaly subgroups on the EUROCAT website, updated each year.		
					Process indicator –		

					integration of Valencia as a new Full Member of EUROCAT Process Indicator – improvement in number of registries meeting earliest data transmission deadline		
	Activity 2 - Statistical Monitoring	Milestone 2 of WP4 -Annual statistical monitoring report 2009 Milestone 4 of WP4 - Annual statistical monitoring report 2010	Month 12 Month 24	Month 12 (added to website Month 13) Month 24 (added to website Month 25)	Output indicator – annual statistical monitoring report Outcome indicator – generation and preliminary investigation of clusters/trends in each registry		
	Activity 3 - Develop statistical monitoring methods						
	Activity 4 - Perinatal mortality						
	Activity 5 - Registry advisory service for new registries	Milestone 5 of WP4 – successful data transmission from new member registries	Months 13-24 Month 26	Months 13-24 By month 24	Registry Advisory Service workshop held at registry leaders meeting, in addition to individual contact throughout the year with new and applicant registries Data has been received from new member registries, Latvia and Slovenia		
5	Activity 1 - EUROCAT coding and classification Committee	Milestone 1 of WP5 - meetings	5 by Month 30	4 by Month 24	n/a		
	Activity 2 - ICD11	Deliverable – ICD11 Coding revision		Month 16	EUROCAT recommendations for third ICD11 proposal sent to		

		submission			Orphanet		
	Activity 3 - Surveillance of cases with multiple congenital anomalies	Milestone 2 of WP5 – Annual Review of multiply malformed cases Milestone 5 of WP5 – Scientific paper on epidemiology of multiple malformations	Month 3, 15 and 27 Month 15	Month 2 and Month 15 Second draft ready by Month 24	Multiple malformations reviewed	Decided to update data included within paper to 2010 – resulted in delay but improved scientific quality	
	Activity 4 - Revision of Guide 1.3 to Guide 1.4	Milestone 3 of WP5 – implementation of EUROCAT Guide 1.4	Month 24	Month 24	Chapter 2.2 of Guide 1.3 updated to version applicable to Guide 1.4 for births 2013.		
	Activity 5 - Revision of Data Quality Indicators	Milestone 4 of WP5 – Publication of revised set of DQI on website	Month 12	Agreed by PMC Month 11, on website Month 14	n/a	Slight delay in getting revised DQI to website was caused by timing of PMC meeting	
6	Activity 1 - Annual Statistical Monitoring	Milestone 1 and 2 of WP6 – Annual Statistical Monitoring Report	Month 12 and 24	Month 12 and 24 (added to website Month 13 and 25)	Output indicator – annual statistical monitoring report Outcome indicator – generation and preliminary investigation of clusters/trends in each registry		
	Activity 2 - Task Force for Evaluation of Clusters (TEC)		Month 18	Month 18	Formed and mandate agreed (see Annex 10)		
	Activity 3 - Response to swine flu epidemic	Relates to Milestone 4 – set of scientific papers on epidemiology of selected anomalies and risk factors	Month 12, 24, 36	Month 12	Paper published, a second paper expected by Month 36		

	<p>Activity 4 - Investigation of specific trends of</p> <ul style="list-style-type: none"> - Hypospadias (UMCG) - Multiple births with congenital anomaly (UU) <p>- Gastroschisis (ULEIC)</p> <p>- Hirschsprungs (UNEW)</p>	Relates to Milestone 4 – set of scientific papers on epidemiology of selected anomalies and risk factors	Month 12, 24, 36	Month 24	<p>Paper expected Month 36</p> <p>Multiple birth paper published, a second multiple birth paper expected by Month 36</p> <p>Paper expected Month 36</p> <p>Paper expected Month 36</p>		
	<p>Activity 5 - Investigation of Epidemiology of Congenital Heart Disease</p> <ul style="list-style-type: none"> - Trends in prevalence of CHD (INSERMU953) - Epidemiology of selected CHD (Hospital Lillebaelt) - Case-control study protocol (UU) 	Relates to Milestone 4 – set of scientific papers on epidemiology of selected anomalies and risk factors	Month 12, 24, 36	<p>By Month 12</p> <p>By Month 24</p>	<p>Paper published</p> <p>Paper published</p>		
	Activity 6 - Actions towards European environmental surveillance	Milestone 5 – Report of feasibility of environmental data linkage and pilot study areas	Month 36				
7	<p>A To collect and review public health actions relevant to primary prevention of birth defects at level of</p> <p>A.1 pre- and peri-conceptual care, namely: folic acid supplementation; maternal lifestyles (smoking, alcohol, recreational drugs); counselling on, and management of chronic maternal conditions (epilepsy, diabetes, obesity, etc.) and use of drugs and health-promoting products (including dietetic or herbal products, etc.) in collaboration with WP9; genetic counselling in collaboration with WP8;</p> <p>A.2 census of sectorial and intersectorial policies in MS regarding primary prevention with potential relevance to birth defects, namely: food safety and nutrition, including promotion of healthy dietary habits; prevention of rubella, toxoplasmosis,</p>	Milestone 1 and 2 of WP7	Month 12		<p>Achieved collection of public health actions relevant to prevention of birth defects</p> <p>Achieved collection of actions to prevent Neural Tube Defects by raising folic acid status</p>		

	etc.; regulations on potential teratogens (environment, workplace, pharmaceuticals); actions on health determinants (physical activity, smoking, alcohol, recreational drugs). Consideration will be also given to investment in research on birth defects and socio-economic and ethnic determinants. WP7 will evaluate a potential consensus approach toward inclusion of the above actions in national plans on RD.						
	B The actions on prevention of neural tube defects (NTD) by raising folic acid status will be considered in detail as a model for the actual development of a consensus approach. This will be performed by: B.1 updated survey of policies in MS B.2 track prevalence rates of NTD through the registries B.3 approaches to assess knowledge and attitude toward folic acid of women in childbearing age B.4 appraisal of strategies to monitor population folate status.						
8	Activity 1. Down syndrome and cardiac anomalies - To analyse the prevalence of cardiac anomalies in babies born with Down syndrome and determine the impact prenatal diagnosis has had on it.	Milestone 1 – submission of scientific paper on prevalence of cardiac anomalies in DS	Month 21		A paper with proposed title “Major Congenital Malformations in babies born with Down syndrome”, intended for submission to the American Journal of Medical Genetics, has been drafted.	This paper will be delayed until the 3rd reporting period, due to delays in acquiring permissions from participant registries.	
	Activity 2. Prevalence of Down syndrome - To include the NDSCR data for England and Wales in EUROCAT website epidemiological tables	Milestone 2 – Submission of scientific paper on changes in the prevalence of DS	Month 31	Month 24	"Twenty-year trends in the prevalence of Down syndrome and other trisomies in Europe: impact of maternal age and prenatal screening" has now been published in European Journal of Human Genetics, EJHG (2013) 21: 27–33		
	Activity 3. Prevalence of genetic syndromes	Milestone 3 – submission of 2 scientific papers	Month 18	Month 18	“Fraser Syndrome: Epidemiological Study in a European Population” was	Due to delays in the editorial process, this paper will not be	

		on descriptive epidemiology of selected genetic syndromes	Month 18		reported as accepted for publication in the 1 st interim report in the American Journal of Medical Genetics.	published until 2013. A second syndrome paper (OAVS) was due to be delivered by Month 18, this paper was delayed due to difficulties with the selection of registries and is not going to be delivered until the 3rd reporting period (Month 25-36).	
	Activity 4. Review of prenatal diagnosis tables						
9	Activity 1. Improve and document medication exposure data (UMCG) - improve coding of medication use in pregnancy by giving training in ATC-coding at the RLM (RUG); develop and implement data quality indicators specifically for medication exposure data (RUG); evaluate data quality up to 2008 on antidepressants (UU), antiasthmatics (Lillebaelt) + antidiabetics (RUG); compile report on information sources on maternal medication used by registries (RUG).	Milestone 2 – 1 st Annual workshop on ATC coding Milestone 2 – Updated report on sources of data on maternal medication use used by registries contributing data to EUROCAT	Month 6 Month 12	Month 6	ATC workshop attended	Due to maternity leave of one of the researchers of the UMCG, the report on sources of medication use has not been finalized yet.	The report is still expected by the end of the project.
	Activity 2. Prescription data linkage - Identify national + regional available prescription data sources for use by registries (UMCG); Conduct + evaluate pilot linkage studies (UMCG).						
	Activity 3. Signal detection and evaluation - Specify and pilot signal detection methods (UMCG); Analyse EUROCAT database in relation to antidepressants (UU), newer						

	antiepileptics including lamotrigine (RUG) and drugs of new concern arising (UMCG).						
	Activity 4. Liaison with EncePP (EMA's European network of centers for Pharmacoepidemiology & Pharmacovigilance), ISPE and ENTIS - Organize joint meeting with ISPE (Int. Society of Pharmacoepidemiology) + ENTIS (European Network Teratology Information services) (RUG)	Milestone 3 – Joint symposium with ISPE and ENTIS (Florence)	Month 24	Month 20	A Joint workshop between EUROCAT and ENTIS was organised at the ISPE meeting in Barcelona, August 2012.		

3. Technical implementation of the project

3.1 Activities related to Horizontal Work Packages:

WP1: Management of the project

Associate partners involved in WP: UU, SFR, PIH, KDB, Lillebaelt, INSERM U953, NCHAI, IMER, ISS, UMCG, FHI, CREAL, QMUL, Oxford

Description of the activities undertaken

Overview of Management Structure and Governance Applicable to Listed Activities

EUROCAT has an exemplary approach to management and governance, which has positively impacted year two of the Joint Action contract.

Project Management Committee (PMC)

The PMC consists of a Steering Committee of elected registry leaders (RL) from full EUROCAT member registries (see below), the Project Leader and the President of the EUROCAT Association, as well as all work package leaders and the Project Manager detailed below.

Steering Committee

- Prof. Helen Dolk (UK, UU)
- Prof. Lorentz Irgens (Norway)
- Prof. Eliza Calzolari (Emilia Romagna, Italy, IMER)
- Dr. Babak Khoshnood (Paris, France, INSERM U953)
- Dr. Vera Nelen (Antwerp, Belgium, PIH) reinstated June 2012
- Dr. Diana Wellesley (Wessex, UK, SUHT)
- Prof. Ingeborg Barisic (Zagreb, Croatia, KDB) President of EUROCAT Association

Work Package Leaders

WP1 Prof. Helen Dolk (UU)

WP2 Prof. Ingeborg Barisic (KDB)

WP3 Prof. Helen Dolk (UU)

WP4 Ms. Maria Loane (UU)

WP5 Dr. Ester Garne (Hospital Lillebaelt)

WP6 Dr. Martine Vrijheid (CREAL)

WP7 Dr. Domenica Taruscio (ISS)

WP8 Prof. Joan Morris (QMUL)

WP9 Dr. Marian Bakker (UMCG)

Project Manager

Dr. Rhonda Curran (UU)

EUROCAT Association

The EUROCAT Association is the association of member EUROCAT registries, which is legally constituted and independent of funding modes. The EUROCAT Association elects a President (currently Prof Ingeborg Barisic, since June 2012) and elects four/five Steering Committee members.

Activity 1 - 27th EUROCAT Registry Leader's Meeting (RLM)

The 27th EUROCAT RLM was held in Budapest, Hungary (14th - 15th June 2012) **and was the second milestone scheduled to be reached by WP1** (Month 24). Administrative support for the RLM was provided by both the main partner (UU) and the hosting partner (NCHAI). This meeting was attended by 74 participants from 23 countries. 30 RLs, by 32 local registry staff, by 8 Central Registry staff and doctoral students, and by 4 other external guests. 32 of 36 associate partners were represented at the meeting. The RLM was minuted and the minutes were made available to all associate partners through the member's only section of the EUROCAT website. The participants list and agenda are detailed in **Annex 1**. During the 27th EUROCAT RLM the following workshops and committee meetings were held – PMC Meeting to discuss next RLM and symposium, Coding and Classification Committee Meeting, PMC with Guide 1.4 Committee Meeting, Website Dissemination Committee Meeting, Folic Acid Committee Meeting, Registry Advisory Workshop, Work Package 9 Workshop, EUROCAT Data Management Program Clinic, EUROCAT Budget System Workshop, Steering Committee Meeting, Lamotrigine Study Meeting.

Activity 2 – Organisation of Project Management Committee Meetings

In addition to the RLM the Project Management Committee (and separately the Steering Committee) met two other times within the reporting period. Firstly on the 28 – 29th March 2012 (Oxford, UK) and most recently on the 12-13th December 2012 (Oxford, UK). Meetings were minuted and the minutes were made available to all associate partners through the member's only section of the EUROCAT website.

Activity 3 – Maintenance of EUROCAT website

During the reporting period the EUROCAT website www.eurocat-network.eu has been the main management and dissemination tool for EUROCAT. EUROCAT members (associate and collaborating partners) have passwords for member entry which gives them extra levels of pages visible only to members. The public and all stakeholders have access to all other parts of the website. The EUROCAT administrator and Project Manager have been responsible for updating the website, which now features an overview of the Joint Action <http://www.eurocat-network.eu/aboutus/jointactioneurocat>. Other WPs have made extensive use of the EUROCAT website for specific applications (i.e. the provision of website data related to WP4). Specific applications of the website relating to WP1 activities within the reporting period include providing an up to date inventory of EUROCAT publications, a portal to link associate partners to registration for the RLM, management of PMC meeting arrangements, posting of relevant announcements which have included new publications, the RLM, other relevant external meetings as well as other dissemination announcements. A registration system for access to online tables has been implemented in 2012. Central Registry is tracing use of the website tables by tracking the number of registrations by country and by type and the number of website table reports generated. If an internal member of EUROCAT is already logged into the Member's only section of the EUROCAT website they do not have to log in separately to view and use the website prevalence tables. In December it was noted that the free text option available to give "Country" was generating incorrect data (i.e. London etc.). This was rectified by changing to a pre-defined Country drop-down menu. For an overview of registration to of EUROCAT's interactive website prevalence tables - **Annex 2**.

Activity 4 – Financial Management

The secure, confidential and password protected online budget management system (EBS), accessible to members only through the EUROCAT website (implemented by the main partner (UU) within the first reporting period) continues to enable associate partners to maintain their accounts, submit timesheets, upload invoices and receipts. As well as maintaining the main partner accounts, administrator access to the online budget management

system enables the co-ordinating partner to monitor expenditure throughout the reporting term. The system continues to make registries more aware of what they agreed to do for the contract and make them more aware of the amount of money they are receiving from the EU. As registries are more aware it is easier for the coordinating partner to produce yearly expenditure summaries and identify who has underspent and who has overspent. As a result and as anticipated within the first reporting period it was easier to distribute the first interim payment – those who did not reply via the online budget management system had their first interim payments deferred. This included Strasbourg (UDS) and Poland Registry (PUMS).

During the reporting period, two grant agreement amendments concerning changes to the budget (see **Annex 3**) were submitted to the Executive Agency (February and December). A decision on both is still pending.

Activity 5 – Reports to and liaison with Executive Agency and DGSanco

Compilation of the 2nd interim report accompanied by financial statements.

Activity 6 – Administrative support to all work packages

Administrative support has been provided throughout the reporting period by both the administrator (Mrs Barbara Norton) and the project manager at EUROCAT Central Registry.

During the reporting period 12 EUROCAT Communications (internal email communications sent to all registry leaders with news, guidelines, deadlines and all information needed for the running of the project) were distributed.

Activity 7 – Overall project management and co-ordination tasks

Corresponds to Activities 1-6 combined.

Problems encountered

As with the 1st interim report there was a delay in submission of the second interim report. As the foreseen date of achievement corresponded with the final month of the reporting period, this did not give a realistic timeframe to collate the report inclusive of month 24 activities. A continuing problem for the coordinating partner associated with financial management is that non-euro country associate partners cannot monitor their “exact” expenditure as the applicable exchange rate will be that of the first day after the end of the budget (1 January 2014). This is a source of concern for affected associate partners. Use of an interim fixed exchange rate for each reporting period would be preferable.

See above for problem specific to website registration.

Some Associate Partners reported problems accessing their funds internally due to the delay in response from the Executive Agency to grant agreement amendment submissions.

Activities planned for the next period

The next Registry Leaders Meeting (milestone 5 of WP1), in Zagreb, Croatia, is planned for the 12-13th June 2013 (Month 30) with pre-meetings on the 11th June 2013.

A PMC teleconference has been scheduled for April 2013 and a meeting in June 2013 (in Zagreb). A third PMC meeting will be arranged (venue and Month still to be confirmed).

The final interim report with financial statements is in planning for Month 36-38.

12 EUROCAT communications are scheduled for the next reporting period.

WP2: Dissemination strategy

Associate partners involved in WP: KDB, UU, SFR, PIH, Lillebaelt, INSERM U953, IMER, ISS, UMCG, FHI, CREAL, QMUL, Oxford, THL, HSE, IFC-CNR, UMCL, NCHAI

Dissemination plan available yes (Annex 4)

Description of the activities undertaken in 2012

This deliverable is the second report on dissemination activities and it is based on “Dissemination Strategy”, which describes initial dissemination plan. Therefore, with this document we extend the previous report with dissemination results that took place in the 2012.

During 2012 the dissemination work package has linked all work packages of the EUROCAT Joint Action project and addressed the various levels of stakeholder engagement. EUROCAT has a large number of collaborators and so it is essential that there is good dissemination of information both internally and externally. To ensure that the information about, and outputs from, the EUROCAT Joint Action are disseminated as widely as possible to the range of stakeholders in the most appropriate format for their requirements, a number of tools as detailed in the dissemination strategy were employed.

EXTERNAL STAKEHOLDERS

1. Website – (See WP1, Activity 3 - Maintenance of the EUROCAT website).

The website is one of the first access points to the project and so it contains an array of information to meet the various needs of the visitor. In order to obtain the useful feedback about the website and to determine if the project is reaching intended users we have introduced a brief Website Evaluation Survey for the visitors of the webpage. The Website Dissemination Committee has met on June 15th during the RLM Meeting in Budapest, Hungary. Different sections of the EUROCAT webpage have been discussed and suggestions made for improvement (See **Annex 5** - minutes of the Website Dissemination Committee meeting in Budapest). The Committee has continued to communicate via email and has contributed with comments and try out to the redesign of the website tables.

The EUROCAT website consists of two individual layers: one public with open access to view the content and one layer that is restricted to EUROCAT members (see section Internal stakeholders).

1.1. Public Website

The public section of the website offers information about activity associated with the EUROCAT Joint Action and its outputs, events and news. The epidemiological information on congenital anomalies, including prevalence, birth outcomes, perinatal mortality and prenatal detection rates updated to 2010 have been presented in a new interactive table format for the regions, countries, years and congenital anomaly subgroups, as selected by the user. Special reports, publications, power point presentations from conferences/symposia, and press releases published in 2012 are also available for download on the EUROCAT website. Notifications of the availability of these documents were distributed through the EUROCAT Communication and EUROCAT Joint Action Newsletter. Website also contains updated information regarding recent achievements, publications and planned events as well as reorganized and updated links to external organisations and websites of interest.

2. Newsletter 2 – electronic version (See **Annex 6**)

The EUROCAT Joint Action Newsletter 2012 has been published online and also distributed to 2154 subscribers via email.

3. 12th European Symposium on Congenital Anomalies, Zagreb, June 14th 2012

Activities for the preparation of the 12th European Symposium on Congenital Anomalies, Zagreb, June 14th 2012 are ongoing. Scientific Committee has agreed on the topics and invited speakers, Symposium leaflet created. Symposium webpage is activated and linked to the EUROCAT webpage (www.eurocat2013.com/). The Symposium has been advertised through a range of media. It was announced in a newsletter to the full email list, letters have been sent to presidents of European National Societies of Human Genetics, and to local stakeholders (Croatian Medical Association, in particular to members of Croatian Rare Disease Society, Croatian Society of Human Genetics, and partners of the Balkan Human Genetics Societies). Additionally, the initial announcements were placed on the ESHG webpage and circulated within Orphanet and Community Genetics newsletters.

4. Networking

Collaborations with other stakeholder groups and other allied projects have resulted in a number of opportunities to further present EUROCAT Joint Action to a wide range of stakeholders. Based on the Liaison Officer Strategy for Collaboration with other networks, organisations and committees liaison officers have continued their activities in contacting other networks and integrating Joint Action outcomes into the work of other committees, projects and organisations. The activities related to rare disease projects/conferences/meetings were particularly productive.

(See **Annex 7** for Liaisons with other networks, organisations and committees in 2012)

5. National EUROCAT Committees

At the RLM in Budapest in June 2012 we have encouraged registries to take action for setting up National EUROCAT Committee (NEC). As planned, the Irish registry presented their experience of setting up NEC at the general assembly. The British Isles Network of Congenital Anomaly Registers (BINOCAR) is working closely with Public Health England (PHE) to secure a national surveillance system involving CARs in every region in England. In 2012 annual general meeting was held at the University of Oxford hosted by CAROBB. BINOCAR data was used in a number of research projects. Two BINOCAR representatives sit on the newly configured National Congenital Anomaly Group chaired by Dr Jem Rashbass of PHE. A national committee established in the Netherlands met on June 5, 2012. Their role is to advise the Ministry of Health on aspects associated with registration of congenital anomalies, to monitor the relation with other perinatal registrations and to stay in contact with the National Board for Perinatal Care. Members are representative from the relevant health professions, gynaecologists, midwives, pathologists, paediatricians, geneticists etc. During 2012, the Irish National Congenital Anomaly Committee enabled progress in improving data capture, particularly in relation to a national NTD prevalence study. The results of this study, carried out by the three Irish EUROCAT registries, are being analysed, and will be available later this year. In Spain and France there is at present no National EUROCAT Committee, but the Spanish Registries included in EUROCAT are working jointly for a research project (IRDIRC Consortium) called SpainRDR (Spanish Rare Diseases Registries Research Network), and in France the registry leaders meet regularly with colleagues at the InVS (French National Institute of Health Surveillance) who follow and evaluate the activities of the registries of congenital anomalies at the national level. The Italian Central Coordination Committee on CA established at the Italian National Centre of Rare Diseases (CNMR) is composed by the Director and experts of CNMR, leaders of regional registries, members of the Italian Ministry of Health and of Italian National Institute of Statistics. In this context, the CNMR is promoting also the EUROCAT Joint Action activities at national level. There have

been initiatives similar to National Committees but including other types of registries. For example, in Finland there is a plan to form general advisory committee covering all Reproductive Registries (Malformation Register, Medical Birth Register, Register on Very Small Babies, Register on Abortions and Sterilisations and IVF statistics) with participants from the Ministry of Health, from other governmental authorities, from related professionals: clinicians, hospitals and hospital districts, from associations of doctors with certain specialities, Association of Midwives etc. In some countries (e.g. Finland, Denmark, Austria, Slovenia) there will be difficulties in setting up a National EUROCAT Committees, either because of the organisation of the health care system or because of the small size of country.

6. Conference Presentations and Posters

Conferences were an important method of disseminating activities to stakeholders in 2012. The PMC has aimed to present results of the EUROCAT Joint Action in academic conferences as well as to special interest conferences (e.g. Rare Diseases Conference). Copies of conference presentations are available on the website for future reference. (See full list in **Annex 8**)

7. Peer-reviewed collaborative (involving more than one registry) publications

Papers providing information on the EUROCAT Joint Action and its outputs have been submitted to peer-reviewed academic journals to maximize the visibility of the project in the scientific community. (See full list in **Annex 9**)

8. Press Releases

The work package teams have prepared press releases to be sent to relevant media. Some of these press releases are also posted on the EUROCAT website. Several topics of published papers (e.g. increasing of the prevalence of congenital anomalies in twins) have raised special press interest. (See full list in **Annex 10**)

9. Other Dissemination

Description of EUROCAT Joint Action was included in the booklet on EU funded collaborative research in rare diseases published by Directorate-General for Research and Innovation (DG Research)

INTERNAL STAKEHOLDERS

1. Website – (See WP1, Activity 3 - Maintenance of the EUROCAT website).

1.2. EUROCAT member's private section

Dissemination activities within the EUROCAT members are also important for maintaining communication and enhancing the project management. The project website contains a private section accessible through a valid login. The private section of the website presents a platform through which private documents are downloaded. Each member was able to access documents produced in 2012 and stored in the restricted access area for upload appropriate to their needs. These documents include: monthly EUROCAT Communications, meeting papers and minutes from Registry Leaders Meeting, Steering Committee, Project Management Committee and Website Committee meetings. This has allowed the confidential sharing of information and decreased email correspondence.

Member Forum was used for communication between different work package groups. The multiple malformation cases that needed to be reviewed and commented upon by Multiple malformations working group were uploaded on the website and a program was

developed that has enabled three geneticist to evaluate cases manually via webpage in order to reach final decision on the classification of cases.

2. Registry Leaders Meeting (See WP1, Activity1, Annex 1)

3. Workshops (See WP1, Activity 1, Annex 1)

Several workshops have been organised during the RLM Meeting in Budapest in order to provide the appropriate setting in which the key elements of the project and main topics of WP4-9 of the EUROCAT Joint Action could be discussed. The activities and outcomes for each of the workshops are given in the form of minutes reports.

4. PMC Meetings and other work package internal dissemination activities

The projects progress is highlighted through Project Management Committee meetings which bring together all work package leaders to a common location to report on activities and to discuss and plan for actions that require inter-work package collaborations during the year. During 2012 two PMC meetings were successfully held in Oxford. In addition to this, each work package organizes teleconferences and physical meetings as they deem necessary. As part of the day-to-day activities, internal dissemination is also carried out via various types of electronic communication.

Problems encountered

None

How were problems resolved

Not applicable

Activities planned for the next period

- During the June 2013 RLM we plan to organise a Workshop for the Website Dissemination Committee to discuss further development of the website.
- Updating website tables for key public health indicators, perinatal mortality, and prenatal diagnosis -Website Evaluation Survey analysis
- Liaison activities with other networks will continue as planned in the strategy with regular reports on activities at PMC meetings. Special emphasis will be put in strengthening collaboration with rare disease projects/networks and committees. Close collaboration with EUCERD and active input in the key recommendations on the development of common European Platform on RD Registries.
- The 12th European Symposium on Congenital Anomalies, Croatia 2013.

WP3: Evaluation of the project

Evaluation plan available **Yes (Annex 11)**

Description of the activities undertaken

Five potential evaluation providers were identified as suitably equipped to evaluate large European projects. In accordance with the University of Ulster's procurement procedures, an invitation to tender was sent to each of the five. Only one response was obtained and was subsequently determined by the EUROCAT PMC to be unsuitable (on the basis of both cost (which was over the allocated budget) and scope). It was determined in agreement with the Commission (via our Scientific Project Coordinator Georgios Margetidis) that it would be possible for us to do a much more informative evaluation ourselves and to use subcontracted consultancy to specifically pursue one element of independent evaluation (as detailed in **Annex 11**).

Problems encountered

An independent evaluator could not be procured on the basis of the responses to the tendering process (see above).

How were problems resolved

An alternative solution was sought and agreed by the Commission (see above).

Activities planned for the next period

Initiation of the website evaluation survey (**Annex 12**) is planned for January 2013. This survey will be live until the 31st December 2013.

Identification of a suitable independent evaluation consultant is planned for January 2013.

Their role in independent evaluation will be planned in consultation with them (in accordance with the evaluation plan in Annex 11) and included in the final evaluation report.

A full evaluation report is planned as a component of the Final Joint Action Report for February 2014.

3.2 Activities related to core work package

WP 4: Registration, Central Database and Surveillance

Associate partners involved in WP: Principally UU, KDB, Hospital Lillebaelt, UMCG, QMUL and all associate partners for transmitting data. WP liaises with all Collaborating partners.

The tasks of WP4 are:

- 1: Database related activities
- 2: Statistical Monitoring
- 3: Develop statistical monitoring methods
- 4: Perinatal mortality
- 5: Create a Registry Advisory Service for new registries

Description of the activities

1. Database related activities

Anonymous data are transmitted to Central Registry using the EUROCAT Data Management Program (EDMP) on 15th February and/or 15th October each year. These data are uploaded to the membership-only website so that registries can confirm that the data are correct and agree excluded cases (cases that do not meet EUROCAT's definition of a congenital anomaly case). Following data confirmation, the data is uploaded to the live website tables:

<http://www.eurocat-network.eu/accessprevalencedata/prevalencetables>. In addition, a description of each registry is uploaded to the website detailing organisational and operational aspects of the registry to aid interpretation and evaluation of the registry prevalence data <http://www.eurocat-network.eu/aboutus/memberregistries>.

Central Registry continues to organise EDMP training workshops at the annual Registry Leaders Meeting (RLM) to answer queries and solve EDMP-related problems. Registry leaders are encouraged to book a one-to-one session and bring any problems that they may have experienced in the previous year for discussion. Also non-EUROCAT members attending the meeting who are thinking of starting collection of congenital anomaly data are invited to see the main features of the package and to see if it would meet their needs.

The EUROCAT central database (ECD) and EDMP are continually updated and refined according to user needs, improvements in surveillance of multiple malformations and medication drug exposure, assessment of data quality and developments in statistical methodology. In 2012 the new subgroup changes approved by the Coding & Classification Committee were implemented in ECD, EDMP and website tables (<http://www.eurocat-network.eu/content/EUROCAT-Guide-1.3-Chapter-3.3-Jan2012.pdf>), requiring major software revisions.

2. Statistical Monitoring

Statistical Monitoring systematically monitors the rates of birth defects over time to detect signals of new or increasing teratogenic exposures requiring public health action. Statistical monitoring for both trends and clusters in time is run by Central Registry in April each year, using confirmed data from registries that fulfil the monitoring criteria. Identified trends are reviewed by the PMC and trends of public health significance are prioritised for registry investigation. Registries report on their preliminary investigations at the annual RLM and an annual Statistical Monitoring Report is produced (in collaboration with WP6).

3. Develop statistical monitoring methods

The statistical monitoring methodology continues to be refined. In 2012, statistical methods to allow for increases in maternal age and changes in prenatal screening for trisomy 18 and trisomy 13 were implemented. In addition, forest plots showing average annual percentage change in prevalence (available by registry and by anomaly) were included in the output. Full details of all changes are listed in the Statistical Monitoring Protocol ([http://www.euocat-network.eu/content/Stat-Mon-Protocol-\(April-2012\)-2010.pdf](http://www.euocat-network.eu/content/Stat-Mon-Protocol-(April-2012)-2010.pdf)).

The effects of coding changes and of incomplete data transmission during the monitoring period on the trend analysis were investigated. The models used in the trend analysis were not sensitive to the coding changes.

Methods of combining data from nearby registers in order to search for clusters amongst rare anomalies were investigated. The results from analysing data from register in England and Wales was examined to determine if the results appeared reasonable. The method is now being extended to allow for any selection of registers to be examined together (i.e. county-wide surveillance).

4. Perinatal Mortality

A meeting with EUROPERISTAT took place in London, March 2012 to discuss collaboration and conduct joint work on perinatal and infant mortality due to congenital anomalies. EUROPERISTAT have some extra prevalence data from national sources not contributing to EUROCAT such as data on selected anomalies or for livebirths only. EUROPERISTAT have data on cause of death which is useful for collaborative studies on perinatal mortality, and data on socioeconomic status which is valuable as EUROCAT does not have socioeconomic denominator data.

5. Registry Advisory Service for new registries

The Registry Advisory Service (RAS) organised a Workshop on June 15 2012 during the Budapest RLM (agenda below):

Agenda

- Procedure for Obtaining EUROCAT Data (Ingeborg Barisic)
- Coding rules for the anomalies - where to find help. Core variables (Ester Garne)
- Definition and coding of Syndromes, Associations and Sequences (Ingeborg Barisic)
- Questions and closing remarks

The meeting was attended by 15 participants, mainly new staff from different registries.

Central Registry (R. Greenlees) has worked with new datasets from Latvia and Slovenia, which are in the process of being evaluated by a member of the RAS. The Slovenian Registry description and Application form (EUROCAT Registry description Questionnaire) have been reviewed and will be resubmitted to PMC in 2013 for approval. The RAS is open for further contacts and work with registries that are in the process of applying for EUROCAT membership (Latvia, West Midlands (UK), Mantova (Italy), Iceland, Georgia). Contacts have been made with Bulgaria and Lithuania with the prospect of developing partnership in 2014.

Northern Ireland has no registry. A report on current sources of data on prevalence of congenital anomalies in Northern Ireland to inform the development of a Northern Irish EUROCAT registry will be published in 2013.

Methodology applied as planned

Yes

Involvement of partners and target groups

All Full and Associate EUROCAT members contribute data to the website tables <http://www.eurocat-network.eu/accessprevalencedata/prevalencetables>. Full EUROCAT members that meet the inclusion criteria are included in EUROCAT Statistical Monitoring <http://www.eurocat-network.eu/content/Stat-Mon-Report-2010.pdf>

Coordination with other projects or activities

We are coordinating with EUROPERISTAT to further develop work on perinatal and infant mortality due to congenital anomalies.

We are coordinating with the EUROMediCAT project (Safety of medication use in pregnancy) jointly with WP9.

EUROCAT data was extracted from the central database for the following projects:

- Epidemiology of Hirschsprung's disease in Europe: a register-based study (JA study, in collaboration with WP6)
- The changing epidemiology of Gastroschisis in Europe: a register-based study (JA study, in collaboration with WP6)
- The impact of prenatal screening and subsequent terminations on the prevalence of CHD anomalies in live born babies with Down syndrome (JA study, in collaboration with WP8)
- Epidemiology of congenital diaphragmatic hernia in Europe: a register-based study (non-JA study)

Outcomes and deliverables achieved

1: Database related activities (Deliverable number 4)

Year 2010 data was uploaded to the website for the following 31 member registries: Antwerp, Hainaut (Belgium); Zagreb (Croatia); Odense (Denmark); French West Indies, Ile de la Reunion, Paris (France); Mainz, Saxony-Anhalt (Germany); Hungary; Dublin, SE Ireland (Ireland); Emilia Romagna, Tuscany (Italy); N Netherlands; Norway, Wielkopolska, Poland; S Portugal; Basque Country, Spain Hospital Network, Valencia Region (Spain); Sweden; Vaud (Switzerland); Ukraine; E Midlands & S Yorkshire, N England, SW England, Thames Valley, Wales and Wessex (UK).

Data up to year 2009 are available for the registries listed above and the following registries Styria (Austria); Czech Republic; Rhone-Alpes (France); Cork & Kerry (Ireland) and Malta. In addition, data up to year 2007 are available for Strasbourg (France), and data up to year 2006 are available for Finland.

Coverage of the 2010 European birth population is outlined in **Annex 13**.

For the 5 year time period 2006-2010, the prevalence of all congenital anomalies was 255.1 per 10,000 births (95% CI 253.6 - 256.6) and the prevalence of all non-chromosomal anomalies was 218.7 per 10,000 births (95% CI 217.3 - 220.1). Congenital heart defects excluding chromosomal anomalies continues to account for almost one-third of these anomalies (32.9%), chromosomal anomalies accounted for 14.3% and neural tube defects (NTD) for 4.2% of all anomalies (**Annex 14**).

Registries with a minimum of 4 years of data in the last 5-year period and time of diagnosis (the "when discovered" variable) known for $\geq 80\%$ of cases are included in the website prenatal diagnosis (PD) tables. PD data 2006-2010 are available for the following 26 registries: Styria (Austria); Hainaut (Belgium); Zagreb (Croatia); Odense (Denmark); Ile de la Reunion, Paris (France); Mainz, Saxony Anhalt (Germany); Hungary; Cork & Kerry, SE Ireland; Emilia Romagna, Tuscany (Italy); Malta; N Netherlands; Norway; S Portugal; Basque Country, Valencia Region (Spain); Vaud (Switzerland); Ukraine; E Midlands & S Yorkshire, N England, Thames Valley, Wales and Wessex (UK). In summary:

- Overall, 30% of all non-chromosomal anomalies and 70% of chromosomal anomalies were prenatally diagnosed. For non-chromosomal anomalies, the proportion prenatally

diagnosed ranged from 38% of cases with transposition of great vessels and club foot to over 90% of anencephalus and gastroschisis cases. For chromosomal anomalies, 90% of trisomy 18 and 13 cases were prenatally diagnosed compared to 63% of trisomy 21 cases.

- The rates of prenatal diagnosis vary greatly between registries, ranging from 10% in Hungary to 60% in Wessex for all non-chromosomal anomalies and from 11% in Malta to 90% in Paris for chromosomal anomalies.

- The rate of TOPFA (termination of pregnancy for fetal anomaly) per 1,000 births for All Anomalies combined varied between registries from 0.14 – 10.54

The website Perinatal Mortality tables were updated to include data for the years 2006-2010 for the following 13 registries: Styria (Austria); Odense (Denmark); Paris (France); Saxony Anhalt (Germany); Tuscany (Italy); N Netherlands; S Portugal; Basque Country, Valencia Region (Spain); Vaud (Switzerland); SW England, Thames Valle and Wessex (UK). In summary:

- The overall rate of late fetal deaths/stillbirths with congenital anomaly is 0.44 per 1,000 births, and the rate of deaths in the first week is 0.36 per 1,000 births, resulting in a total perinatal mortality rate of 0.81 per 1,000 births associated with congenital anomaly .

- The main congenital anomaly subgroups contributing to perinatal mortality are chromosomal anomalies (27% of perinatal deaths have chromosomal anomaly), congenital heart defects (24%) and nervous system anomalies (16%).

- Perinatal mortality associated with congenital anomaly varies from 0.27 per 1,000 births in South Portugal to 1.11 per 1,000 births in Vaud.

- Perinatal mortality/TOPFA rate associated with congenital anomaly varies from 0.91 per 1,000 births in South Portugal to 11.41 per 1,000 births in Paris.

As monogenic syndromes are too rare to include in the usual EUROCAT subgroups, a new addition to the website tables in 2012 was to include a table showing the prevalence of selected monogenic syndromes Data was uploaded to the website tables for the following 21 registries combined, 2005-2009: Styria (Austria), Antwerp (Belgium); Odense (Denmark), Ile de Reunion, Strasbourg (France), Mainz, Saxony Anhalt (Germany); Cork and Kerry, Dublin (Ireland), Emilia Romagna (Italy); Malta; N Netherlands; Vaud (Switzerland), Barcelona, Basque Country (Spain); Ukraine; E Midlands & S Yorkshire, N England, Thames Valley, Wales and Wessex (UK). Only syndromes with ≥ 5 cases are included in the table. Prevalence ranged from 0.02 per 10,000 births for Acrocephalopolysyndactyly, Bardet-Biedl syndrome and Dubowitz syndrome to 0.65 per 10,000 births for Di George syndrome.

2: Statistical Monitoring (Deliverable number 5)

The EUROCAT Statistical Monitoring Report 2010 (<http://www.eurocat-network.eu/content/Stat-Mon-Report-2010.pdf>) describes statistical monitoring of both clusters and trends in Europe for the ten year period 2001-2010 (see **Annex 15**). Key findings were:

- Rates of neural tube defects (NTDs) declined on average by 1.7% per year, with rates for spina bifida declining on average by 2.1% per year.

- Prevalence of congenital heart defects (CHD) decreased over time. However increasing trends were detected in two of the more severe types of CHD: Tetralogy of Fallot increased on average by 2.3% per year and single ventricle increased on average by 5.9% per year.

- Increasing trends were found for Oesophageal atresia with or without trachea-oesophageal fistula, duodenal atresia and stenosis, and atresia and stenosis of other parts of the small intestine. In contrast, atresia of bile ducts decreased by an average of 9% per year.

- The prevalence of the abdominal wall defect gastroschisis increased on average by 1.6% per year. Four out of five registries with the highest prevalence rates were located in the UK.

- Prevalence of the 3 chromosomal autosomal trisomies increased on average by 1.0% to 2.4% per year (Down syndrome, 1%; Edward syndrome, 2.3%; Patau syndrome, 2.4%). This increase in prevalence was explained by the increase in the proportion of older mothers giving birth.

Problems encountered

Some registries encountered difficulties at a local level during this reporting period:

- Funding difficulties – Styria (Austria) had no local funding in 2012 to employ someone to collect data and enter it into EDMP, hence the delay in data transmission.
- Staff shortages – Strasbourg (France) and Wielkopolska (Poland). It is difficult to find suitable replacements for staff that have left or on maternity leave.
- Registry staff required to take on additional tasks for other projects, so less time for EUROCAT. For instance, S Portugal also collect data for the national Portuguese registry.
- Changes in leadership – The Thames Valley registry leader retired, so the registry is currently seeking a replacement.
- Personal reasons – The Barcelona registry closed in June 2012.

How were problems resolved

We have a clear timeline for all database related activities so that registries can plan their local workloads accordingly. We aim to automate all website epidemiological tables in EDMP, in order to minimise the amount of time needed to generate and confirm data at local registry level. We continue to offer support and assistance relating to EDMP both at the RLM and by email communication.

Activities planned for the next period

Implementation of new website tables

- In 2013, year 2011 data will be entered into the central database and uploaded to the website: <http://www.eurocat-network.eu/accessprevalencedata/prevalencetables>
- Automate the Prenatal Diagnosis tables In ECD and EDMP, and upload 2007-2011 data on the website, in collaboration with WP2 and WP8.
- Automate the Perinatal Mortality tables In ECD and EDMP, and upload 2007-2011 data on the website, in collaboration with WP2
- Upload Data Quality Indicators for years 2006-2010, in collaboration with WP5
- Conduct statistical monitoring 2002-2011 with data from registries that fulfil monitoring data criteria, in collaboration with WP6. Publish Statistical Monitoring Report 2011.
- Continue to develop statistical monitoring methods i.e. develop methods for running cluster analysis by country and exclude genetic syndromes and skeletal dysplasias from monitoring
- During RLM in June 2013, RAS will organise a Workshop for new and applicant members, as well as the new world affiliates
- Work with Slovenia and Latvia towards full membership

WP 5: Coding and Classification, Data Quality

Associate partners involved in WP: Hospital Lillebaelt, The Coding and Classification Committee (Hospital Lillebaelt, KDB, SUHT, IMER, CARIS, UDS), UU, UNEW

Description of the activities This WP has 5 activities.

1. EUROCAT Coding and Classification Committee: Two meetings have been held in 2012: A short meeting in March in Oxford after the PMC meeting to discuss the third ICD11 proposal from Orphanet and a meeting at the RLM in Budapest in June (½ day). At the June meeting exclusions of cases with known aetiology for the statistical monitoring was agreed, coding tips were written and the epidemiology on multiple malformations was discussed. Coding queries from local registries have been answered throughout the year.

2. ICD11: The third ICD11 proposal from Orphanet was released February 17th. The coding committee discussed this proposal at the meeting in Oxford in March. A document with EUROCAT recommendations for improvements in the malformation chapter was sent to Orphanet April 1st. The beta version of ICD11 for public consultation was released in Summer 2012. Due to technical problems Segolene Ayme advised that EUROCAT did not work on the version before the website was stable regarding the content. At the EUCERD meeting in Luxembourg in November we were informed that the website now worked properly and EUROCAT could start sending comments.

3. Surveillance of cases with multiple congenital anomalies: The website tool for manual classification of potential multiple cases was available to the geneticists in the beginning of 2012. All potential multiple cases from 2010 and 2009 (approx 4000 cases) have now been classified by the three geneticists using the website tool (2010 cases in spring 2012 and 2009 cases in autumn 2012). A meeting is planned in February 2013 to discuss the methodology of the surveillance of multiples using the outcome of first two years of data.

The first draft of the epidemiology paper on multiple malformation cases from the pilot study including cases from 2004 was ready for discussion at the coding committee meeting in Budapest in June 2012. As the 2010 data had been reviewed at that time, it was decided that the quality of the paper had a higher priority than the date of delivery of the scientific paper. In September two authors (Elisa Calzolari and Ingeborg Barisic) visited the Central Registry in Belfast to update the paper with the 2010 data. A revised version of the paper is now waiting for approval at the Coding Committee meeting 27th of February 2013 before circulating to involved local registries for comments and approval for submission to the journal.

4. Revision of Guide 1.3 to Guide 1.4: The variables for the new Guide 1.4 have been pilot-tested in Spring 2012. The final proposal has been discussed at the RLM in Budapest and later approved by the PMC. The document describing the variables was circulated to all registries in December for use for cases born from January 2013. The EDMP has been updated and the new version is now available for the local registries.

5. Revision of Data Quality Indicators: The revised set of DQI has been approved by the PMC in November 2011. The revised DQI was applied to the 2010 data received at Central Registry in February 2012. The document was available for the local registries at the RLM in Budapest in June 2012.

Methodology applied as planned

Yes

Involvement of partners and target groups

The Coding and Classification committee has performed the first 3 tasks.
The Guide 1.4 Working Group is responsible for the work with the new variables.

Coordination with other projects or activities

The ICD11 work has been done in collaboration with Orphanet and EUCERD.

Outcomes and deliverables achieved

The milestone of a revised set of DQI has been achieved (month 12)
The milestone of implementation of Guide 1.4 has been achieved (month 24)
Review of multiple malformed cases for 2009 and 2010 has been done (month 2 and 15)
2 meetings in Coding Committee in 2012
Epidemiology paper on multiple malformation: second draft written.
EUROCAT recommendations for third ICD11 proposal sent to Orphanet in April 2012

Problems encountered

The problems mentioned in the first Interim report are now solved.

How were problems resolved

Activities planned for the next period

Coding committee meeting in February with statisticians to discuss surveillance of multiples.
A EUROCAT response to the ICD11 beta version will be written.
Coding meetings in June at the RLM in Zagreb and late Autumn to finalise the first statistical monitoring of multiples.
Updating of minor anomalies for exclusion.
Review of CHD literature and the EUROCAT CHD subgroups to be done in autumn 2013.

WP 6: Investigation of Trends, Clusters, and New Exposures

Associate partners involved in WP: CREAL, FHI, Hospital Lillebaelt, ULEIC, UMCG, UNEW, UU, CSISP, PIH, IFC-CNR, ASPB, Oxford, SUHT, Participating registries – SFR, PIH, IRSPG, KDB, Hospital Lillebaelt, THL, INSERM U953, UDS, UMC-Cmainz, OVGU, NCHAI, AO “G Rummo”, IMEER, ISS, ICF-CNR, BKUS, VEC, MCAR CHIR, UMCG, RUG, FHI, PUMS, INSA, UMCL, ASPB, BIOEF, CREAL, ASEREMAC, CSISP, ULEIC, UNEW, QMUL, Oxford, CARIS, SUHT

ACTIVITY 1: ANNUAL STATISTICAL MONITORING

Description of the activity

Trends and clusters signalled by statistical monitoring (WP4) are investigated by registries and reported on at the annual Registry Leaders Meeting, and an annual Statistical Monitoring Report is produced (In collaboration with WP4).

Methodology applied as planned

Yes

Involvement of partners and target groups

Full EUROCAT members that meet the inclusion criteria are included in EUROCAT Statistical Monitoring. The Task Force for Evaluation of Clusters (TEC) provides advice on clusters identified in annual monitoring.

Outcomes and deliverables achieved

The EUROCAT Statistical Monitoring Report 2010 was published on the website: <http://www.eurocat-network.eu/content/Stat-Mon-Report-2010.pdf>. This report describes statistical monitoring of both clusters and trends in Europe using data up to birth year 2010. Details of the cluster and trends identified at pan-Europe level (all registries combined), in individual registries and the results of the subsequent local registry investigations are presented. The Task Force for Evaluation of Clusters (TEC) discussed the registry preliminary cluster investigations in an open session at the Budapest RLM, and comments/ advice were incorporated in the Report. Individual investigations into selected trends identified in the statistical monitoring are ongoing.

Problems Encountered

The cluster investigation report templates were inadequately completed by some registries, due to lack of time and resources to conduct a proper investigation. When a cluster is detected registries are sent a number of documents associated with the analysis. Among this is a standardised form referred to as the cluster template. Both the PMC and TEC highlighted the need for the full completion and expedient return of the investigation template. Should clusters be identified as a cause for concern, it is important that these are investigated further in a timely manner with the appropriate authorities notified. Also the comprehensive completion of the cluster template at the preliminary investigations stage facilitates the TEC in providing advice. At the 2012 RLM Central Registry delivered a presentation on the completion of the cluster template, highlighting sections of the template that were considered cause for concern due to limited completion by the registries. One specific area was the section on aetiological factors, which is of particular importance in helping to justify the conclusion of the preliminary investigations. Key issues identified included the provision of limited information, and also the lack of clarity in identifying which factors had/had not been investigated and the associated reasons for not investigating certain factors. There are a number of reasons why this section of the report may be poorly completed. For example one general issue for many of the registries is that their database may have incomplete data. It was

recognised that registries should use their judgement to determine which factors should be investigated at the preliminary stage. Registries were reminded that advice could also be obtained from the TEC regarding which factors to focus investigations on. A discussion between the TEC panel and registry leaders led to suggestions of a more detailed template being developed, listing the aetiological factors that should be investigated, where possible, with a response format that allows the registries to clearly indicate if they did or did not investigate these factors. The feasibility of developing a new template for the next Annual Statistical Monitoring is under review.

How were Problems Resolved

At the 2012 RLM, a session was devoted to completing the cluster template, with particular emphasis on completing the aetiological factors section. For future reports, registries are asked to clearly identify which aetiological factors were/were not investigated. A discussion between the TEC panel and registry leaders led to suggestions of a more detailed template being developed, listing the aetiological factors that should be investigated, where possible, with a response format that allows the registries to clearly indicate if they did or did not investigate these factors. The feasibility of developing a new template for the next Annual Statistical Monitoring is under review.

Activities planned for the next period

Conduct statistical monitoring 2002-2011, in collaboration with WP4. Publish Statistical Monitoring Report 2011.

ACTIVITY 2: TASK FORCE FOR EVALUATION OF CLUSTERS (TEC)

Description of the activity

The TEC is a permanent committee, reporting to PMC and has the following remit:

- To comment on the output of cluster investigations conducted by EUROCAT, including its presentation and possible uses, at the request of the PMC.
- To serve as a consulting unit in cases of clusters, commissioned by EUROCAT or individual member registries.

Members:

Ingeborg Barisic (Zagreb, Croatia)
Helen Dolk (Belfast, Northern Ireland)
Lorentz M Irgens, chair (Bergen, Norway)
Petter Kristensen (Oslo, Norway)
Rolv Terje Lie (Bergen, Norway)
Nichola McCullough secretary (Belfast, Northern Ireland)
Vera Nelen (Antwerp, Belgium)

Methodology applied as planned

Yes

Involvement of partners and target groups

See membership of TEC outlined above.

Outcomes and deliverables achieved

Prior to the RLM, the TEC reviewed the EUROCAT Statistical Monitoring Report 2010. At the RLM in Budapest the TEC held an open consultation session. The aim of this was to inform the registries of the role of the TEC, to provide them with the opportunity to receive advice on any clusters detected in their registry and to discuss in general how the preliminary investigation of clusters by the registries could be improved. It was highlighted by members

of the TEC that as a dedicated committee they would have more time to investigate the cluster compared to registries, and that there was expertise available to provide advice on the medical genetic components of clusters. A key concern raised by the registry leaders was the difficulty in obtaining and interpreting the aetiological data needed to inform the preliminary investigation of clusters. In particular the paucity of population-based exposure data for comparison was highlighted. It was suggested that available data on exposures between registries could be compared to determine if there is something different about the detected cluster. Registries were reminded that the purpose of the preliminary investigation of clusters was not to prove cause, but to generate hypotheses that can be tested through further research. Also identified was the variability in the quality of reports sent to Central Registry, using the cluster template. This is outlined in the next section. The high number of “explained excesses of cases” were discussed, and the importance of continuing with high quality surveillance in order to prevent another thalidomide type event was emphasised. Registries were reminded that EUROCAT’s statistical monitoring is the only surveillance of congenital anomalies that takes place in Europe at present. The TEC continues to be available for consultation on clusters identified by registries.

Problems Encountered

See problems encountered in Activity 1.

How were Problems Resolved

See how problems were resolved in Activity 1.

Activities planned for the next period

Report for TEC on evaluation of EUROCAT response to swine flu pandemic.

ACTIVITY 3: RESPONSE TO SWINE FLU EPIDEMIC

Description of the activity

In the context of the EUROCAT surveillance response to 2009 H1N1 pandemic influenza we conducted i) a survey of European pandemic influenza vaccination and antiviral policies with respect to pregnancy, ii) analysis of the effect of season on congenital anomaly prevalence and births, iii) systematic review and meta-analysis of the association between influenza infection during pregnancy and congenital anomalies, iv) ecological time series analysis of the effect of the 2009 H1N1 influenza pandemic on congenital anomaly prevalence and v) case-malformed control analysis investigating the odds of 1st trimester pandemic influenza exposure between EUROCAT defined congenital anomaly subgroups.

Methodology applied as planned

Methodology was applied as planned. Some non-methodological issues were encountered (see below).

Involvement of partners and target groups

The survey of European policies was conducted in cooperation with the European Medicines Agency (EMA) and involved 23 EUROCAT registries.

Outcomes and deliverables achieved

The policy survey has been published - Luteijn M, Dolk H and Marnoch G (2011). Difference in pandemic influenza vaccination policies for pregnant women in Europe. *BioMed Central Public Health*. 11: 819. The systematic review, seasonality study, ecological time series analysis and case-malformed control analysis are in various stages of completion and are scheduled for submission in peer-reviewed journals in 2013.

Problems Encountered

One of the objectives of conducting a policy survey of European pandemic influenza vaccination and antiviral policies was to gather population data of exposure of pregnant women to pandemic influenza vaccine and antivirals. Only few European Departments of Health were able to provide some type of exposure data. Recorded instances of 1st trimester pandemic influenza vaccine (n=5) and neuraminidase inhibitor (n=6) exposure in the study population of the pandemic influenza case-malformed control study turned out to be lower than expected.

How were Problems Resolved

We intended to utilize pandemic influenza vaccination counts of pregnant women in our ecological time series analysis. Instead of using vaccination counts, we created a proxy variable for pandemic influenza vaccination policy based on results of the policy survey as exposure. The analyses for 1st trimester pandemic influenza vaccination and neuraminidase inhibitor exposure were dropped from the case-malformed control study and instead we opted to report the few exposures in the form of a case series.

Activities planned for the next period

We plan to follow up the study of the effect of the 2009-2010 pandemic influenza season on congenital anomaly prevalence with a more general influenza study which will involve additional influenza seasons and EUROCAT registries.

ACTIVITY 4: INVESTIGATION OF SPECIFIC TRENDS OF:**4.1 Hypospadias (UMCG)****Description of the activity**

This study aims to investigate the trends of hypospadias between 2001 and 2010 in Europe in relation to hypospadias type and registration policies of the different EUROCAT registries.

Methodology applied as planned

Yes, for this study we include all EUROAT full member registries, who register hypospadias subtypes and who have data over the complete period 2001 – 2010 and give detailed information about ascertainment of hypospadias cases via a questionnaire that was specifically designed for this study. We include all cases with hypospadias (isolated or associated with other anomalies) born between 1 January 2001 and 31 December 2010. We will analyse the prevalence of isolated hypospadias (all types and subtypes), syndromal hypospadias and hypospadias with other congenital anomalies according to year of birth for all of Europe. In addition, we will analyse the prevalence of isolated hypospadias (all types and subtypes) according to register and year of birth.

Involvement of partners and target groups

Will be reported on in 2013.

Outcomes and deliverables achieved

A study protocol was written and permission was achieved granted by the EUROCAT Steering Committee.

Problems Encountered

None

How were Problems Resolved

Not applicable

Activities planned for the next period

We will receive EUROCAT data in March 2013. Evaluation of the questionnaires and analysis of the data will be undertaken in April/May and a paper will be submitted for publication later in 2013.

4.2 Multiple births with CA (UU)

Description of the activity

- To assess the public health consequences of the rise in the rate of multiple births in Europe in terms of the associated risk of congenital anomalies
- To describe the epidemiology of Down Syndrome in multiple births in Europe
- To explore the association of specific non-chromosomal congenital anomalies with multiple birth in the context of specific aetiologic pathways

Methodology applied as planned

The core study population of 5.4 million births (1984-2007), from 19 registries in 14 countries, was extended to 14.8 million with the addition of National Down Syndrome Cytogenic Registry (England and Wales) data for analysis of Down Syndrome cases. Poisson regression used to assess risk of all and of specific congenital anomalies in multiple relative to singleton births

Involvement of partners and target groups

B. Boyle, R. McConkey, E. Garne, M. Loane, MC. Addor, MK. Bakker, PA. Boyd, M. Gatt⁷, R. Greenlees, M. Haeusler, K. Klungsoyr, A. Latos-Bielenska, N. Lelong, R. McDonnell, J. Métneki, C. Mullaney, V. Nelen, M. O'Mahony, A. Pierini, J. Rankin, A. Rissmann, D. Tucker, D. Wellesley, H Dolk. Trends in the prevalence, risk and pregnancy outcome of multiple births with congenital anomaly: a registry based study in 14 European countries 1984-2007. BJOG, 2013 – involved 19 registries in 14 countries.

B. Boyle, J Morris, R. McConkey, E. Garne, M. Loane, MC. Addor, , M. Gatt, , M. Haeusler, A. Latos-Bielenska, N. Lelong, R. McDonnell, , C. Mullaney, , M. O'Mahony, H Dolk, The prevalence and risk of Down Syndrome in monozygotic and dizygotic multiple births in Europe: implications for prenatal screening – involved 10 registries in 8 countries.

Outcomes and deliverables achieved

One paper published, one paper ready for submission.

Problems Encountered

There were a number of duplications of cases from multiple births registered. There were some differences in interpretation encountered in the registration of a multiple birth as opposed to a multiple pregnancy.

How were Problems Resolved

A validation exercise was carried out, with duplicates identified and removed from the database. The “nrbaby” variable was reviewed and the coding instructions changed in Guide 1.4.

Activities planned for the next period

The exploration of specific anomalies, is close to completion. Further analysis regarding the relationship between twinning, assisted reproductive therapies and congenital anomalies will be carried out.

4.3 Gastroschisis (ULEIC)

Description of the activity

Data has been received from 23 full member registries (Antwerp, Basque Country, Cork & Kerry, Dublin, Emilia Romagna, EMSYCAR, Hainaut, N Netherlands, NORCAS, Norway, Odense, Paris, Saxony Anhalt, SE Ireland, Styria, Thames Valley, Tuscany, Ukraine, Valencia, Vaud, Wales, Wessex, Zagreb) and 1 associate registry (Czech Republic). Data has been checked and reviewed. Czech Republic data is being manipulated to fit with the data from the full EUROCAT registries.

Initial analysis has been carried out to investigate the changing epidemiology of gastroschisis including calculation of birth prevalence rates by register, maternal age specific prevalence and associations with associated anomalies, sex distribution and outcome. To allow for trends to be studied only those registers with 10 years of data available will be included in the final analyses so Valencia (2007 data only) and Ukraine (2005-10 only) will be excluded.

Data are currently being made as described in our protocol.

Methodology applied as planned

Yes

Involvement of partners and target groups

The analysis and outline plan of a paper are currently being developed within EMSYCAR. Once a draft paper is developed this will be circulated to all participating registers for comment and discussion/further analysis.

Outcomes and deliverables achieved

We hope to have a draft paper ready for circulation by the end of April 2013.

Problems Encountered

None

How were Problems Resolved

Not applicable

Activities planned for the next period

Finalise analysis and complete first draft of paper. Circulate paper for comment. Finalise and submit for publication.

4.4 Hirschprung (UNEW)**Description of the activity**

A descriptive epidemiological study of Hirschsprung's disease in Europe. This project began during the last reporting period when the data had been received from the participating registries. Analysis of that data was undertaken during 2012.

Methodology applied as planned

The analysis involved both descriptive statistics and multilevel poisson regression.

Involvement of partners and target groups

This paper involved data from 31 EUROCAT registries.

Outcomes and deliverables achieved

We are at the penultimate draft stage for this paper; expected date of submission is April 2013.

Problems Encountered

None

How were Problems Resolved

Not applicable

Activities planned for the next period

Deliverable will be the published paper - no further activity in relation to this analysis.

ACTIVITY 5: INVESTIGATION OF EPIDEMIOLOGY OF CONGENITAL HEART DISEASE (CHD)**5.1 Trends in prevalence of CHD (INSERM U953)****Description of the activity**

In the last reporting period a paper on the trends in CHD was submitted to the Journal of Pediatrics and was under revision at the time of the first interim report.

Methodology applied as planned

Yes

Involvement of partners and target groups

This paper involved data from 29 EUROCAT registries.

Outcomes and deliverables achieved

The article was published in its final version in January (2013) in the Journal of Pediatrics. Khoshnood B, Loane M, Garne E, Addor M-C, Arriola L, Bakker M, Barisic I, Bianca S, Boyd P, Calzolari E, Doray B, Draper E, Gatt M, Haeusler M, Klungsoyr Melve K, Latos-Bielenska A, McDonnell R, Mullaney C, Nelen V, O'Mahony M, Pierini A, Queisser-Luft A, Randrianaivo-Ranjatoelina H, Rankin J, Rissmann A, Salvador J, Tucker D, Verellen-Dumoulin C, Wellesley D, Zymak-Zakutnya, N and Dolk H (2012). Recent decrease in the prevalence of congenital heart defects in Europe. Journal of Pediatrics. 162: (1). 108-113. Access link <http://www.sciencedirect.com/science/article/pii/S0022347612006762#>

Problems Encountered

None

How were Problems Resolved

Not applicable

Activities planned for the next period

For the future, it is planned to follow-up on this analysis with a more specific trends analysis for certain individual CHD. This is likely to be completed outside of the Joint Action by Winter of 2014.

5.2 Epidemiology of selected CHD (Hospital Lillebaelt)**Description of the activity**

A paper on the epidemiology of Atrioventricular septal defects among infants in Europe was submitted for publication in the last reporting period (Christensen N, et al. "Atrioventricular septal defects among infants in Europe; A population based study of prevalence, associated anomalies and survival").

Methodology applied as planned

Yes

Involvement of partners and target groups

This work was done in collaboration with Hans Christian Andersen Children's Hospital in Odense and involved 13 EUROCAT registries.

Outcomes and deliverables achieved

Paper published in Cardiology in the Young. Access link

<http://journals.cambridge.org/download.php?file=%2FCTY%2FS1047951112001400a.pdf&code=856d7aae22d55983d990e75cf703ee45>

Problems Encountered

None

How were Problems Resolved

Not applicable

Activities planned for the next period

None

5.3 Case-control study protocol (UU)

Description of the activity

CHD are the most common group of congenital anomaly. There is a need for aetiological research to guide primary prevention. A protocol for a CHD case-control study was developed to pilot in Northern Ireland, focusing on folic acid, smoking, obesity and maternal antidepressant use, for which the scientific literature remains inconclusive. This protocol was submitted to a local charity for extra funding during the period 2011/2012. We were not successful in this round. We have now revised the protocol in line with the peer review comments that were received and are awaiting outcome of our application. This is due in April 2013.

Methodology applied as planned

Yes

Involvement of partners and target groups

We have made a joint application with two consultant paediatric cardiologists who are based in the regional centre for paediatric cardiology care in Northern Ireland. We have also established links with a NI charity for CHD. We have established links to a number of lead midwives in NI. The Welsh EUROCAT registry will use our protocol to conduct a similar case control study, but with independent funding. The data will then be pooled. The protocol will also be made available to other EUROCAT partners in future.

Outcomes and deliverables achieved

None

Problems Encountered

None

How were Problems Resolved

Not applicable

Activities planned for the next period

Elaborate questionnaire for case-control protocol.

ACTIVITY 6: ACTIONS TOWARDS EUROPEAN ENVIRONMENTAL SURVEILLANCE

Description of the activity

Feasibility of linkage with environmental pollution map (CREAL)

Literature reviews on air pollution + congenital anomalies

Inventory of European pollutant maps, including from the ESCAPE project, + the European pollutant release transfer registry – E-PRTR

Establish contacts with relevant exposure experts

Feasibility of geographical linkage studies in EUROCAT registries

Air pollution pilot study: ASPB, CSISP, IFC-CNR, PIH, UNEW, Oxford, SUHT. The pilot study will prepare ethics applications, select cases and controls in defined years + regions (focusing on those for which air pollution maps will be available from the ESCAPE project), Geocode case + control addresses, Linkage to pollution maps if possible

Feasibility of epidemiological investigation in small polluted areas (hot-spots) - IFC-CNR

Preparation of common protocols for epidemiological investigations related to both smaller (hot-spot) + larger-scale environmental surveillance

Methodology applied as planned

Methodology has been fully applied in one registry, but other registries have implemented less than envisaged during 2012 (see below)

Involvement of partners and target groups

See above in description of activity

Outcomes and deliverables achieved

A literature review on air pollution and congenital anomalies was published (outside the JA), giving a very useful basis for further work (Vrijheid et al., 2012). During 2012, this activity has completed an extensive study in the Barcelona area: residential addresses of all malformed cases (total 2247) and control births (total 2991) on the Barcelona congenital anomaly registry were geocoded and linked to spatial air pollution maps from the ESCAPE project. Then, spatial-temporal exposure estimates were calculated for each pregnancy and risk estimates were calculated for a number of malformation groups and several air pollutants. The scientific paper related to this work has been submitted and is awaiting reviewer reports. The study in Barcelona has formed the basis for the development of a pilot protocol in other registries interested in contributing to the pilot study (ASPB, CSISP, IFC-CNR, PIH, UNEW). Start of the work in these registries has incurred some delays because it was preferable to wait until Barcelona study had been finalised and the protocol details fully worked out. The pilot study in the other registries will be carried out in 2013 and will include the selection of a small number of cases and controls for geographical linkage in each region. Problems encountered include that in some registries substantial efforts will be needed to obtain addresses of cases (needed to obtain geocodes) – some have to go back to hospital records to find the addresses. In other registries it will be difficult to obtain control data with address information. Further, the GIS work needed is extensive and requires good connection to be established with experts. The pilot report will detail these problems.

With regard to the feasibility of epidemiological investigation in small polluted areas (“hot-spots”), work will take a similar approach to what has been done already in Italy as part of the SENTIERI Project (2007-2010) (Pirastu et al., *Epidemiol Prev* 34 (5-6) Suppl. 3, 2010 and 35 (5-6) Suppl. 4, 2011). This task will develop a protocol to carry out a survey on polluted sites presents in the areas covered by the EUROCAT registries has been defined. A feasibility

study to validate the protocol is in progress within the WP6 participants. After that, the survey towards all the EUROCAT registries will be conducted and the study planned.

Problems Encountered

Currently linkage and extension to other centres is not possible because ESCAPE has encountered delays, so the exposure maps are not yet available in all regions (e.g. whole of England and whole of Belgium). Therefore, in the UK registries it has been decided not to carry out the pilot study due to the late availability of the pollution maps in the UK and because the geocoding work in the UK registries has already been tested in previous geographical analyses.

The feasibility of epidemiological investigation in small polluted areas (hot-spots) has not progressed but no funding has been committed to this.

How were Problems Resolved

Activities planned for the next period

Completion of the geocoding pilot study in the interested registries.

Preparation of the pilot study report and protocol for epidemiological investigations related to larger-scale environmental surveillance.

WP7: Primary Prevention of Congenital Anomalies

Associate partners involved in WP: UU, KDB, UDS, NCHAI, IMER, ISS, IFC-CNR, MCAR DHIR, UMCG, UMCL, ASEREMAC, AO “G Rummo”, PUMS, INSERM U953

WP7 has two major activities (A and B). The main objective is to build a consensus approach among Joint Action partners on a range of policies relevant to congenital anomalies primary prevention. The final aim is to include targeted congenital anomalies primary prevention actions and recommendations in the EU Member States (MS) national plans/strategies for Rare Diseases (RD).

ACTIVITY A

Description of activity A

To collect and review public health actions relevant to primary prevention of congenital anomalies (CA) at level of:

A.1 pre- and peri-conceptional care, namely: folic acid (FA) supplementation; maternal lifestyles (smoking, alcohol, recreational drugs); counselling and management of chronic maternal conditions (epilepsy, diabetes, obesity, etc.) and use of drugs and health-promoting products (including dietetic or herbal products, etc.) in collaboration with WP9; genetic counselling in collaboration with WP8

A.2 census of sectorial and intersectorial policies in MS regarding primary prevention with potential relevance to CA, namely: food safety and nutrition, including promotion of healthy dietary habits; prevention of rubella, toxoplasmosis, etc.; regulations on potential teratogens (environment, workplace, pharmaceuticals); actions on health determinants (physical activity, smoking, alcohol, recreational drugs). Consideration will be also useful to improve research on CA as well as socio-economic and ethnic determinants. WP7 will evaluate a potential consensus approach toward inclusion of the above actions in national plans on RD.

Methodology applied as planned (Activity A)

To achieve the above mentioned goals (A1 and A2), WP7 developed a survey to collect the existing health policies regarding primary prevention with relevance to CA in European countries. In collaboration with WP7 partners, we elaborated two questionnaires to collect data.

Activity A1

From January to December 2012

Folic acid and folate questionnaire has been closed for collecting data in December 2011.

Folic acid and folate questionnaire has been analysed to perform a draft of “Prevention of NTD with folic acid” Report. This document represents the current state of art on actions to prevent NTD by raising folic acid status at EU MS level.

Activity A2

From January to December 2012:

The draft of the “Public health actions on primary prevention of CA” questionnaire has been sent by e-mail to all WP7 partners to finalise the main structure of questionnaire in December 2011. The questionnaire aimed to collect policies and actions related to CA risk factors (except FA and folate).

We collected reviews and contributions to all WP7 partners in January- February 2012.

The final version of the questionnaire has been improved and finalised with the contribution of:

- Maternal lifestyles - Elisa Calzolari and Amanda Neville

- Food safety section - Alberto Mantovani (ISS), Francesca Baldi (ISS) and Stefania Ruggeri (INRAN)
- Infectious diseases, chronic diseases section - Domenica Taruscio, Pietro Carbone (ISS) and Cristina Morciano (ISS)
- Drugs and medications section - Marian Bakker (With WP9)
- Genetic factors and genetic counselling section - Elisa Calzolari and Amanda Neville (with WP8)
- Environment, home and workplace - Fabrizio Bianchi, Pietro Carbone (ISS) and Orietta Granata (ISS)

We adapted SurveyMonkey to our needs.

In a preliminary stage (April-May 2012), we invited collaborators from Italy, Spain and United Kingdom to fill the questionnaire, in order to assess their appraisal in the approach we followed to collect data. Contents and design of this questionnaire were then discussed during September 2012 and finally approved in October 2012.

The 2nd questionnaire was submitted through the SurveyMonkey web platform on the 20th of October, 2012. We invited (by e-mail) 27 respondents per 27 European countries (a unique respondent in each country) to take part in this survey. The first deadline was fixed on the 20th of November, 2012. The data collected with the 2nd questionnaire will be analysed and used to carry out the “Public Health Actions” Report.

From April to December 2012, WP7 have reached a consensus on main field for CA primary prevention among the JA EUROCAT experts and a shared document on CA primary prevention recommendations was delivered.

A draft was prepared considering seven specific ISSUES (to CA primary prevention) on April 2012. This document named “EUROCAT /EUROPLAN Recommendations on policies to be considered for the primary prevention of congenital anomalies in National Plans and Strategies on Rare Diseases” was discussed during several joint meetings to validate it from both a scientific evidence and applicability to local setting point of view.

The document was presented during a specific session at the RLM (Budapest, June 13-15, 2012). It has been revised taking into account the input of EUROCAT Registry Leaders and the comments of EUROCAT Project Management Committee during June 2012. We collected scientific references to support the document with evidence based literature during July 2012 and we finalised this paper completing the footnotes at the end of July 2012. After the approval by EUROCAT Steering Committee (December 2012), the document will be sent to the policy officer at the Directorate of Public Health at the European Commission in Luxembourg (Dr. Antoni Montserrat) in order to be included in the Agenda of EUCERD (European Union Committee of Experts on Rare Diseases) Meeting: on 31 January – 1 February 2013.

Involvement of partners and target groups (Activity A)

An important role of the WP7 activities is to support the construction of a network in EU Countries to exchange experiences regarding the activities, initiatives and best practices for the primary prevention of CA.

All these efforts are finalised at including CA primary prevention in National plans/strategies on Rare Diseases which should be in place by the end of 2013.

In this respect, we facilitated in 2011 the process of networking by:

- developing the European survey;
- implementing the contents of the two questionnaires;

- involving EUROCAT and EUCERD Members to collect data through the use of the two questionnaires

We facilitated in 2012 the process of networking by:

- establishing in EUROCAT a “Folic acid committee” that will be chaired by Domenica Taruscio and embedded within the current WP7 – Primary Prevention of Congenital Anomalies (The main goals of committee are: plan future actions on folic acid; respond to requests from EUROCAT; consider what dissemination from EUROCAT is needed);
- involving JA EUROCAT experts to perform recommendations for primary prevention on CA;
- making contact with policy officer at the Directorate of Public Health at the European Commission in Luxembourg (Dr. Antoni Montserrat) to facilitate the involvement of EUCERD members in the inclusion process of primary prevention on CA in the national plan/strategy for rare diseases.

Coordination with other projects or activities (Activity A)

In collaboration with EUROPLAN project (European Project for Rare Diseases National Plans Development), WP7 is highlighting CA primary prevention as an essential component of national plans/strategies for Rare Diseases in the EU – MS. Moreover, from March 2012 WP7, jointly with EUROPLAN activities, will facilitate this inclusion process.

During the EUROPLAN workshop (ISS, Rome, 10th -11st September 2012) WP7 coordinator agreed with Antoni Montserrat (EU Commission) the specific procedures and times for the approval of recommendations on primary prevention of CA by EUCERD Members.

The involvement of all EUCERD Members will improve the wording of recommendations, allow wide buy-in and improve uptake once finalised. The Member State representatives of the EUCERD are involved on the progress in their country towards the elaboration of a national plan or strategy for rare diseases. So they are the main experts that should implement CA Primary Prevention Recommendation in national plan/strategies for RD.

Outcomes and deliverables achieved (Activity A)

Milestone 1 - Achieved collection of public health actions relevant to prevention of CA – M12

Milestone 2 - Achieved collection of actions to prevent NTD by raising folic acid status – M12

Deliverables - Report on Primary Prevention of CA – due in M36

Milestone 1 preliminary results

At the end of the first deadline (November 20th, 2012) data on “Public health actions on primary prevention of CA” questionnaires were collected from 8 countries (Czech Republic, Hungary, Republic of Moldova, Ireland, Spain, Latvia, UK, Denmark).

Milestone 2 preliminary results

Data on “Folic acid and folate” were collected and analysed from 18 EU MS and 4 non EU-MS. Data collected with the questionnaire have been merged with data reported in several official documents published by the EUROCAT network and EFSA. Preliminary results of the analysis are shown in the draft of “Prevention of NTD with folic acid”.

Deliverables

The advanced draft of “Report on actions to prevent NTD by raising folic acid status at EU Member State (MS) level: updated survey of policies in EU MS – Part II” was sent to all the respondents at the 1st questionnaire to validate data reported.

The “EUROCAT/EUROPLAN Recommendations on policies to be considered for the primary prevention of congenital anomalies in National Plans and Strategies on Rare Diseases” was delivered. This documents was presented during a specific session at the EUROCAT Registry Leaders’ Meeting at Budapest (June 13-15, 2012) and PMC Meeting at Oxford (December 12-13, 2012). The document will be the core and the most important part of “Report on potential consensus approach toward inclusion of primary prevention actions in national plans on Rare Diseases (RD) - Part III”

We carried out the draft of “Report on other public health actions relevant to prevention of CA EU Member State (MS) level: updated survey of policies in EU MS - Part I”.

Problems encountered (Activity A)

The elaboration and finalization of the two questionnaires was very laborious and quite complex. The results on the FA and folate survey were validated by a few respondents. For this specific reason, answer interpretations and data analysis took a long time.

Data validation is the critically important step to ensure that only valid and clean data is reported in the final report.

Other operative problems encountered for filling in the 2nd questionnaire were:

1. The questionnaire has been considered too complex to be filled by unique respondent per country.
2. The thorough review of all the requested information would require more resources (time/personnel)

The Istituto Superiore di Sanità (ISS) asked for a sensible decrease of the total budget thus implying a corresponding reduction in personnel involved in the project (see first interim report).

Reduction of personnel impacted in the ability to complete WP7 activities and in particular on the scheduling of the activity results.

From the current perspective, we are working to achieve on time the WP7 milestones and deliverables planned in the project timetable.

In particular we are working to complete Part II and Part III of the final report that will be finalized within the next year.

How were problems resolved (Activity A)

To resolve operative problems encountered for filling in the 2nd questionnaire:

1. we sent to each respondent a pdf and word copy of questionnaire to facilitate the collection of useful information;
2. the deadline for completing the questionnaire was extended on December 12, 2012.

From the current perspective, we are optimistic to achieve the final objectives on time and we currently have already gathered a lot of information about CA primary prevention with FA and folate.

Activities planned for the next period (Activity A)

The data collected with the 2nd questionnaire will be analysed and validated by M25. At the same time we will finalize the part II and part III of the report and we will start to prepare

“Report on others public health actions relevant to prevention of CA EU Member State (MS) level: updated survey of policies in EU MS- Part I”. A draft of this report will be circulated to all respondents to confirm/validate results and information reported.
We estimate to complete the final report before the end of October 2013.

We will facilitate the process to include in National Plan/strategies for RD the “Recommendation for CA primary prevention”. This action, jointly with EUROPLAN project 2012-2015, will be done through WP7 participation at 2013 EUCERD meeting. In fact EUROPLAN 2012-2015, embedded in the EUCERD Joint Action as Work Package 4, is currently building an interactive network of policy makers and it is providing technical and scientific support to EU Countries for the development and implementation of national plans/strategies for rare diseases in MS.

The final version of “Recommendation for CA primary prevention” will constitute a part of the document, together with the other EUROPLAN recommendations, that we will be used during EUROPLAN Meetings by policy makers; moreover, we will disseminate them among all stakeholders involved in the elaboration of national plans/strategies in Rare Diseases.

ACTIVITY B

The actions on prevention of Neural Tube Defects (NTD) by raising folate acid (FA) intake/ folate status will be considered in detail as a model for the actual development of a consensus approach. This will be performed by 4 activities (detailed below).

The main deliverable of Activity B will be component parts within the final WP7 report (“Primary Prevention of Congenital Anomalies in the European Union”) that includes consideration of:

I. Appraisal of strategies / methods to monitor folate status on a population level with respect to:

1. the relevance of (permanent) monitoring of the folate status of women shortly before and during their pregnancies for;
 - a. scientific research
 - b. policy making (evaluation of the promotion of FA intake and monitoring of intake patterns)
 - c. individual care
2. critical factors with respect to the feasibility of the implementation of different methods of (permanent) monitoring for each of these objectives.

II. Exploration of the feasibility of strategies / methods identified

The exploration of the feasibility will be focused initially on the Dutch situation and on (pilot) implementation in the EUROCAT region NNL.

The information contained within the report will also be based on a review of the applicable scientific and policy literature and consultations with an expert advisory team.

B.1 updated survey of policies in Member States (MS)

Description of the Activity

The objective of this activity is to collect information on public health actions to describe progress in developing and implementing public health policies on primary prevention of congenital anomalies by raising FA intake and folate status in all European countries up to the end of 2011.

Methodology applied as planned

Used the 2 Questionnaires developed for Activity A

Questionnaire 1. Policies for Primary Prevention of NTD with FA and Folate

Questionnaire 2. Public Health Actions on Primary Prevention of Congenital Anomalies

Questionnaire 1 stopped collecting data in December 2011 (and this was reported on in the first interim report). The questionnaire was designed to update previous data reported in earlier official documents produced by EUROCAT and the European Food Safety Authority (EFSA). Data derived from Questionnaire 1 were analysed and used to create a draft of a component of the WP7 report - "Part 1. Report on actions to prevent neural tube defects by raising folic acid status at EU MS level: Updated survey of policies in EU MS". The draft was circulated to all respondents who participated in the survey to confirm/validate the data and the information reported.

Status of Questionnaire 2 is reported in Activity A.

Involvement of partners and target groups

To develop and finalise the Questionnaire 1 we involved all partners in WP7. To collect data by European countries we sent invitations to participate in this survey to the full membership list of EUROCAT (68) and EUCERD (108). Data collected using Questionnaire 1, were merged with data reported in several official documents published by the EUROCAT network and EFSA. The draft component of the WP7 report (described above) was circulated to all respondents who participated in the survey to confirm/validate the data and the information reported.

For Questionnaire 2, see report for Activity A.

Outcomes and deliverables achieved

Not due until completion of final report in next reporting period.

Problems encountered

None

Activities planned for the next period

Completion of the final report (see also Activity A for further detail).

B.2 track prevalence rates of NTD through the registries

Description of Activity

We analysed trends in the prevalence of NTD in Europe using data from EUROCAT registries (1991-2009). The results of the analyses were presented at the annual meeting in Budapest in June 2012.

Methodology applied as planned

Methodology was applied as planned - statistical analysis used mixed modelling of the trends to take into account heterogeneities across registries.

Involvement of partners and target groups

EUROCAT registries providing data - final results to be communicated by WP7 and WP2 - Dissemination, including article to be published in a scientific journal plus communications through the EUROCAT website and the newsletter.

Outcomes and deliverables achieved

(Preliminary) outcomes and deliverables achieved: analyses done / results presented at the EUROCAT annual RLM in June 2012 and manuscript to be submitted by March 2013

Problems encountered

None

Activities planned for the next period

We will finish any additional analyses on NTD prevalence that may be needed and draft the paper and send it to the main co-authors (Maria Loane, Helen Dolk and Hermien deWalle) for comments early in 2013. We will then send the final draft to other co-authors (registry leaders/their representatives) and finalise the manuscript and submit it by March 2013.

B.3 approaches to assess knowledge and attitude toward FA of women in childbearing age

Description of Activity

Knowledge and awareness toward FA were approached through a standardised questionnaire specifically developed to interview women during pregnancy or early after delivery. The questionnaire has been used in the EUROCAT Tuscany region to perform a survey in 2002 and in 2010. The questionnaire includes items on source of information on FA, FA in medical counselling, time of FA consumption, type of FA consumed, reasons of FA consumption, scientific knowledge on FA and other vitamins, knowledge on food rich with FA, knowledge on FA and congenital anomalies, knowledge on other risk factors for congenital anomalies, knowledge on recommendations of FA, information on present and previous pregnancies, personal data.

Methodology applied as planned

A knowledge, attitudes, and behaviour (KAB) questionnaire was performed in the Italian language as a prototype for investigating the intake of FA and factors influencing folic acid intake.

The original questionnaire was administered to 400 childbearing age women in 9 maternity units during a survey carried out in Tuscany on 2010.

Based on this survey, an extensive list of topics was identified and researched for the questionnaire. Although the questionnaire was maintained in its original structure, selected questions were revised, some were deleted, and new questions were added.

The core portion of the questionnaire includes questions about the following topic:

- Current vitamin/supplement usage and frequency behaviour
- Information sources for health and pregnancy information, especially previous discussions with health care providers;
- Attitude toward/knowledge of the benefits of vitamins/supplements to women of childbearing age;
- Awareness and knowledge of folic acid
- Sources of folic acid information

Surveys also include questions about pregnancy intention; this information will yield the ability to make comparisons among pregnancy prospecting, those who don't exclude it and those who are not planning it.

Finally the questionnaires have a few final demographic and background questions for considering confounding factors and to perform subgroup stratified analyses.

Involvement of partners and target groups

Full and Associated EUROCAT members will be involved to define main topics of methodology and questionnaire in order to assess knowledge and attitude toward FA of women in childbearing age, country by country.

Outcomes and deliverables achieved

A KAB questionnaire in Italian language was performed as prototype for investigating the knowledge, awareness and behaviour about FA use.

Problems encountered

None

Activities planned for next period

We will translate the questionnaire into English to share it with EUROCAT partners and to finalise the operating protocol for using it.

B.4 appraisal of strategies to monitor population folate status

Description of the Activity

In 2011 the project plan was developed and discussed at the PMC meeting November 2011. UMCG agreed with MediClara on the workplan for exploration of relevance and feasibility of strategies to monitor (population) folate status with respect to the prevention and scientific research of congenital anomalies. The assignment was given in December 2011.

Methodology applied as planned

A literature study with respect to parameters and methods for measuring population folate status has been performed.

A method has been developed for systematic appraisal of several FA monitoring scenarios. MediClara has started with evaluating the scenarios and critical factors with respect to feasibility of implementation.

Involvement of partners and target groups

MediClara was involved for evaluating the scenarios and critical factors with respect to feasibility of implementation. An advisory team has been established including Prof. LTW de Jong-van den Berg, Prof. H. Blom and Dr. H. deWalle. EUROCAT registries will be recruited among the participating registries/institutions in WP7.

Outcomes and deliverable achieved

Activities planned for the next period

The draft report regarding “appraisal of strategies to monitor population folate status” will be circulated to the EUROCAT registries for comments in January 2013, after which the report can be finalised.

Other relevant outcomes and deliverables achieved in relation to Activity B

A “FA committee” was established and embedded within the current WP7 – Primary Prevention of Congenital Anomalies. The main goals of the committee will be: i) to plan future actions on FA, ii) to respond to EUROCAT requests, and iii) to consider what kind of EUROCAT dissemination relating to FA is needed.

WP8: Prenatal Screening, Down Syndrome and Genetic Syndromes

Associate partners involved in WP: QMUL, KDB, Hospital Lillebaelt, SUHT, UU, SFR, PIH, IRSPG, THL, INSERM U953, UDS, UMC-Mainz, OVGU, NCHAI, AO “G Rummo”, IMER, ISS, ICF-CNR, BKUS, VEC, MCAR CHIR, UMCg, RUG, FHI, PUMS, INSA, UMCL, ASPB, BIOEF, CREAL, ASEREMAC, CSISP, ULEIC, UNEW, QMUL, Oxford, CARIS

Description of the activities

Activity 1 - Down syndrome and cardiac anomalies: *Many fetuses with Down syndrome have cardiac anomalies. Prenatal screening tests for Down syndrome may preferentially detect fetuses with cardiac anomalies. Analysis of the EUROCAT database to determine the impact of prenatal screening on the presence and severity of cardiac anomalies in babies born with Down syndrome.*

A protocol was written and approved by the EUROCAT Steering Committee in the last reporting period. In this reporting period data was requested from the EUROCAT registries. Data was received from those registries that had given permission, cleaned and analysed in accordance with the protocol. A paper with proposed title “Major Congenital Malformations in babies born with Down syndrome”, intended for submission to the American Journal of Medical Genetics, has been drafted. This paper relates to Milestone 1 of WP8 which was due in Month 21. This paper will be delayed until the 3rd reporting period, due to delays in acquiring permissions from participant registries.

Activity 2 - Prevalence of Down syndrome: *The increases in Down syndrome diagnoses in Europe due to delaying childbearing and the introduction of earlier prenatal screening have been quantified up to 2007. Estimates up to 2011 will be calculated. The Central Database for this task will be expanded to include the England and Wales National Down Syndrome Cytogenetic Register data which will also be incorporated in EUROCAT website epidemiological tables.*

Data could not be combined into the website epidemiological tables as originally intended (as highlighted by the failure to meet the assigned process indicator “Integration of England and Wales NDSCR into Central database”) - see problems encountered. An alternative solution was suggested that in effect now combines Activity 2 and 4 (see problems resolved).

Activity 3 - Prevalence of genetic syndromes. *Studies on the epidemiological characteristics of rare genetic syndromes, mostly single gene syndromes, are limited, because they require the analyses of large populations and a well-organised diagnostic network. EUROCAT data covers 21 million births in Europe from 1980 to 2007 and cases will be extracted for 8 specific syndromes. Clinical geneticists will review all cases.*

Activity 4 - Review of prenatal diagnosis tables. *Modifications to increase the amount of available information in the tables (number of conditions, information on timing or diagnostic techniques) will be agreed for implementation in WP4. To support this, proposal will be made to WP5 revisions to EUROCAT variable codes to ensure that new advances in prenatal screening and diagnosis can be coded.*

Draft versions of the new website prenatal diagnosis tables containing English and Welsh data from the National Down Syndrome Cytogenetic Register (NDSCR) were presented to the EUROCAT Project Management Committee (PMC) in March and in December of 2012. The draft tables were also presented to the wider EUROCAT membership during the Registry Leaders Meeting in Budapest (June 2012). Following feedback from the EUROCAT PMC and the general EUROCAT membership, website prenatal diagnosis tables containing data

from the NDSCR are being developed, to go live on the EUROCAT test website (EUROCAT member's only access).

Methodology applied as planned

Yes with the exception of Activity 2, as explained below.

Involvement of partners and target groups

Yes partners involved

Coordination with other projects or activities

Coordinated with WP4

Outcomes and deliverables achieved

Activity 1 – Paper now expected in 3rd reporting period.

Activity 2 – A EUROCAT paper related to Activity 2, "Twenty-year trends in the prevalence of Down syndrome and other trisomies in Europe: impact of maternal age and prenatal screening" has now been published in European Journal of Human Genetics, EJHG (2013) 21: 27–33 (**Milestone 2 of WP8**). This paper describes trends and geographical differences in total and livebirth prevalence of trisomies 21 (Down syndrome), 18 (Edward syndrome) and 13 (Patau syndrome) with regard to increasing maternal age and prenatal diagnosis in Europe, using data from 21 EUROCAT registries in 12 countries covering over 6 million births. In every 10,000 births, 22 resulted in a Down syndrome pregnancy, 5 resulted in an Edward syndrome pregnancy and 2 resulted in a Patau syndrome pregnancy. Between 1990 and 2009, the proportion of births to mothers aged 35 years and older in Europe increased from 13% in 1990 to 19% in 2009. This rise in the proportion of births to older mothers has led to an increase in the number of trisomy-affected pregnancies in Europe. For trisomy 21, there was a three-fold variation in live birth prevalence between countries with the lowest livebirth rates occurring in Spain and Switzerland and the highest rates occurring in Ireland and Malta where termination of pregnancy is illegal. Livebirth prevalence has nonetheless remained stable in most countries due to increasing prenatal diagnosis and subsequent terminations.

Website prevalence rates have been updated to 2010. NDSCR data incorporated in prenatal tables (See Activity 4).

Activity 3 – In the last reporting period we reported on submission of a paper on "Fraser Syndrome: Epidemiological Study in a European Population". During the 2nd reporting period the American Journal of Medical Genetics have asked that we exclude clinical data, as they thought that clinical data on these cases had already been published in a previous paper dealing with genetic testing of Fraser Syndrome. We made contact again with participating registries to ensure that in most/all of the cases no genetic testing was performed, and that the data on our patients had not been published in a previous paper. We have informed the Journal of this and sent the revised submission which has now been accepted for publication in 2013.

Also in the last reporting period we reported a study on prenatal diagnosis of Oculo-auriculo-vertebral spectrum (OAVS). A paper on this study has been drafted and is currently being circulated amongst co-authors for final approval. The working title is "Oculoauriculovertebral Spectrum: a Registry-Based Study in Europe".

Also in the last reporting period we reported first results on the Beckwith Wiedeman Syndrome analysis. Analysis has been expanded further in 2012. It is intended to draft and submit a related manuscript during 2013.

Treacher Collins syndrome data is currently being analysed. It is intended to draft and submit a related manuscript during 2013.

Activity 4 – none due in this reporting period. The new prenatal diagnosis variable has been trialled during 2012 and has now been incorporated into WP4 (see WP5 for further detail on how).

Problems encountered

Activity 1 – see above. Delays in acquiring permission to release data from participant registries have pushed the month of delivery from Month 21 into the 3rd reporting period.

Activity 2 – The NDSCR contains data on Down, Edwards and Patau syndrome diagnoses that are also available in the other registers from England and Wales. The NDSCR does not contain any data on any other anomalies. The NDSCR data covers all of England and Wales and therefore the numbers of cases is large. The number of Down syndrome cases from the NDSCR cannot be combined with data on any other anomalies from the registers in England and Wales as the NDSCR covers the whole country and the other registries only cover 35% of the country. Comparisons between anomalies would be incorrect. The number of Down syndrome cases from the NDSCR cannot be combined with data on Down syndrome from the registers in England and Wales as this would be double counting. EUROCAT's web based prevalence tables were designed to be interactive and flexible to allow users to examine any set of anomalies across any specific registers both using individual registers and combined registers. If the NDSCR data were available this facility would allow the above errors (i.e double counting) to occur. In order to retain the flexibility of the web-based tables, the NDSCR data cannot be made available on them. EUROCAT also has web-based Prenatal Diagnosis Tables. These are preformed tables for only a restricted number of registries and certain congenital anomalies. There is no opportunity to combine data from different registers or to combine data from different anomalies.

Activity 3 – delay in final acceptance of publication on Fraser syndrome paper (see above). Delays in the publication peer-review/editorial process (see above) led to the first syndrome paper (Fraser syndrome) being delivered in Month 24 as opposed to Month 9 (although first submission was made within the first reporting period as intended). A second syndrome paper (OAVS) was due to be delivered by Month 18, this paper was also delayed due to difficulties with the selection of registries and is not going to be delivered until the 3rd reporting period (Month 25-36).

How were problems resolved

Activity 2 - The NDSCR data will be presented as part of the new prenatal diagnosis tables planned within the 3rd reporting period whilst excluding the data from the other English and Welsh registers.

This solution enables the flexibility of the prevalence tables to be maintained whilst enabling detailed information on the prenatal diagnosis of Down, Edwards and Patau syndrome to be provided on the maximum number of cases in EUROCAT.

Activities planned for the next period

Activity 1 – Paper to be circulated to co-authors and submitted during 2013.

Activity 2 - A press release relating to the twenty year trends in the prevalence of Down syndrome publication is planned for early in the next reporting period.

Activity 3 – The OAVS, Beckwith Wiedeman and Treacher Collins syndrome papers will be submitted in 2013.

Activity 4 - EUROCAT registries will trial use of the website prenatal diagnosis tables containing data from the NDSCR to determine if the tables are acceptable to them. Final feedback will be collated on the basis of this trial, any necessary amendments implemented. Once approved by the Website Dissemination Committee the tables will then be made publically available on the EUROCAT website. Website tables will be updated to include 2011 data.

WP9: Medication During Pregnancy

Associate partners involved in WP: Principally UMCG, CARIS, FHI, IFC-CNR, IMER, Hospital Lillebaelt, RUG, UU, for data PIH, UMC-Mainz, BIOEF, HSE, KDB, IMER, IRSPG, MCAR DHIR, UMCG, FHI, Hospital Lillebaelt, INSERM U953, PUMS, UDS, IFC-CNR, CARIS and Collaborating Partner 7 (Switzerland).

Description of the activities

Activity 1 - Improve and document medication exposure data (UMCG) - improve coding of medication use in pregnancy by giving training in ATC-coding at the RLM (RUG); develop and implement data quality indicators (DQI) specifically for medication exposure data (RUG); evaluate data quality up to 2008 on antidepressants (UU), antiasthmatics (Lillebaelt) and antidiabetics (RUG); compile report on information sources on maternal medication used by registries (RUG).

Since most registries know how to find ATC codes and use them for coding the medications, the RLM in Budapest was used to discuss the new variable to be implemented in Guide 1.4: First trimester use in pregnancy. The results of the first pilot indicated that an extra category should be added: yes/no/undetermined/unknown, in which undetermined means that sources were consulted, but the information on medication use was not clear and unknown refers to the situation in which the sources could not be consulted. This new variable was piloted among 5 registries and included in the new Guide 1.4 in December 2012.

Also a questionnaire/table was distributed to the registries at the Budapest RLM for information on data sources used for collecting information on medication use in pregnancy. This information will be collated with the information from a questionnaire referred to in Activity 3.1 (below) for a report and paper on the usefulness of congenital anomaly register data on studies of medication use in pregnancy.

Activity 2 - Prescription data linkage - Identify national and regional available prescription data sources for use by registries (UMCG); Conduct and evaluate pilot linkage studies (UMCG).

The registry in Valencia has already expressed interest in the protocol and software module that have been developed for the EUROMediCAT project. UMCG will contact them when the software module has been used in the EUROMediCAT project and the first results are known.

Activity 3 - Signal detection and evaluation - Specify and pilot signal detection methods (UMCG); Analyse EUROCAT database in relation to antidepressants (UU), newer antiepileptics including lamotrigine (RUG) and drugs of new concern arising (UMCG).

UMCG and RUG have done a study in which they have tested a methodology to identify signals by comparing prevalence of maternal medication use in malformed cases (EUROCAT NNL) to the prescription rates in the general pregnant population using data from a population-based prescription database (IADB.nl), the case-population surveillance approach. The paper is in its final stages before submission.

3.1 SSRI study (UU)

The SSRI study data analysis was completed and the final results were presented at the Budapest Registry Leaders Meeting. All registries responded to the SSRI drug exposure information sources/data coding questionnaire and that was useful in guiding the analysis and interpretation of the data. A paper is being written with the results for publication.

3.2 Lamotrigine (RUG)

RUG is currently working on the lamotrigine 4th update report. In total 27,057 additional malformed registrations are added in the 4th update. The total number of malformed registrations in the 4th update is 179,573, of which 21,874 are chromosomal and 157,699 are non-chromosomal. RUG is performing a background descriptive epidemiological study of clubfoot which will serve as context for the lamotrigine study. A total of 20 registrations with clubfoot in the period of 2005-present was randomly selected from each registry. A questionnaire on laterality, treatment and family history is needed, to be answered by checking the paediatric records. The 4th update report is expected to be finished by December 2012.

Oral presentation on lamotrigine use during pregnancy and risk of oral clefts using 3rd update data was presented by Hao Wang at the international conference on pharmacoepidemiology (August 2012). A poster on lamotrigine use and risk of clubfoot was presented in the same conference by Hao Wang.

3.3 *Drugs of new concern/Drug signal queries*

Several pharmaceutical companies have contacted the Central registry with respect to the use of methylphenidate (a medication prescribed for attention deficit hyperactivity disorder). There are 5 cases with maternal exposure to methylphenidate (N06BA04) in the EUROCAT database, for the years 1995-2010. Since we expect more queries from researchers and pharmaceutical companies a EUROCAT Medication Enquiry form, and a EUROCAT response form was developed for use in this type of query.

Activity 4 - Liaison with the European Medicines Agency's European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), International Society for Pharmacoepidemiology (ISPE) and European Network Teratology Information Services (ENTIS) - Organize joint meeting with International Society of Pharmacoepidemiology (ISPE) and European Network Teratology Information Services (ENTIS) (RUG)

A joint symposium was organized at the International Conference on Pharmacoepidemiology (ICPE) in Barcelona on biases and confounding in studies on medication use in pregnancy. Speakers were Hao Wang (EUROCAT and RUG, Netherlands), Corinne de Vries (University of Bath, UK), Rachel Charlton (University of Bath, UK), Heli Malm (ENTIS and Helsinki University Central Hospital, Finland) and Kristin Palmsten (Harvard School of Public Health, USA).

Prof Dolk (UU) and Prof de Jong-van den Berg (RUG) are members of the ENCePP. Prof de Jong-van den Berg presented at the plenary ENCePP meeting in October 2012 the different approaches on signal detection and signal evaluation of adverse effects of medication use in pregnancy. The EUROCAT database and Antiepileptic Drug (AED) studies were included in this presentation.

Methodology applied as planned

Yes

Involvement of partners and target groups

Data on medication using ATC codes up to 2010 have been provided by 21 registries, 5 registries have provided data on medication use but not up to 2010, or not for all medications. 6 registries have not sent data on medication use in pregnancy. **See Annex 16.**

Coordination with other projects or activities

WP4 for software development and data quality

WP5 for development of DQI

EUROmediCAT in relation to data quality and studies on AEDs and Selective Serotonin Reuptake Inhibitors (SSRIs)

Outcomes and deliverables achieved

A Joint workshop between EUROCAT and ENTIS was organised at the ICPE meeting in Barcelona, August 2012.

Problems encountered

Due to maternity leave of one of the researchers of the UMCG, the report on sources of medication use has not been finalized yet.

How were problems resolved

Will be completed in next reporting period.

Activities planned for the next period

- Finalize report on data sources of medication use
- Finalize paper on signal detection method: case-population approach
- Finalize paper on epidemiology of clubfoot

Use updated dataset to evaluate data on antiasthmatics (LIL) and antidiabetics (RUG) (will be done as part of EUROmediCAT)



Minutes of 27th EUROCAT Registry Leaders' Meeting

**Budapest Hungary
13-15th June 2012**

For Further Information:

**EUROCAT Central Registry
Room 12L09
University of Ulster
Newtownabbey, Co Antrim
Northern Ireland, BT37 0QB**

Tel: +44 (0)28 90366639

Fax: +44 (0)28 90368341

Email: EUROCAT@ulster.ac.uk

Web: www.EUROCAT.ulster.ac.uk

Funded by the Public Health Programme 2008-2013 of the European Commission
WHO Collaborating Centre for the Surveillance of Congenital Anomalies



Programme for 27th Registry Leaders' Meeting Budapest, Hungary, 13-15th June 2012

Wednesday 13th (Pre-meeting Closed Sessions)

- 14.00-18.00** **Coding and Classification Committee Closed Meeting in Apartman 223** (Attendees: Ester, Elisa, Ingeborg, Diana, David, Berenice)
- 17.00-19.30** **Registration in front of the main lecture room (TEA Saloon)**
- 19.00** **Welcome Reception, with performance (approx. 20 mins) in TEA Saloon**

Thursday 14th (Open Sessions)

- 08.00** **Registration opens outside the TEA Saloon**
- Session 1** **(TEA Saloon - Chair: Lorentz, Co-Chair: Ingeborg)**
- 08.30-08.35** **Welcome and apologies (Judit and Lorentz)**
- 08.35-08.40** **Welcome from the Hungarian Under Secretary (Prof. Ildikó Horváth)**
- 08.40-08.45** **Approval of minutes from last RLM (Lorentz)**
- 08.45-08.55** **Thalidomide at 50 (Rhonda/Eva)**
- 08.55-09.00** **Update on Rare Diseases Policies (Dr. Karl Freese)**
- 09.00-09.15** **News from new/applicant registries and collaborating partners**
- Rosie Thompson (SWCAR: 5 mins)
- Current results of prenatal diagnosis in Czech Republic (Antonin Sipek Jr: 10 mins)
- 09.15-09.20** **WP1: *Co-ordination of the Joint Action* (Rhonda)**
- issues to highlight
- 09.20-10.15** **WP2: *Dissemination of the Joint Action* (Ingeborg)**
- Short overview on WP2 activities (Ingeborg: 15 mins)
- Liaisons with other networks
 - EUCERD (Ester: 10 mins)
 - EURORDIS (Domenica: 10 mins)
 - EUROPERISTAT (Hermien: 10 mins)
- National Committees
 - Irish National Committee (Carmel: 10 mins)

10.15-10.30 **Tea/Coffee – always in front of TEA Saloon in Foyer**

Session 2 (TEA Saloon - Chair: Lorentz, Co-Chair: Ingeborg & TEC panel: Petter, Nichola, Vera)

- 10.30-11.00** **WP2: *Dissemination of the Joint Action* (Ingeborg)**
- New website tables (Joan/Anna)
- 11.00-11.55** **WP4: *Central Database and Surveillance* and WP6: *Investigation of Trends, Clusters and New Exposures***

- How national networks can use the EUROCAT website to disseminate their prevalence information: the example of BINOCAR (Joan: 10 mins)
- Statistical Monitoring: Clusters
 - Cluster Template Form (Nichola: 10 mins)
 - Bladder exstrophy (Central Registry: 5 mins)
 - Bladder exstrophy (Marian: 5 mins)
 - Anencephalus (Rosie: 5 mins)
- Discussion (20 mins)
 - Role of TEC

11.55-12.40 WP5: Registration, Coding and Classification, Data Quality

- New and revised variables (Ester)

12.40-13.30 Buffet Lunch Danube Restaurant (same level and opposite TEA Saloon (main room))

Session 3 (TEA Saloon - Chair: Babak, Co-Chair: Elisa)

13.30-14.50 WP6: Investigation of Trends, Clusters and New Exposures

- Swine flu (Michiel: 30 mins)
- The Risk of CA in Multiple Births (Breidge: 20 mins)
- Congenital heart diseases based on Hungarian Case-Control Surveillance of Congenital Abnormalities, 2007-2008 (Janos Sandor: 15 mins)
- Arsenic in drinking water and congenital heart anomalies (Peter Rudnai: 15 mins)

Session 4 (TEA Saloon - Chair: Babak, Co-Chair: Elisa)

14.50-16.15 WP4: Central Database and Surveillance and WP6: Investigation of Trends, Clusters and New Exposures (cont'd)

- Survey of the use of the Statistical Monitoring Report (Nichola: 5 mins)
- New trend outputs (Joan: 15 mins)
- Statistical Monitoring: New Increasing Trends
 - Tetralogy of fallot (Central Registry: 5 mins)
 - Tetralogy of fallot (David: 5 mins)
 - Craniosynostosis (Central Registry: 5 mins)
 - Complete absence of limb (Central Registry: 5 mins)
- Statistical Monitoring: Increasing Trends
 - Cystic malformation of lung (Central Registry: 5 mins)
 - Cystic malformation of lung (David: 5 mins)
 - Gastroschisis/UK versus rest of Europe (Central Registry: 5 mins)
 - Gastroschisis study protocol (Liz: 5 mins)
- Statistical Monitoring: Decreasing Trends
 - EUROCAT NTD trends study (Babak: 5 mins)
 - Maternal age associated with anencephalus (Maria: 5 mins)
- Discussion time for session (15 mins)

16.15-16.30 Tea/coffee

16.30-17.30 Parallel Sessions

<p>PMC with Guide 1.4 Committee (Closed Meeting in TEA Saloon, Attendees: Lorentz, Elisa, Babak, Diana,</p>	<p>EDMP Clinic in COFFEE Saloon (James Densem) There will be a presentation on</p>	<p>EUROCAT Budget System (in Apartman 223) - Barbara will be available to advise and answer any</p>
--	--	--

<p>Helen, Ingeborg, Maria, Ester, Domenica, Joan, Marian, Amanda, Hermien, Ruth, Rhonda)</p> <p>PMC stay back in meeting room</p> <p style="text-align: center;">↓</p>	<p><u>Setting up local variables and importing extra drugs</u></p> <ul style="list-style-type: none"> a new feature within EDMP allows you to import more than the standard 5 drug codes <p>flexibility of EDMP for collecting more than the standard EUROCAT variables</p>	<p>enquiries</p>
--	--	------------------

17.30-17.45 PMC meeting to discuss topics of interest for the Croatian Symposium

17.45-18.30 Parallel Sessions

<p>SC Meeting (Closed in Apartman 223)</p> <ul style="list-style-type: none"> - Lorentz - Elisa - Babak - Diana - Ingeborg 	<p>EUROCAT Budget System in Apartman 323</p> <p>- Barbara will be available to advise and answer any enquiries</p>	<p>Folic Acid Committee (Closed in COFFEE Saloon)</p> <p><u>WP7 FA Working Group</u></p> <ul style="list-style-type: none"> - Domenica - Elisa* - Eva - Miriam - Anna <u>Et al.</u> 	<p>EDMP Clinic in TEA Saloon (James Densem, Ruth Greenlees & Maria Loane)</p> <p>One to one opportunities to speak about use of the EUROCAT Data Management Program. Ruth will demonstrate the reporting function within EDMP James will demonstrate setting up user defined groupings Maria will answer specific registry queries. Bring data if you have a specific problem</p>
--	---	--	---

* Amanda to represent Elisa

19.30 Buffet dinner with folklore entertainment in PANORAMA restaurant/terrace

Friday 15th (Open Sessions)

Session 1 (TEA Saloon - Chair: Diana, Co-Chair: Marian)

08.30-09.30 Parallel Sessions

<p>Registry Advisory Service (RAS in COFFEE Saloon) for new/applicant members (please opt in by informing Central Registry if you want to attend)</p> <p>RAS Objectives: to help new or applicant members of EUROCAT or new staff of EUROCAT registries as well as other interested parties to get acquainted with EUROCAT methodology and coding</p> <p>Agenda</p> <ul style="list-style-type: none"> - Procedure for Obtaining EUROCAT Data (Ingeborg Barisic) - Coding rules for the anomalies - where to find help. Core variables (Ester Garne) - Definition and coding of Syndromes, Associations and Sequences (Ingeborg Barisic) - Questions and closing remarks 	<p>WP9 Workshop (in TEA Saloon) – Attendees: Lolkje, Hao, Marian, Helen, Kacie, Joan, Maria, Vera, Larraitz, Elisa, Annukka, Kari, Christine, Awi, Miriam, Ester, Babak, Anke, Anna P, Marie-Claude, David, Ingeborg, Berenice</p> <p>AND any registries with data on medication use in pregnancy</p> <ul style="list-style-type: none"> - Importing extra drug data in EDMP (James) - Sources of medication use in pregnancy: update of information - Demonstration of diabetic software 	<p>EDMP Clinic (in Apartman 223) There will be a presentation on <u>Statistical Monitoring</u></p> <ul style="list-style-type: none"> • How to run your own statistical monitoring for any time period • Running the analysis on smaller localities within your region <p>Running reports to help investigate trends and clusters for completion of the template sent from Central Registry</p>	<p>EUROCAT Budget System (in Apartman 323) - Barbara will be available to advise and answer any enquiries</p>
---	--	--	--

09.30-10.15 **WP8: Prenatal Screening, Down Syndrome and Genetic Syndromes** (Joan)
- Prenatal website tables

10.15-10.45 **Tea/Coffee**

10.45-12.15 **WP7: Primary Prevention of Congenital Anomalies** (Domenica)
- Consensus on EUROCAT recommendation for inclusion in National Plans

12.15-12.30 **2013 RLM Croatia** (Ingeborg)

12.30-13.30 **EUROCAT Association Meeting** (Closed Meeting, Attendees: Registry Leaders Only)

13.30-14.20 **Buffet Lunch in Danube Restaurant**

14.20-15.00 **WP9: Medication During Pregnancy**

- Update on activities (Marian: 10 mins)
- EUROCAT Antidepressant Study: Update (Anthony: 20 mins)
- The Lamotrigine Club Foot Study (Hao Wang: 10 mins)

15.00-15.50 Lamotrigine Study (Closed Meeting in TEA Saloon, Attendees: Lolkje, Hao, Marian, Kacie, Joan, Maria, Vera, Larraitz, Elisa, Annukka, Kari, Christine, Awi, Miriam, Ester, Babak, Anke, Anna P, David, Ingeborg, Berenice)

15.50-16.10 Tea/coffee

16.10-17.00 Website Dissemination Committee Meeting (Closed Meeting Attendees: Ingeborg, Elisa, Rhonda, Ester, Ruth, Lorentz, Babak, Maria, Joan, Diana, Barbara, Hermien)

Documents to bring with you:

- Minutes of last RLM (Antwerp)
- Participants list
- Joint Action Application (with WP descriptions)
- Executive summary of the 2009 Statistical Monitoring Report
- Draft recommendation on primary prevention of congenital anomalies
- Pan-Europe all non-chromosomal anomalies
- Cluster Results_Year Birth 2010

Please bring the following essential documents if attending the Registry Advisory Service workshop:

EUROCAT Guide 1.3 <http://www.eurocat-network.eu/content/EUROCAT-Guide-1.3.pdf>

Q-Chapters (with BPA Extension) - <http://www.eurocat-network.eu/content/EUROCAT-Q-Chapter-2008.pdf> EUROCAT Guide 6: Definition and Coding of Syndromes <http://www.eurocat-network.eu/content/EUROCAT-Syndrome-Guide-6-2008.pdf>

Participant List

Present: Diana Akhmedzhanova, Larraitz Arriola, Marian Bakker, Eszter Balku, Ingeborg Barisic, Judit Beres, Eva Bermejo, Breidge Boyle, Paula Braz, Judith Budd, Elisa Calzolari, Clara Caverro, Johanna Costigan, Rhonda Curran, Saeed Dastgiri, Virginia Delany, Lolkje De Jong-van den Berg, James Densem, Berenice Doray, Karl Freese, Ester Garne, Miriam Gatt, Dorit Goetz, Ruth Greenlees, Ieva Grinfelde, Jon Gunnar Tufta, Martin Haeusler, Ildiko Horvath, Lorentz Irgens, Babak Khoshnood, Valeria Klujber, Kari Klungsoyr, Andrea Koehn, Petter Kristensen, Maria Loane, Michiel Luteijn, Carmen Martos, Carlos Matias Dias, Nichola McCullough, Julia Metneki, Myriam Mols, Joan Morris, Carmel Mullaney, Vera Nelen, Amanda Neville, Barbara Norton, Anna Pierini, Annette Queisser-Wahrendorf, Hanitra Randrianaivo, Anke Rissman, Annukka Ritvanen, Catherine Rounding, Goradz Rudolf, Edith Said, Nicole Siemensma-Muhlenberg, Antonin Sipek Jr, Anna Springett, Ildiko Szy, Domenica Taruscio, Rosie Thompson, Guy Thys, David Tucker, Deiene Urcelay, Andrea Valek, Magdolna Vamos, Christine Verellen-Dumoulin, Jozsef Vitrai, Nathalie Volders, Zoltan Voko, Hao Wang, Diana Wellesley, Anthony Wemakor, Awi Wiesel, Natalya Zymak-Zakutnya (75 participants, 23 countries)

Apologies: Lorentz announced apologies which were received from the following:

Helen Dolk (Central Registry), Liz Draper (EMSYCAR), Judith Rankin (Northern England), Elena Szabova (Slovakia), Anna Latos-Bielenska and Jan Mejnartowicz (Wielkopolska), Hermien De Walle (Netherlands), Bob McDonnell (Dublin), Mary O'Mahoney (Cork and Kerry), Fabrizio Bianchi (Tuscany), Karin Kallen (Sweden), Martine Vrijheid (CREAL), Gioacchino Scarano (Campania), Joaquin Salvador (ASPB), Hanitra Randrianaivo (Ile de la Reunion), Bruno Schaub (French West Indies), Tone Bjorge – Norway (but represented by Lorentz Irgens, Kari Klungsoyr and Jon Gunnar Tufta), Oscar Zurriaga – Valencia Region (but represented by Carmen Martos and Clara Caverro), Marie-Claude Addor (Switzerland), Wladimir Wartecki – Ukraine (but represented by Natalya Zymak-Zakutnya and Diana Akhmedzhanova), Antonin Sipek – Czech Republic (but represented by his son Antonin Sipek), Emmanuelle Amar (Rhône Alps), Marie-Luisa Martinez-Frias – ECEMC (but represented by Eva Bermejo), Sebastiano Bianca (Sicily)

Annex 2: Overview of registration to view and use EUROCAT's interactive website prevalence tables (March to December 2012)

Registrations By Country	
United Kingdom	35
France	13
Poland	12
Ireland	11
Belgium	10
Italy	8
USA	8
Denmark	8
Northern Ireland	6
Germany	6
Switzerland	5
Spain	4
MALTA	4
Finland	4
england	4
India	3
Netherlands	3
US	3
Wales	2
Scotland	2
Portugal	2
Austria	2
United States	2
The Netherlands	2
Italia	2
Pakistan	2
Hungary	1
Denmark	1
N. Ireland	1
London	1
New York	1
Ireland	1
United Kingdom	1
JAPAN	1
België	1
Canada	1
Ukraine	1
Croatia	1
Sudan	1
Wales, United Kingdom	1
UK	1
Moldova	1
Isle of Reunion	1
Czech Republic	1
Asturias, Spain	1
Sweden	1
Total	183

Registrations By Type	
Public Health or Epidemiology Academic	56
Student	34
Other Academic	14
National Government Official with responsibility for Public Health or Health Services	11
Paediatrician or surgeon	10
Obstetrician	8
Medical Geneticist	7
Pharmacovigilance Officer within industry	6
Regional / Municipal Government of Health Authority Official	6
Journalist	2
Other - Researcher	2
Affected person / parent of affected person	2
Nurse	2
Other - Website programmer	1
Other - Website programmers	1
Patient Organisation - Fondation Jérôme Lejeune	1
Other - Healthcare professionals involved in Primary Prevention of malformations	1

Other - secretary of M.C.Addor	1
Other - Scientific consultant	1
Other - Pharmaceutical physician	1
Other - Consultant	1
Other - Medical research	1
Other - adult congenital heart disease trainee	1
Other - Pharmaceutical industry	1
Other - ANESTESIOLOGIST	1
Other - information officer (EDMP data manager)	1
Other - Epidemiologist in Industry	1
Other - European Parliament	1
Other - retired academic	1
Other - Pharmaceutical epidemiology	1
Other - Registered Charity	1
National Government Official with responsibility for Environment	1
Other - environmental activist	1
Patient Organisation - Spina Bifida and Hydrocephalus	1
Patient Organisation - Down Syndrome	1
Other - private health consulting firm	1
Total	183

Reports Generated by Month		
Month	Members	Registrants
March 2012	0	55
April 2012	0	97
May 2012	0	23
June 2012	163	185
July 2012	258	34
August 2012	27	154
September 2012	68	162
October 2012	119	322
November 2012	67	266
December 2012	11	163
Total	713	1461

Annex 3: Overview of proposed budget changes documented in two grant agreement amendments submitted to the Executive Agency

1st Grant Amendment		
Univeristy of Ulster		
Project Management to attend PMC	2,624.00	
Belgium, Antwerp		
Vera Nelen no longer on PMC	-6,456.00	
Croatia, Zagreb		
Ingeborg Barisic to attend PMC	4,608.00	
Italy, ISS		
Reduced staff for WP7	-13,400.00	
Netherlands, North		
Marian Bakker to attend PMC	4,608.00	
Spain, CREAL		
Martine Vrijheid to attend PMC	4,608.00	
UK, QMUL		
Joan Morris to attend PMC	3,408.00	
Sub-Total	0.00	
2nd Grant Amendment		
University of Ulster		
Reduce PMC subsistence rate	-148.00	
Reduce Evaluation	-17,500.00	
New researcher	40,915.00	
Belgium, Antwerp		
Left-over spend from Symposium	-3,592.00	
Vera Nelen back on PMC	1,800.00	
Vera Nelen back on PMC	1,656.00	
Croatia, Zagreb		
Extra money for Symposium	3,122.00	
Netherlands, Pharmacy		
Lolkje not on PMC	-3,446.00	
Lolkje not on PMC	-3,312.00	
Norway		
No longer doing Evaluation	-10,000.00	
No longer doing TEC	-9,495.00	
Sub-Total	0.00	

Annex 4: Dissemination Plan

As part of EUROCAT joint action proposal we have developed a dissemination plan for sharing outcomes with stakeholders, relevant institutions, organizations, and individuals.

1. Purpose of the dissemination

The purpose of the dissemination activity is to raise awareness on the importance of registries and databases on congenital anomalies (CA) coordinated at European level, on the possibilities that they offer in terms of collecting data, coding and classification of rare disorders, public health planning, primary prevention, and research in the field of CA.

The purpose of the dissemination activities is also to raise the profile of EUROCAT network, and to gain wider support for setting up registries for CA across Europe.

The results of the EUROCAT Joint action will serve to inform and educate larger community on the importance of prevention strategies for CA. Through dissemination of the EUROCAT-Joint Action results we would like to engage actively the community in improving health status of women in childbearing age.

2. Key messages

We plan to disseminate the main expected outcomes of the EUROCAT-Joint Action project.

- a) The availability of easily accessible epidemiological information on prevalence of CA, perinatal mortality due to CA, and prenatal detection rates, on the EUROCAT website (www.eurocat-network.eu)
- b) The importance of sustainable surveillance and prevention policy for CA across Europe, as population characteristics, morbidity and environment are constantly changing over time (high maternal age, chronic diseases and obesity, new infections and pollutants, new medications, and changing immigration) and need close follow up.
- c) The importance of detection, investigation and reporting of clusters and trends in CA prevalence, including the establishment of the Task Force for Evaluation of Clusters that will build the capacity for rapid response when needed
- d) The results of assessment of possible teratogenic impact of new environmental exposures, as swine flu, maternal chronic diseases and new drugs
- e) The need of linkage between registries and other electronic information systems, e.g. European pollution information system, and prescription databases
- f) The importance of inclusion of the strategies for primary prevention of CA in the National plans for rare diseases with special emphasis on the raising of the periconceptual folic acid status
- g) Evaluation of the impact of delayed childbearing and changes in prenatal screening policies and techniques on CA, especially on Down syndrome
- h) Development of the effective pregnancy-related pharmacovigilance system in Europe (EUROmediCAT)
- i) Importance of the constant work on the improvement of the coding and classification of rare diseases
- j) Importance of the research in the field of CA

3. Audience

The audience for EUROCAT – Joint Action outcomes includes all interested in the rare diseases, in particular CA.

The stakeholder analysis identified the following groups and individuals that will be interested in the project outputs, or whose support/approval is essential for further development of EUROCAT-Joint Action activities.

Internal stakeholders (associated and collaborative partners of the EUROCAT Joint Action) – Dissemination plan aims to keep all the partners well informed about different aspects of the Joint Action. It will assure sharing of results within the Joint Action, across work packages, and getting feedback from partners facing similar problems and issues, or working on the same problem from different perspective.

External stakeholders

- a) *Health professionals* e.g. paediatricians, obstetricians, paediatric pathologists, medical geneticists and genetic counsellors and midwives actively involved in the care of children with congenital anomalies and / or pregnant women.
- b) *Public health professionals* and those involved in *health service planning* at regional, national, EU and WHO levels.
- c) *Governmental/public regulation agencies* in several domains (industrial, air quality, environmental protection agencies, food, medications)
- d) Patient organisations
- e) *Scientific research community* in areas such as epidemiology and public health, clinical genetics, embryology
- f) *Politicians and policy makers*

The community

Some outputs of this Joint Action are of interest also to the wider community, e.g. main messages concerning healthy lifestyle in childbearing age, recommendations/guidelines for the prevention of CA, evaluation of the use of new drugs in pregnancy, data on teratogenic impact of new environmental exposures, evaluation of the effectiveness of methods of secondary prevention (e.g. prenatal ultrasound or biochemical screening) etc.

4. Dissemination Methods

To get the right message to the right audience, we plan to use a wide variety of dissemination methods.

Method	Purpose	Target Audience	Month of Delivery (if applicable)
Project website	Awareness Information Engagement Promotion	Open access for different audiences –internal and external stakeholders, wider community Restricted access - for internal stakeholders	Continuous monthly update
Promotional leaflet (electronic and print version)	Awareness Information Engagement Promotion	Internal and external stakeholders, wider community	3
Newsletter	Awareness Information	Internal and external stakeholders, wider community	12, 24, 36
Registry Leaders Meetings - Antwerp (June 2013) - Budapest (June 2012) - Zagreb (June 2013)	Awareness Information Engagement	Internal stakeholders, DGSANCO representatives and invited representatives of other networks	6, 18, 30
Workshops	Engagement	Internal stakeholders and invited representatives from new/applying registries	6, 18, 30 as a part of RLMs
Conference presentations and posters	Information Promotion	Scientific/clinical research community	ad hoc
Peer-reviewed journals	Information Promotion	Scientific/clinical research community	- Multiple malformation paper 15 - 6 scientific papers on genetic syndromes ,18, 36, 21, 31, - EUROMediCAT papers 36
Reports and other documents	Information	DG Sanco and EAHC, Public health officials, scientific/clinical community	- Interim and Final Report 18, 36 - Evaluation Report, 36 - Statistical Monitoring Reports, 12, 24 - Investigation Reports 12, 24, 36 - Report on Primary Prevention, 24
EUROCAT Communications	Information Engagement	Internal stakeholders	Monthly
Press releases	Awareness	Community	ad hoc
Two European Symposia on Congenital Anomalies	Information Engagement Promotion	Scientific/clinical community	6, 30

The dissemination strategy will ensure that the Joint Action has a high profile, the community learns from its achievements, and outputs are embedded and taken up. Project Management Committee (PMC) will discuss about ways to collaborate on dissemination. Dissemination strategy outlined here will be discussed and evaluated at PMC meetings (3/year). Available outcomes of WP4-9 will be reviewed and decided on the best ways to present the results.

5. *Timing*

EUROCAT-Joint Action deliverables will be distributed to the target audience as planned (see above). At the PMC meeting it will be decided when different dissemination activities without pre-determined timing will be most relevant.

6. *Collaboration*

Co-ordination of liaison with other networks, organizations and committees, especially those involved in rare diseases, exploring the possibilities of joint projects, exchange of information, experience and expertise will be developed. Liaison officers have been nominated as follows.

Network/organisation	Liaison (partner institute, name)
European Expert Committee on Rare Diseases	Lillebaelt- Ester Garne
ICBDSR	UMCG-Marian Bakker
European Conference on Rare Diseases	IMER - Elisa Calzolari IFC-CNR – Fabrizio Bianchi KDB – Ingeborg Barisic ISS – Domenica Tarusco
EUROPLAN	ISS- Domenica Tarusco
EURORDIS	ISS – Domenica Tarusco, UMCL- Borut Peterlin KDB- Ingeborg Barisic
ENTIS	UMCG-Marian Bakker
ESHG	UMCL – Borut Peterlin KDB – Ingeborg Barisic
EUROPERISTAT	UMCG-Hermien de Walle
SCPE	Lillebaelt- Ester Garne
Biobanking and Biomolecular Resources Infrastructure-BBMRI	NCHAI-Judith Beres

7. **National EUROCAT Committees**

The EUROCAT – Joint Action will promote the setting up of National EUROCAT Committees or equivalent, with representation from Registries, Ministries of Health, Patient Groups and Professional Associations. The main goals of these bodies is to strengthen connections with local stakeholders, present EUROCAT Reports and other outputs, and to encourage contacts with media and wider audiences addressing issues of common interest. These committees will embed registries of CA in the local community, connecting them with patients, government institutions and professional clinical and scientific community. This will eventually improve their chances for future sustainability.

8. *Evaluation*

Survey of Newsletter Recipients and Website Users and number of established National EUROCAT Committees at the end of EUROCAT-Joint Action.

Annex 5: Minutes of Website Dissemination Committee Meeting, Budapest June 2012

Website Dissemination Committee Meeting, Budapest (RLM), Hungary 15th June 2012

Present: Babak Khoshnood, Diana Wellesley, Ingeborg Barisic, Elisa Calzolari, Ruth Greenlees, Rhonda Curran, Barbara Norton, Maria Loane, Joan Morris, Anna Springett

Apologies: Helen Dolk, Lorentz Irgens, Bob McDonnell, Hermien de Walle, Ester Garne,

Chair: Ingeborg Barisic

1. Prevalence tables

It was agreed that the new website prevalence tables that went live prior to the RLM in Budapest would continue to use the EUROCAT definitions: of prevalence (i.e. total prevalence, livebirth prevalence). This ensures comparability with older EUROCAT publications.

Prenatal diagnosis tables

When the format has been finalised (following discussion at RLM) Joan/Anna will send powerpoint version to all members of the website dissemination committee and to all registries who have supplied data.

As the prenatal diagnosis (PD) tables are only available on the live website for the most recent 5-year period, the previous year's data tables will be archived in a dedicated place on the member's only website to allow comparison and so that the information is not lost.

We aim to have all the data in the new format, reviewed by applicable registries and live on the website just after the next Project Management Committee meeting.

Registries will confirm the data for the prenatal tables when they are confirming the other data.

2. Perinatal mortality and key public health indicator tables/figures

Ingeborg advised the committee that work on the key public health indicator tables was just beginning.

Hermien de Walle had been invited to attend the website dissemination committee meeting but was unable to attend. Discussion on perinatal mortality tables was postponed until the next committee meeting, when Hermien may then be available.

3. Updating of the website

Everyone needs to accept some responsibility for updating the website and providing Barbara with the necessary information and materials.

Work package leaders should supply work package specific updates (if applicable/available) for the website once every 3 months. Rhonda will send a reminder email once every 3 months

and collate the information to be circulated to the website dissemination committee, that will then decide how and if it should feature on the website.

4. 12th European Symposium on Congenital Anomalies, Croatia 2013

The next symposium should be advertised early and we will aim for high visibility. On the website this should include clear access to information and registration and nice inviting pictures.

Patricia Boyd will be invited as a guest speaker.

5. Cluster Advisory Service section on the website

The content that the Taskforce for Evaluation of Clusters (TEC) had created has been added to the Cluster Advisory Service section of the website. Lorentz (Chair of TEC) was not present at meeting. The content should be reviewed and maintained by the TEC and supplied to the website dissemination committee to review and pass to Barbara.

Other proposals considered:

1. Current projects

Rhonda will restructure the project section of the website (and will provide the new projects table) and advise Barbara of the changes to be made.

2. Consider dividing Announcements into Meetings & Events, New publications, News on congenital anomalies

It was decided that we need more announcements and that relevant publications of interest to EUROCAT (not necessarily EUROCAT papers) as well as other relevant news pieces could also be announced.

The announcements section on the home page will be restructured into 3 sections (by Barbara) - Meetings & Events, New publications, News on congenital anomalies?

Suggestions of announcements to be added to these sections will be passed to and approved by the website dissemination committee and then supplied to Barbara to be added.

Barbara will ask all members (via the EUROCAT Communication) to remember to populate the announcements section (by sending suggestions to Barbara who will periodically (monthly if available) pass to the committee). Committee members should also collate suggestions.

3. Making the website more friendly to the general public

Website committee will consider drafting short lay descriptions of issues of importance for the public under the prevention and risk factors section on the website. A science writer may be utilised for this purpose. Links out to useful sources of lay information may also be used. Consider a section "For Parents" where this reliable information can be accessed.

4. Reorganise and add new useful links

More links should be added and existing links reorganised into suitable headings. Links to member registry websites should also be listed. More links to patient organisations should be listed and to other useful sources of lay information.

5. Updating gallery with photos from related conferences

Gallery needs to be updated with more photos, including from meetings and events that members have attended. Barbara will ask all members (via the EUROCAT Communication) to remember to populate the gallery section (by sending suggestions to Barbara who will periodically (monthly if available) pass to the committee). Members will be asked to supply details of the venue, date attended, the topic of presentation and an accompanying photo. Committee members should also collate photos.

6. Member's forum

The committee will continue to try and encourage the use of the website forum.

Website Dissemination Committee Communication

Teleconferences will be organised when specific topics have been identified that require discussion otherwise the committee will communicate via email. Barbara requests that the FINAL version comes from Ingeborg, clearly identified as such.

Annex 6: EUROCAT 2012 Newsletter (supplied separately as a pdf)

Also accessed via <http://www.eurocat-network.eu/content/EUROCAT-Newsletter-6.pdf>

Annex 7: Liaisons with other networks, organisations and committees in 2012

Network/organisation	Liaison (partner institute, name)
European Expert Committee on Rare Diseases	<p>Lillebaelt- Ester Garne</p> <p>January 26-27th: EUCERD meeting in Luxembourg</p> <p>June 20-21st: EUCERD meeting in Luxembourg</p> <p>September 27-28th: meeting in Paris on cross-referencing of terminologies</p> <p>November 13th: EUCERD Joint Action workshop on registries in Luxembourg</p> <p>November 14-15th: EUCERD meeting in Luxembourg (also attended by KDB – Ingeborg Barisic and UMCL- Borut Peterlin - country representative as a country representative)</p>
ICBDSR	<p>UMCG-Marian Bakker</p> <p>October 31 -November 2nd: the Annual Meeting of the ICBDSR which was held together with the 10th Annual Scientific Meeting of the Canadian Congenital Anomalies Surveillance Network (CCASN) in Ottawa. At the scientific symposium UMCG presented on the EUROmedICAT project. David Tucker (WALES) was asked to be on a committee that will develop a new format for the ICBDSR annual report tables, because of his involvement in the EUROCAT coding committee.</p>
European Conference on Rare Diseases	<p>May 24-25th: 6th European Conference on Rare Diseases, Bruxelles, Belgium</p> <p>ISS – Domenica Taruscio</p> <p>- oral communication “Brief overview EUROPLAN 2012-2015 First steps “; Informal Meeting EUROPLAN 2012-2015. The WP2 of EUROCAT JA activities, among other topics, were presented to EURORDIS as well as to EUROPLAN Members</p> <p>- poster presentation “Training general practitioners and paediatricians on rare disease diagnostic suspect and effective communication”</p> <p>KDB – Ingeborg Barisic - poster presentation: -Barisic I, Odak Lj, Loane M, Garne E, Wellesley D, Calzolari E, Dolk H and EUROCAT Working Group. “Fraser syndrome: data on a rare genetic syndrome in a European population”</p> <p>Lillebaelt- Ester Garne - poster presentation: Garne E, Loane M, Barisic I, Wellesley D, Dolk H, EUROCAT Working Group. “Prevalence of genetic syndromes and rare chromosomal abnormalities in Europe”</p> <p>IFC-CNR –Fabrizio Bianchi - participant</p>
EUROPLAN	<p>September 10-11th: EUROPLAN inception workshop on national planning for rare diseases</p> <p>ISS- Domenica Taruscio - oral communication “European project for rare diseases national plans development “</p> <p>ISS- Rita Maria Ferrelli - oral communications “Strengths and weaknesses in developing national plans; Lessons learnt from successes and failures in developing national plans; The Delphi process for selecting indicators. “</p> <p>KDB – Ingeborg Barisic - participant</p> <p>The WP2 of EUROCAT JA activities, among other topics, were presented to participants (EURORDIS members, public health operators and clinicians) of the Workshop.</p>
EPIRARE	<p>Lillebaelt- Ester Garne</p> <p>May 23rd: EPIRARE steering committee meeting in Bruxelles. Present as advisory board member.</p> <p>October 8-10th: EPIRARE conference and Steering committee meeting in Rome.</p> <p>KDB – Ingeborg Barisic - oral presentation: “Congenital anomaly registries improve the knowledge on genetic syndromes in Europe”</p> <p>IMER – Elisa Calzolari - participant</p> <p>IFC-CNR –Fabrizio Bianchi - participant</p>

	Document produced by EPIRARE: “Developing a European Platform for Rare Disease Registries” discussed at the PMC in Oxford, December 2012 and EUROCAT response send to authors.
ENTIS	UMCG -Marian Bakker UMCG organised with ENTIS a joint symposium at the International Conference of Pharmaco Epidemiology in Barcelona on biases and confounding in studies on medication use in pregnancy. Speakers were Hao Wang (EUROCAT and RUG, Netherlands), Corinne de Vries (University of Bath, UK), Rachel Charlton (University of Bath, UK), Heli Malm (ENTIS and Helsinki University Central Hospital, Finland) and Kristin Palmsten (Harvard School of Public Health, USA).
ESHG	UMCL – Borut Peterlin - - Board member - PPPC member - Quality Committee member KDB – Ingeborg Barisic June 23-27th : ESHG Conference 2012 in Nürnberg, Germany. - Barisic I, Dumic K, Morožin Pohovski L, Petkovic I, Riegel M, Schinzel A. “Array CGH characterisation of ring chromosome 9 formation due to inverted duplication and terminal deletion in a patient with sex-reversal” - Morožin Pohovski L, Barisic I. “MLPA as screening method in detection of submicroscopic rearrangements detected in patients with developmental delay/intellectual disability”
EUROPERISTAT	UMCG-Hermien de Walle March 8th : Euro-Peristat meeting with EUROCAT in London. Next meeting planned in the beginning of the next year.
SCPE	Lillebaelt- Ester Garne June 25 -27th : SCPE annual meeting in Madrid Two presentations given
Other	IMER – Elisa Calzolari Regional level The dissemination activities principally in the Emilia Romagna Region and other Italian registries. IMER website www.registroimer has a link to EUROCAT on the home page in order to disseminate EUROCAT data and activities. The IMER Annual Report contains many comparisons with EUROCAT data providing a context in which regional data can be interpreted. Selected IMER and EUROCAT data are included in the Annual Report on Rare Disease in Emilia Romagna Region supporting the link between the Rare Diseases and Birth Defects. The IMER Annual Convention was held on 30 March 2012 with around 200 delegates. The subject of the convention was Urinary tract anomalies and EUROCAT data has been used for comparison and reference The Annual Training Course for IMER Reference Centres Corso di aggiornamento sulla epidemiologia e percorsi diagnostico-assistenziali delle malformazioni congenite(Emilia Romagna Region) on 24th November included a Presentation on syndromes highlighting the new EUROCAT Syndrome Prevalance tables (Amanda J Neville) National level A presentation on Primary Prevention of birth defects with a focus on the role of the congenital malformation registries was a keynote address at the ISS Convention in Rome on 5th November International level A contact has been established with the PHG Born healthy team www.bornhealthy.com and meeting is planned for 5th December 2012 ISS – Domenica Taruscio National level

	<p>April 21st 2012, Congress: “Le Malattie Rare incontrano gli Operatori Sanitari”, Cortona, Italy - oral communication: “National and International activities of the Italian National Centre for Rare Diseases“ The WP2 of EUROCAT JA activities, among other topics, were presented participants (mainly clinicians, public health operators and patients) of the Congress</p> <p>June 6th 2012: Congress “ Malattie Rare e Farmaci Orfani -Esigenze cliniche e sinergie terapeutiche” , Firenze, Italy - oral communication “National and International activities of the Italian National Centre for Rare Diseases” The WP2 of EUROCAT JA activities, among other topics, were presented participants (mainly clinicians, public health operators and patients) of the Congress</p> <p>December 3-5th 2012: IV Congresso Nazionale Congiunto SIMMESN e SIMGePed, Venezia, Mestre, Italy</p> <p>International level</p> <p>April 2-3rd 2012: Euro/Mediterranean Conference on Research and Innovation, Barcellona (E)- oral presentation and participation to Session “Fighting diseases and improving well/being“ The WP2 of EUROCAT JA activities, among other topics, were presented participants (relevant stakeholders involved in public health coming from all Mediterranean Countries) of the Conference</p> <p>April 6-13th 2012: Congress: Rare Disease School 2012, Salonicco, Greece - oral communication “Gathering expertise on rare diseases at European and International level” The WP2 of EUROCAT JA activities, among other topics, were presented participants (public health operators and clinicians) of the Congress.</p> <p>June 20-24th 2012: First Eurasian Conference for Rare Diseases and Orphan Drugs, Moscow, Russia The WP2 of EUROCAT JA activities, among other topics, were presented participants (EURORDIS and other patients Federations, public health operators and clinicians) of the Conference.</p> <p>October 22-23th 2012: International Conference on Mediterranean countries and EU opportunities, Amman, Jordan</p> <p>UMCL- Borut Peterlin SIGN (Slovenian-Italian Genetic Network) -Coordinator PHGEN II (Public Health Genomics Network) - Scientific committee member EUROClleftNet - Scientific committee member</p>
--	--

Annex 8: Conference Presentations 2012

Baldacci Silvia, Pierini Anna, Santoro Michele, Spadoni Isabella, Bianchi Fabrizio. Prevalence and mortality of congenital heart defects in Tuscany: a population based study. Abstract inviato all'European Congress of Epidemiology. Abstracts. The IEA-EEF European Congress of Epidemiology 2012: Epidemiology for a Fair and Healthy Society. Porto, 5-8 settembre 2012. Eur J Epidemiol (2012) 27:S40.

Baldacci S., Pierini A., Santoro M., Spadoni I., Bianchi F. Prevalence and Mortality of Congenital heart defects in Tuscany Region 1992-2009. In: Giornale Italiano di Cardiologia. Abstract, vol. 13 - (supplemento 1 al numero 10) p. 10S. Il Pensiero Scientifico Editore, 2012. Abstract del XLII Congresso Nazionale della Società Italiana di Cardiologia Pediatrica. Jesi, 11-13 ottobre 2012.

Fabrizio Bianchi, Federica Pieroni, David Paoli, Sonia Marrucci, Maria Cristina Imiotti, Cecilia Berni, Francesca Micalizzi, Silvano Pucci, Michele Lipucci Di Paola, Anna Pierini. The Regional Health System on Rare Diseases in Tuscany (Italy). Abstract inviato all'European Conference on Rare Disease & Orphan Products. Bruxelles, 23-25 maggio 2012.

Anna Pierini, Federica Pieroni, David Paoli, Maria Cristina Imiotti, Sonia Marrucci, Cecilia Berni, Silvano Pucci, Michele Lipucci Di Paola, Fabrizio Bianchi. The Regional Registry on Rare Diseases in Tuscany. Abstract in via to all 'European Conference on Rare Disease & Orphan Products. Bruxelles, 23-25 maggio 2012.

Wladimir Werteleki "Congenital Malformations among a population isolate living in relative proximity to Chornobyl" at the Medical and Ecological Consequences of the Fukushima Nuclear Accident Symposium in New York on 11-12 March, 2012.

Valencia Region Registry made an oral presentation in Spanish Epidemiology Association Meeting in Santander, October 2012, "Anomalías Congénitas e Industrias Contaminantes en la Comunitat Valenciana", Authors: C. Cavero, M. Estarlich, MA. Martinez-Beneito, J. García-Pérez, O. Zurriaga, G. López-Abente, C. Martos

Garne E. Congenital anomaly surveillance in Europe: the EUROCAT project. SCPE Annual Meeting, Madrid 2012

Garne E. Rare diseases – a priority area in EU Health Policy. SCPE annual meeting, Madrid 2012

Elisa Calzolari. Why should we promote Primary Prevention? ISS (Italian Superior Health Institute) meeting on Primary Prevention of Congenital Malformations, Rome Italy 5 November 2012

Congenital Anomalies- Challenges of a birth Defect Registry
National Pediatric Conference 30.-31.3.12 in Leipzig, Germany
Anke Rissmann

Prevalence of Fragile X- Syndrom in Saxony-Anhalt
National Pediatric Conference 30.-31.3.12 in Leipzig, Germany
Anke Rissmann

Epidemiology of the Anorectal Malformations
National Pediatric Conference 30.-31.3.12 in Leipzig, Germany
Anke Rissmann

Challenge Folic acid: Prevention of Neural tube defects
Rare disease day 28.2.1013, University Magdeburg, Germany
Anke Rissmann

Using a surveillance system to identify risk factors of congenital anorectal malformations
ICBDSR Annual Meeting 2012
Anke Rissmann

Congenital Anomalies- data from a birth defects registry
Neuropaediatric Association Germany, May 2012
Anke Rissmann

Babak Khoshnood, Nathalie Lelong, Véronique Vodovar, Marie Kassis, François Goffinet
(INSERM U953). Registres de malformations congénitales : un outil pour la surveillance, la
recherche et l'évaluation des actions de santé, National Academy of Medicine

Marie-Claude Addor, Capoccia et al June 2012 Swiss Society of Gynecology and Obstetrics
Interlaken Switzerland

Marie-Claude Addor, Stoppa et al poster BPES September 2012 congress of the European
Society of Pediatric Endocrinology Leipzig Germany

12 presentations were delivered by EUROCAT members at the British Isles Network of
Congenital Anomaly Registers Biennial Scientific Meeting 'Congenital Anomalies - New
Frontiers in Diagnosis and Management' on Tuesday 25th September 2012, St Anne's College
~ Oxford, OX2 6HT

Annex 9: EUROCAT Collaborative Publications 2012

Barisic I, Loane M, Curran R, Garne E, Vrijheid M, Taruscio D, Morris J, Bakker M, Irgens L, Calzolari E, Khoshnood B, Wellesley D and Dolk H (2012). Joint Action EUROCAT 2011-2013 funded by the Public Health Programme 2008-2013 of the European Commission. *Croatian Journal of Public Health*. 8: (31). 25-32.

Best KE, Tennant P, Addor M-C, Bianchi F, Boyd P, Calzolari E, Dias C M, Doray B, Draper E, Garne E, Gatt M, Greenlees R, Haeusler M, Khoshnood B, McDonnell R, Mullaney C, Nelen V, Randrianaivo-Ranjatoelina H, Rissmann A, Salvador J, Tucker D, Wellesley D and Rankin J (2012). Epidemiology of small intestinal atresia in Europe: A register-based study. *Archives of Disease in Childhood - Fetal and Neonatal Edition*.

Best KE, Tennant P, Addor M-C, Bianchi F, Boyd P, Calzolari E, Dias C M, Doray B, Draper E, Garne E, Gatt M, Greenlees R, Haeusler M, Khoshnood B, McDonnell R, Mullaney C, Nelen V, Randrianaivo-Ranjatoelina H, Rissmann A, Salvador J, Tucker D, Wellesley D and Rankin J (2012). Epidemiology of amll intestinal atresia in Europe: a register-based study. *Archives of Disease in Childhood - Fetal and Neonatal Edition*. 97: F353-F358.

Christensen N, Andersen H-J, Garne E, Wellesley D, Addor M-C, Haeusler M, Khoshnood B, Mullaney C, Rankin J and Tucker D (2012). Atrioventricular septal defects among infants in Europe: a population based study of prevalence, associated anomalies, and survival. *Cardiology in the Young*.

Dolk H, de Jong-van den Berg L, Loane M, Wang, H and Morris J (2012). Newer anticonvulsants: Lamotrigine. *Birth Defects Research Part A Clinical and Molecular Teratology*. 94: 959-959.

EUROCAT (2012). EUROCAT Newsletter March 2012. EUROCAT Central Registry, University of Ulster.

EUROCAT (2012). EUROCAT Statistical Monitoring Executive Summary 2009. EUROCAT Central Registry, University of Ulster.

EUROCAT (2012). EUROCAT Statistical Monitoring Report 2009. EUROCAT Central Registry, University of Ulster.

EUROCAT (2012). EUROCAT Special Report: Congenital Anomalies are a Major Group of Mainly Rare Diseases. EUROCAT Central Registry, University of Ulster.

Garne E, Loane M, Dolk H, Barisic I, Addor M-C, Arriola L, Bakker M, Calzolari E, Dias C M, Doray B, Gatt M, Klungsoyr Melve K, Nelen V, O'Mahony M, Pierini A, Randrianaivo-Ranjatoelina H, Rankin J, Rissmann A, Tucker D, Verellen-Dumoulin C and Wiesel A (2012). Spectrum of congenital anomalies in pregnancies with pregestational diabetes. *Birth Defects Research (Part A)*. 94: 134-140.

Howe DT, Rankin J and Draper E (2012). Schizencephaly prevalence, prenatal diagnosis and clues to etiology: a register-based study. *Ultrasound in Obstetrics and Gynecology*. 39: (1). 75-82.

Khoshnood B, Loane M, Garne E, Addor M-C, Arriola L, Bakker M, Barisic I, Bianca S, Boyd P, Calzolari E, Doray B, Draper E, Gatt M, Haeusler M, Klungsoyr Melve K, Latos-

Bielenska A, McDonnell R, Mullaney C, Nelen V, O'Mahony M, Pierini A, Queisser-Luft A, Randrianaivo-Ranjatoelina H, Rankin J, Rissmann A, Salvador J, Tucker D, Verellen-Dumoulin C, Wellesley D, Zymak-Zakutnya, N and Dolk H (2012). Recent decrease in the prevalence of congenital heart defects in Europe. *Journal of Pediatrics*. 162: (1). 108-113.

Luteijn M, Dolk H and EUROCAT Working Group (2012). Seasonality of Congenital Anomalies in Europe, from '4th Congress of European Academy of Paediatric Societies', 5-9 October 2012, Istanbul. *Archives of Disease in Childhood*. 97: (S2). A72-A73.

Modell B, Berry RJ, Boyle CA, Christianson A, Darlison M, Dolk H, Howson CP, Mastroiacovo P, Mossey P and Rankin J (2012). Global, Regional and National Causes of Child Mortality. *The Lancet*. 380: (3). 1556

Nassar N, Leoncini E, Amar E, Arteaga-Vazquez J, Bakker M, Bower C, Canfield M, Castilla E, Cocchi G, Correa A, Csaky-Szunyogh M, Feldkamp M, Khoshnood B, Landau D, Lelong N, Lopez-Camelo J, Lowry B, McDonnell R, Merlob P, Metneki J, Morgan M, Mutchinick O, Palmer NM, Rissmann A, Siffel C, Sipek A, Szabova E, Tucker D and Mastroiacovo P (2012). Prevalence of esophageal atresia among 18 International Birth Defects Surveillance Programs. *Birth Defects Research (Part A)*. 94: 893-899.

Pedersen R, Calzolari E, Husby S, Garne E and EUROCAT Working Group (2012). Oesophageal atresia: prevalence, prenatal diagnosis and associated anomalies in 23 European regions. *Archives of Disease in Childhood*. 97: 227-232.

Wellesley D, Dolk H, Boyd P, Greenlees R, Haeusler M, Nelen V, Garne E, Khoshnood B, Doray B, Rissmann A, Mullaney C, Calzolari E, Bakker M, Salvador J, Addor M-C, Draper E, Rankin J and Tucker D (2012). Rare chromosome abnormalities, prevalence and prenatal diagnosis rates from population based congenital anomaly registers in Europe. *European Journal of Human Genetics*. 20: (5). 521-526.

Wemakor, A, Dolk H, Casson K and de Jong-van den Berg L (2012). Prevalence and patterns of antidepressant use among women of reproductive age in Northern Ireland (NI). *Pharmacoepidemiology and Drug Safety*. 21: (3). 426

Annex 10: EUROCAT Press Releases 2012

Press Release – June 2012

University of Ulster Research Reveals Changes in Birth Defect Prevalence across Europe

The number of babies born with birth defects (major congenital anomalies) across Europe has fallen over the decade (2000-2009), University of Ulster research has revealed. According to the Statistical Monitoring Report of the European Surveillance of Congenital Anomalies (EUROCAT), the overall occurrence of spina bifida and heart defects have declined by 10 per cent and 14 per cent respectively within these last ten years. The author of the report, Professor Helen Dolk, from the Institute of Nursing Research at the University's Jordanstown campus, one of the top three UK nursing research centres, said: "Congenital anomalies are a major cause of foetal death, infant mortality and childhood morbidity so a key aim of public health authorities should be to reduce their occurrence.

"This report suggests that primary prevention programmes across some parts of Europe may be having a positive effect on some types of birth defects. For example folic acid supplementation if begun prior to conception and voluntary food fortification aim to reduce the occurrence of neural tube defects including spina bifida. EUROCAT is currently working on recommendations for a wide range of primary prevention measures to be included in National Plans for Rare Diseases."

The research has been carried out by a team at the University of Ulster's World Health Organisation Collaborating Centre for the Surveillance of Congenital Anomalies in collaboration with partners across Europe.

However the EUROCAT report also revealed increases in the occurrence of three syndromes involving an extra chromosome: Down syndrome, Edward syndrome and Patau syndrome. The proportion of pregnancies affected by Down syndrome has increased by 5%, now occurring in almost 22 out of every 10,000 pregnancies. Edward syndrome affects approximately six in every 10,000 pregnancies and Patau syndrome approximately two in every 10,000.

Professor Dolk said: "Analysis has shown that the increase in Down syndrome is a consequence of the trend in Europe for women to delay childbirth until later in life. Older maternal age is a known risk factor for Down syndrome."

The proportion of pregnancies affected by gastroschisis - an abdominal wall defect that requires babies to have corrective surgery - is also continuing to rise, going up by 29 per cent over the decade to 3 per 10,000 pregnancies.

"Young maternal age and certain maternal lifestyle factors are known to increase the risk of having a baby with gastroschisis, for example smoking during early pregnancy, low maternal BMI and low socioeconomic status. However the causes of the increase over time are not known," the Professor said.

She also stressed the importance of continued monitoring of birth defects and the need to support registries across Europe to collect comparative data.

"There are currently 39 registries located in 21 countries throughout Europe sending their data to the EUROCAT Central Registry located at the University's Jordanstown campus.

Currently there is no local EUROCAT registry in Northern Ireland.

“Reliable data collected by these surveillance systems is crucial in the development and evaluation of public health policies addressing health needs and in facilitating further research into the causes of congenital anomalies.”

EUROCAT Joint Action 2011-2013 is funded by the Public Health Programme 2008-2013 of the European Commission.

The full report can be accessed on the EUROCAT website: <http://www.eurocatnetwork.eu/content/Stat-Mon-Report-2009-Combined.pdf>

Contact:

Professor Helen Dolk
EUROCAT Project Leader, University of Ulster
Tel: +44 28 90366639
Email: h.dolk@ulster.ac.uk

Annex 11: EUROCAT Evaluation Plan

1. Process Evaluation

Process evaluation relates to planning, organisation and assuring quality of implementation of project activities, identifying and overcoming obstacles and verifying that the stated objectives have been met. This will include determining that the process/output indicators, the milestones and the deliverables have been met.

The process indicators measure the progress of activities in the EUROCAT Joint Action and the way these are carried out (e.g. annual data transmission by EUROCAT registries, by how many?, did they meet the deadline?).

Output indicators measure the quantity, quality and timeliness of the products of the EUROCAT Joint Action activity (e.g. update of website prevalence tables for all congenital anomaly subgroups, how many EUROCAT registries provided data to enable this?, was this achieved annually as planned?).

Process evaluation will be internally conducted by the Project Management Committee and the Steering Committee.

2. Effect Evaluation

Effect evaluation relates to evaluation of the outcome and impact during the period of the EUROCAT Joint Action and for a five year period predating commencement of the EUROCAT Joint Action.

Outcome indicators measure the intermediate results generated by the EUROCAT Joint Action outputs (e.g. improvement in Data Quality Indicators in EUROCAT registries).

Impact indicators measure the quality and quantity of long-term results generated by the EUROCAT Joint Action output (e.g. citations of EUROCAT prevalence data/published papers).

Methods of effect evaluation:

(a) Citation Tracking

Citation tracking (of peer-reviewed journal publications) will be performed in preparation of the final report, using Scopus Citation Tracker (SciVerse). Publications to be tracked include:
1. A selection of collaborative key peer-reviewed journal publications published as a result of activity undertaken by the EUROCAT Network during the last funding contract (2007-2010)

- Boyd P, Haeusler M and Barisic I (2011). EUROCAT Report 9: Surveillance of Congenital Anomalies in Europe 1980-2008. Birth Defects Research (Part A). 91: S1
- Boyd P, Barisic I, Haeusler M, Loane M, Garne E and Dolk H (2011). Paper 1: The EUROCAT network: organization and processes. Birth Defects Research (Part A). 91: 2-15.
- Khoshnood B, Greenlees R, Loane M, Dolk H, EUROCAT Project Management Committee and EUROCAT Working Group (2011). Paper 2: EUROCAT public health indicators for congenital anomalies in Europe. Birth Defects Research (Part A). 91: S16-S22.
- Loane M, Dolk H, Garne E, Greenlees R and EUROCAT Working Group (2011). Paper 3: EUROCAT Data Quality Indicators for population-based registries of congenital anomalies. Birth Defects Research (Part A). 91: S23-S30.
- Loane M, Dolk H, Kelly A, Teljeur C, Greenlees R, Densem J and EUROCAT Working Group (2011). Paper 4: EUROCAT Statistical Monitoring: Identification of ten year trends of congenital anomalies in Europe. Birth Defects Research (Part A). 91: S31-S43.
- Garne E, Dolk H, Loane M, Wellesley D, Barisic I, Calzolari E and Densem J (2011). Paper 5: Surveillance of multiple congenital anomalies: implementation of a computer algorithm in European registers for classification of cases. Birth Defects Research (Part A). 91: S44-S50.

- Greenlees R, Neville A, Addor M-C, Amar E, Arriola L, Bakker M, Boyd P, Calzolari E, Doray B, Draper E, Vollset S E, Garne E, Gatt M, Haeusler M, Kallen K, Khoshnood B, Latos- Bielenska A, Martinez-Frias M-L, Materna-Kiryluk A, Dias C M, McDonnell R, Mullaney C, Nelen V, O'Mahony M, Pierini A, Queisser-Luft A, Randrianaivo-Ranjatoelina H, Rankin J, Rissmann A, Ritvanen A, Salvador J, Sipek A, Tucker D, Verellen-Dumoulin C, Wellesley D and Wertelecki W (2011). Paper 6: EUROCAT member registries: organization and activities. *Birth Defects Research (Part A)*. 91: S51-S100.
- Jentink J, Loane M, Dolk H, Barisic I, Garne E, Morris J, de Jong-van den Berg L and EUROCAT Antiepileptic Study Working Group (2010). Valproic acid monotherapy in pregnancy and major congenital malformations. *The New England Journal of Medicine*. 362: (23). 2185-2193.
- Jentink J, Dolk H, Loane M, Morris J, Wellesley D, Garne E, de Jong-van den Berg L and EUROCAT Antiepileptic Study Working Group (2010). Intrauterine exposure to carbamazepine and specific congenital malformations: systematic review and case-control study. *British Medical Journal*. 341: C6581
- Dolk H, Jentink J, Loane M, Morris J, de Jong-van den Berg L and EUROCAT Antiepileptic Drug Working Group (2008). Does Lamotrigine use in pregnancy increase orofacial cleft risk relative to other malformations. *Neurology*. 71: 714-722.
- Dolk H, Loane M, Garne E and EUROCAT Working Group (2011). Congenital heart defects in Europe: Prevalence and perinatal mortality, 2000 to 2005. *Circulation*. 123: 841-849.
- Best KE, Tennant P, Addor M-C, Bianchi F, Boyd P, Calzolari E, Dias C M, Doray B, Draper E, Garne E, Gatt M, Greenlees R, Haeusler M, Khoshnood B, McDonnell R, Mullaney C, Nelen V, Randrianaivo-Ranjatoelina H, Rissmann A, Salvador J, Tucker D, Wellesley D and Rankin J (2012). Epidemiology of small intestinal atresia in Europe: a register-based study. *Archives of Disease in Childhood - Fetal and Neonatal Edition*. 97: F353-F358.
- Garne E, Loane M, Dolk H, Barisic I, Addor M-C, Arriola L, Bakker M, Calzolari E, Dias C M, Doray B, Gatt M, Klungsoyr Melve K, Nelen V, O'Mahony M, Pierini A, Randrianaivo-Ranjatoelina H, Rankin J, Rissmann A, Tucker D, Verellen-Dumoulin C and Wiesel A (2012). Spectrum of congenital anomalies in pregnancies with pregestational diabetes. *Birth Defects Research (Part A)*. 94: 134-140.
- Khoshnood B, Loane M, Garne E, Addor M-C, Arriola L, Bakker M, Barisic I, Bianca S, Boyd P, Calzolari E, Doray B, Draper E, Gatt M, Haeusler M, Klungsoyr Melve K, Latos- Bielenska A, McDonnell R, Mullaney C, Nelen V, O'Mahony M, Pierini A, Queisser-Luft A, Randrianaivo-Ranjatoelina H, Rankin J, Rissmann A, Salvador J, Tucker D, Verellen-Dumoulin C, Wellesley D, Zymak-Zakutnya, N and Dolk H (2012). Recent decrease in the prevalence of congenital heart defects in Europe. *Journal of Pediatrics*. 162: (1). 108-113.
- Pedersen R, Calzolari E, Husby S, Garne E and EUROCAT Working Group (2012). Oesophageal atresia: prevalence, prenatal diagnosis and associated anomalies in 23 European regions. *Archives of Disease in Childhood*. 97: 227-232.
- Wellesley D, Dolk H, Boyd P, Greenlees R, Haeusler M, Nelen V, Garne E, Khoshnood B, Doray B, Rissmann A, Mullaney C, Calzolari E, Bakker M, Salvador J, Addor M-C, Draper E, Rankin J and Tucker D (2012). Rare chromosome abnormalities, prevalence and prenatal diagnosis rates from population based congenital anomaly registers in Europe. *European Journal of Human Genetics*. 20: (5). 521-526.

- Boyd P, Loane M, Garne E, Khoshnood B, Dolk H and EUROCAT Working Group (2011). Sex chromosome trisomies in Europe: prevalence, prenatal detection and outcome of pregnancy. *European Journal of Human Genetics*. 19: 231-234.
- Loane M, Dolk H, Morris J and EUROCAT Working Group (2009). Maternal age-specific risk of non-chromosomal anomalies. *British Journal of Gynaecology*. 116: 1111-1119.

2. All peer-reviewed journal publications that have arisen as a result of activity undertaken by the EUROCAT Network during the Joint Action (2011-2013)

3. EUROCAT Guide 1.3 is extensively cited in peer-reviewed publications. As this document is made available on the EUROCAT website, there are no formal mechanisms to trace citation of this document. We will conduct web-based searches to determine the breadth and reach of the citation profile of EUROCAT Guide 1.3. We will also rely on members of the EUROCAT Network to inform us of citations of EUROCAT Guide 1.3.

(b) Google Analytics

Google analytics will be employed to determine the visitor profile to the EUROCAT website between 2010 and 2013 (e.g. number of returning and new visitors).

(c) Website Tables Registration

EUROCAT Central Registry traces and profiles use of the website tables (since registration began in March 2012) by tracking the number of registrations by country and by type and the number of website table reports generated. An overview of website table registration will be provided in the final evaluation report.

(d) External Enquiries/Feedback

EUROCAT Central Registry logs external enquiries or feedback regarding EUROCAT data and/or activity - An overview of those received during the time period of the EUROCAT Joint Action will be provided in the final evaluation report.

(e) Media Interest

EUROCAT Central Registry makes an effort to trace reference to EUROCAT data/activity in the media – An overview of which will be provided in the final evaluation report.

(f) Web-based Evaluation Survey

EUROCAT is obtaining constructive feedback (January 2013 through December 2013) about its website and other outputs via a web-based evaluation survey tool (of 10 short questions taking no longer than 10 minutes to complete) in order to determine if EUROCAT is reaching its intended user and if EUROCAT's output is appropriate for that user.

In addition to a pop-up invitation to take the survey upon visiting the EUROCAT website, a link to the survey has been disseminated via the EUROCAT Central Registry mailing list (that continues to be updated throughout the timeframe of the EUROCAT Joint Action) and the EUROCAT newsletter. EUROCAT Central Registry will encourage further dissemination of the survey link by the broader EUROCAT membership via reminders in EUROCAT communication emails and via an evaluation strategy presentation at the final EUROCAT Registry Leader's Meeting in June 2013.

Results from the web-based evaluation survey will be included as part of the final evaluation report.

(g) Evaluation of EUROCAT Symposiums

The Antwerp based symposium (in June 2011) was evaluated by E-mail questionnaire. The Zagreb based symposium (in June 2013) will also be evaluated by E-mail questionnaire. Summaries of both evaluations will be included in the final evaluation report.

(h) Independent Evaluation

A questionnaire (created by an external subcontractor and accessed via an online survey tool) will be employed to focus on perception of “value” of the EUROCAT outputs/outcomes by targeted end-users (split across 3 evaluation panels).

Members of all three evaluation panels will have to provide their email addresses and agree to have their names published in the evaluation report, but all responses will remain anonymised.

Evaluation Panel 1 - Each Registry Leader will respond to the questionnaire and will be asked to identify 4 additional respondents (within their country/region) and confirm their intent to participate and provide the following information to the independent evaluator via Central Registry. Those registries/countries that have established National Committees will use them where possible.

Registry:				
Respondent Group	Name	Role	Affiliation	Email
Registry Leader				
Public Health Authority				
Clinician				
Patient/Patient Organisation				
Department of Health – Rare Diseases (e.g. EUCERD rep)				

Evaluation Panel 2 – will consist of representatives from WHO, Europe (DG Sanco/EAHC), EMA, EUROPERISTAT, EURORDIS, Orphanet, and Professional Societies.

Evaluation Panel 3 – will consist of proactive volunteers identified by putting a request out via the EUROCAT Central Registry emailing database.

Annex 12: EUROCAT Website Evaluation Survey



INTRODUCTION

EUROCAT will finish its current Joint Action contract with the EU Public Health Programme (2008-2013) in December 2013.

The purpose of EUROCAT's dissemination activity is to raise awareness of the importance of congenital anomaly registries and databases coordinated at European level, on the possibilities that they offer in terms of collecting data, coding and classification of rare disorders, public health planning, primary prevention, and research in the field of congenital anomalies. The purpose of the dissemination activity is also to raise the profile of the EUROCAT network, and to gain wider support for the setting up congenital anomaly registries across Europe. The results of the EUROCAT Joint action will serve to inform and educate the wider community on the importance of prevention strategies for congenital anomalies. Through dissemination of the EUROCAT Joint Action results we would like to actively engage the community in relation to improving the health status of women of childbearing age.

EUROCAT wishes to obtain constructive feedback about its website and other outputs in order to determine if we are reaching our intended user and if our output is appropriate for that user. You are likely to be in receipt of this survey because you accessed the EUROCAT website, or you have been identified by EUROCAT or an associate of EUROCAT as a target user. We welcome the opportunity to gain a better understanding of your expectations of and opinions on EUROCAT. This questionnaire (of 10 short questions) should take no longer than 10 minutes to complete.

The results of the website evaluation survey will be made publically available on the EUROCAT website by February 2014.

WE THANK YOU IN ADVANCE OF YOUR PARTICIPATION.

1. Which professional or user perspective represents your interest in EUROCAT?

- Affected person or parent of affected person
- National government official with responsibility for public health or health services
- National government official with responsibility for rare diseases
- National government official with responsibility for environment
- Regional or municipal government or health authority official
- European Commission, WHO or other international organisation official

- Hospital or health service manager
- Paediatrician
- Obstetrician
- Medical geneticist
- Nurse
- Midwife
- Public health or epidemiology academic
- Other academic
- Pharmacovigilance officer within industry
- Student
- Other (please specify)

2. Which country do you live in?

3. Which one or more of the following topics is relevant to you?

- Prevalence of congenital anomalies
- Causes and primary prevention of congenital anomalies
- Prenatal screening for congenital anomalies
- Other (please specify)

4. Which one or more types of congenital anomalies are of particular interest to you in terms of your need for information from EUROCAT?

- Congenital heart defects
- Neural tube defects
- Orofacial clefts
- Chromosomal including Down syndrome
- Genetic syndromes
- Abdominal wall defects (e.g. gastroschisis)
- Limb defects
- Other (please specify)

5. Which one or more of the following risk factors for congenital anomaly are of particular interest to you in terms of your need for information from EUROCAT?

- Folic acid
- Medicinal drug exposures during pregnancy
- Environmental pollutants
- Genetic factors
- None of the above
- Other (please specify)

6. Please rate how useful you have found the following outputs from EUROCAT in the period 2011-2013:

	very useful	useful	not useful	did not know about it	not relevant to me
Interactive Website Prevalence Tables	<input type="radio"/>				
Website Prenatal Diagnosis Tables	<input type="radio"/>				
Website Perinatal Mortality Tables/Key Public Health Indicators	<input type="radio"/>				
Annual Statistical Monitoring Reports concerning time trends and clusters	<input type="radio"/>				
Guide 1.3/1.4: Instruction for the registration of congenital anomalies	<input type="radio"/>				
EUROCAT Special Report (2012): Congenital Anomalies are a Major Group of Mainly Rare Diseases	<input type="radio"/>				
EUROCAT Publication List	<input type="radio"/>				
EUROCAT Newsletter (if you would like to receive the Newsletter please include your email address below)	<input type="radio"/>				

7. Have you received information about one or more EUROCAT member registries in your country?

- Yes
- No
- Not applicable

8. Do you know about the European Scientific Symposium on the Prevention of Congenital Anomalies which EUROCAT organises every two years?

- Yes, I participated in Antwerp, Belgium (2011) or Zagreb, Croatia (2013)
- No, but I would like to find out more and perhaps participate in future (if so please provide your email address below)
- I would not be interested or able to participate

9. Do you find the EUROCAT Website easy to use?

- Yes
- No (if no please specify why)

10. Please give any further comments you may have about EUROCAT. In particular what information you would like to see on the EUROCAT website.

Annex 13: Coverage of the European Population, Birth Year 2010, by EUROCAT Full or Associate Member Registries

Country	EUROCAT Registry	Year started EUROCAT data transmission	Annual Births 2010, Registry	Annual Births 2010, Country ¹	% Country Covered
EU					
EU (Present EU Member States)			1,588,051	5,361,874	29.6
Belgium	Antwerp	1990	21,445		
	Hainaut	1980	12,403		
	Total		33,848	126,827	26.7
Bulgaria				75,637	0.0
Czech Republic	Czech Republic ^{2,3}	2000	117,153	117,153	100.0
Denmark	Odense	1980	5,059	63,096	8.0
Germany	Mainz	1990	3,168		
	Saxony-Anhalt	1987	17,363		
	Total		20,531	678,959	3.0
Estonia				15,813	0.0
Ireland	Cork & Kerry	1996	10,248*		
	Dublin	1980	27,815*		
	South East	1997	7,969*		
	Total		46,032	73,720	62.4
Greece				114,182	0.0
Spain	Barcelona	1992	14,862*		
	Basque Country	1990	21,246		
	Spain Hospital Network ²	1980	87,086		
	Valencia Region	2007	51,739		
	Total		174,933	482,885	36.2
France	French West Indies	2009	10,456		
	Isle de la Reunion	2002	14,543*		
	Paris	1981	27,400		
	Rhone-Alpes ²	2006	60,083		
	Strasbourg	1982	13,239*		
	Total		125,721	834,559	15.1
Italy	Emilia Romagna	1981	42,154		
	Tuscany	1980	30,836		
	Total		72,990	561,165	13.0
Cyprus				9,959	0.0

Latvia				19,336	0.0
Lithuania				35,954	0.0
Luxembourg				5,824	0.0
Hungary	Hungary ³	1998	90,722	90,722	100.0
Malta	Malta ³	1986	4,036	4,036	100.0
Netherlands	Northern	1981	17,569	183,982	9.5
Austria	Styria	1985	10,442	78,728	13.3
Poland	Wielkopolska	1999	40,396		
	Rest of Poland ^{2, 3}	1999	371,811		
	Total		412,207	412,207	100.0
Portugal	South	1990	21,202	101,058	21.0
Romania				212,476	0.0
Slovenia				22,312	0.0
Slovakia				60,217	0.0
Finland	Finland ^{2, 3}	1993	61,161	61,161	100.0
Sweden	Sweden ^{2, 3}	2001	114,480	114,890	99.6
UK	E Mid & S York	1998	75,698		
	Northern England	2000	34,461		
	South West England	2005	51,328		
	Thames Valley	1991	31,321		
	Wales	1998	36,142		
	Wessex	1994	31,135		
	Total		260,085	806,351	32.3
Non EU					
<i>Candidate countries in EUROCAT</i>					
Croatia	Zagreb	1983	6,870*	43,372	15.8
<i>EFTA countries in EUROCAT</i>					
Norway	Norway ³	1980	62,770	62,770	100.0
Switzerland	Vaud	1989	8,169	80,194	10.2
Ukraine	Ukraine ⁴	2005	31,094	494,408	6.3

¹ Source: EUROSTAT crude birth rate (accessed 06-03-2012)

http://epp.eurostat.ec.europa.eu/portal/page/portal/population/data/main_tables

² Associate EUROCAT Registries (transmit aggregate data only)

³ Source of annual births in country provided by registry rather than EUROSTAT

⁴ http://www.ukrstat.gov.ua/operativ/operativ2010/ds/kn/kn_e/kn1210_e.html (accessed 12-03-2012)

*Provisional estimated figures provided by the registry

Annex 14: Prevalence rates (including and excluding chromosomal cases) for all EUROCAT anomaly subgroups, 2006-2010, all full member registries

Anomaly	LB N	FD N	TOPFA N	LB+FD+TOPFA N	LB+FD+TOPFA Rate	Excluding Chromosomal	
						LB+FD+TOPFA N	LB+FD+TOPFA Rate
All Anomalies	86957	1872	17336	106165	255.08	91020	218.69
Nervous system	5134	396	4752	10282	24.7	9381	22.54
Neural Tube Defects	1036	157	2781	3974	9.55	3824	9.19
Anencephalus and similar	121	93	1242	1456	3.5	1423	3.42
Encephalocele	141	19	340	500	1.2	479	1.15
Spina Bifida	774	45	1199	2018	4.85	1922	4.62
Hydrocephalus	1372	94	972	2438	5.86	2225	5.35
Microcephaly	958	43	68	1069	2.58	977	2.36
Arhinencephaly/holoprosencephaly	118	33	393	544	1.31	367	0.88
Eye	1590	15	97	1702	4.09	1562	3.75
Anophthalmos/microphthalmos	359	8	59	426	1.02	363	0.87
Anophthalmos	71	4	24	99	0.24	89	0.21
Congenital cataract	500	1	4	505	1.21	479	1.15
Congenital glaucoma	153	0	1	154	0.37	151	0.36
Ear, face and neck	703	22	105	830	1.99	732	1.76
Anotia	122	2	13	137	0.33	126	0.3
Congenital heart defects	30410	487	2600	33497	80.48	29981	72.04
Severe CHD §	6844	225	1432	8501	20.43	7139	17.15
Common arterial truncus	200	15	82	297	0.71	266	0.64
Transposition of great vessels	1300	13	134	1447	3.48	1404	3.37
Single ventricle	200	11	117	328	0.79	308	0.74
Ventricular septal defect	13359	146	673	14178	34.07	12840	30.85
Atrial septal defect	9435	39	153	9627	23.13	8705	20.92
Atrioventricular septal defect	1186	71	354	1611	3.87	721	1.73
Tetralogy of Fallot	1173	23	151	1347	3.24	1194	2.87
Tricuspid atresia and stenosis	177	9	43	229	0.55	217	0.52

Anomaly	LB N	FD N	TOPFA N	LB+FD+TOPFA N	LB+FD+TOPFA Rate	Excluding Chromosomal	
						LB+FD+TOPFA N	LB+FD+TOPFA Rate
Ebstein's anomaly	148	18	27	193	0.46	186	0.45
Pulmonary valve stenosis	1609	4	43	1656	3.98	1605	3.86
Pulmonary valve atresia	319	7	102	428	1.03	396	0.95
Aortic valve atresia/stenosis §	468	7	39	514	1.23	492	1.18
Hypoplastic left heart	641	42	444	1127	2.71	1043	2.51
Hypoplastic right heart §	130	9	60	199	0.48	184	0.44
Coarctation of aorta	1424	22	80	1526	3.67	1389	3.34
Total anomalous pulm venous return	243	1	17	261	0.63	247	0.59
PDA as only CHD in term infants (>=37 weeks)	1581	1	0	1582	3.8	1454	3.49
Respiratory	1956	131	548	2635	6.33	2368	5.69
Choanal atresia	333	6	10	349	0.84	319	0.77
Cystic adenomatous mal of lung §	303	5	41	349	0.84	346	0.83
Oro-facial clefts	5509	82	534	6125	14.72	5711	13.72
Cleft lip with or without palate	3269	59	395	3723	8.95	3445	8.28
Cleft palate	2240	23	139	2402	5.77	2266	5.44
Digestive system	6356	165	863	7384	17.74	6743	16.2
Oesophageal atresia with or without tracheo-oesophageal fistula	928	30	66	1024	2.46	944	2.27
Duodenal atresia or stenosis	496	22	25	543	1.3	392	0.94
Atresia or stenosis of other parts of small intestine	366	4	12	382	0.92	372	0.89
Ano-rectal atresia and stenosis	1032	28	231	1291	3.1	1207	2.9
Hirschsprung's disease	519	0	1	520	1.25	479	1.15
Atresia of bile ducts	105	1	4	110	0.26	107	0.26
Annular pancreas	66	0	5	71	0.17	55	0.13
Diaphragmatic hernia	885	43	239	1167	2.8	1064	2.56

Anomaly	LB N	FD N	TOPFA N	LB+FD+TOPFA N	LB+FD+TOPFA Rate	Excluding Chromosomal	
						LB+FD+TOPFA N	LB+FD+TOPFA Rate
Abdominal wall defects	1548	129	971	2648	6.36	2270	5.45
Gastroschisis	980	45	176	1201	2.89	1180	2.84
Omphalocele	487	76	658	1221	2.93	875	2.1
Urinary	11876	240	1787	13903	33.4	13312	31.98
Bilateral renal agenesis including Potter syndrome	116	40	336	492	1.18	479	1.15
Renal dysplasia	1309	41	365	1715	4.12	1645	3.95
Congenital hydronephrosis	3972	38	204	4214	10.13	4067	9.77
Bladder exstrophy and/or epispadia	222	3	52	277	0.67	271	0.65
Posterior urethral valve and/or prune belly	296	3	93	392	0.94	379	0.91
Genital	8936	59	253	9248	22.22	9048	21.74
Hypospadias	7466	18	37	7521	18.07	7449	17.9
Indeterminate sex	213	15	57	285	0.68	254	0.61
Limb	15360	282	1524	17166	41.24	16316	39.2
Limb reduction	1486	90	586	2162	5.19	2016	4.84
Upper limb reduction	1055	61	403	1519	3.65	1411	3.39
Lower limb reduction	504	42	284	830	1.99	780	1.87
Complete absence of a limb	19	8	56	83	0.2	83	0.2
Club foot - talipes equinovarus	3912	87	435	4434	10.65	4240	10.19
Hip dislocation and/or dysplasia	3249	4	4	3257	7.83	3222	7.74
Polydactyly	3473	41	208	3722	8.94	3516	8.45
Syndactyly	1985	36	113	2134	5.13	2011	4.83
Skeletal dysplasias §	354	21	359	734	1.76	726	1.74
Craniosynostosis	828	7	36	871	2.09	829	1.99
Congenital constriction bands/amniotic band	105	23	96	224	0.54	221	0.53
Situs inversus	193	4	58	255	0.61	250	0.6

Anomaly	LB N	FD N	TOPFA N	LB+FD+TOPFA N	LB+FD+TOPFA Rate	Excluding Chromosomal	
						LB+FD+TOPFA N	LB+FD+TOPFA Rate
Conjoined twins	11	8	61	80	0.19	80	0.19
Congenital skin disorders	643	7	32	682	1.64	651	1.56
Teratogenic syndromes with malformations §	416	27	80	523	1.26	517	1.24
Fetal alcohol syndrome §	188	3	6	197	0.47	196	0.47
Valproate syndrome §	27	0	2	29	0.07	28	0.07
Maternal infections resulting in malformations	160	19	60	239	0.57	237	0.57
Genetic syndromes + microdeletions	1602	50	306	1958	4.7	1882	4.52
Sequences	594	55	315	964	2.32	935	2.25
Chromosomal	6165	591	8389	15145	36.39	0	0
Down Syndrome	4055	215	4533	8803	21.15	0	0
Patau syndrome/trisomy 13	161	42	636	839	2.02	0	0
Edwards syndrome/trisomy 18	347	154	1555	2056	4.94	0	0
Turner syndrome	258	64	593	915	2.2	0	0
Klinefelter syndrome	186	9	129	324	0.78	0	0

LB= Livebirth

FD= Fetal death from 20 weeks gestation

TOPFA= Termination of Pregnancy following prenatal diagnosis of a congenital anomaly



EUROCAT Statistical Monitoring Report – 2010 Executive Summary

(Uploaded to EUROCAT website January 2013)

EUROCAT Central Registry
University of Ulster
Newtownabbey, Co Antrim
Northern Ireland, BT37 0QB

Tel: +44 28 9036 6639
Fax: +44 28 9036 8341
Email: eurocat@ulster.ac.uk
Web: www.eurocat-network.eu

EUROCAT Joint Action 2011-2013 is funded by the Public Health Programme 2008-2013 of the European Commission

WHO Collaborating Centre for the Surveillance of Congenital Anomalies



EUROCAT 2010 Statistical Monitoring of Congenital Anomalies: Key Findings

Congenital anomalies are a leading cause of fetal death, infant mortality and morbidity in childhood. EUROCAT is a European network of population-based registries with the general objective of supporting the reduction of the public health burden of congenital anomalies by conducting coordinated epidemiological surveillance.

EUROCAT annually performs statistical monitoring for both trends and clusters in time in order to detect signals of new or increasing teratogenic exposures and monitor progress in the prevention of congenital anomalies. Total prevalence rates of 81 subgroups of congenital anomalies, including all cases of livebirths, stillbirths and late fetal deaths from 20 weeks gestational age, and terminations of pregnancy for fetal anomaly are monitored and reported. This report concerns the ten year period 2001-2010, including data from 24 EUROCAT registries. In the period 2001-2010, 82% of cases notified to the registries were liveborn, 2% were stillborn and 16% were terminations of pregnancy for fetal anomaly.

Our key findings concentrate on the pan-European analysis, which gives a snapshot of the situation in Europe. Within the main report, information on trends in the rates of congenital anomalies in individual registries is also presented.

Key findings

- In this year's pan-Europe analysis a *decreasing* trend was identified for **Neural tube defects (NTDs)** which declined on average by 1.7% per year to 9.42 per 10,000 births in 2009-2010. In particular, rates for **Spina bifida** declined on average by 2.1% per year to 4.67 in 2009-2010. The decreasing pan-Europe trend for NTDs suggests that public health measures, such as folic acid supplementation are becoming effective. However the decline has been shallow, and mainly occurred in the first half of the decade.
- Congenital heart defects (CHD) account for a third of all congenital anomaly cases. A *decreasing* trend was detected for the subgroup **CHD overall** which decreased on average by 0.6% per year to 62.37 per 10,000 births in 2009-2010. **Ventricular septal defect (VSD) and Atrial septal defect (ASD)**, the most common and less severe types of CHD, both decreased; Potential explanations for the decline in CHD include folic acid supplementation and better management of maternal illness or

decline in maternal smoking. However, *increasing* trends were detected in some of the more severe types of CHD with **Tetralogy of Fallot**, a type of cyanotic congenital heart defect increasing on average by 2.3% per year to 3.26 per 10,000 births 2009-2010, and **Single ventricle** increasing on average by 5.9% per year to 0.74 per 10,000 births in 2009-2010.

- *Increasing* trends were found for several subgroups of digestive anomalies: **Oesophageal atresia with or without trachea-oesophageal fistula, Duodenal atresia and stenosis, Atresia and Stenosis of other parts of the small intestine.** The rare digestive system anomaly **Atresia of the bile ducts (biliary atresia)** *declined* markedly by an average of 9% per year to 0.17 per 10,000 births in 2009-2010. Maternal infective causes have been suggested as aetiological factors for biliary atresia.
- For the fourth consecutive year of pan-Europe monitoring an *increasing* trend was observed for the abdominal wall defect **Gastroschisis**, a rare type of defect that requires corrective surgery at birth. An average increase of 1.6 % per year was detected, with average rates rising to 2.87 per 10,000 births in 2009-2010. The largest increase in rates occurred in the early part of the decade. Gastroschisis is associated with risk factors such as low socioeconomic status (SES), young maternal age, low maternal body mass index (BMI) and maternal smoking. Four out of five registries with the highest prevalence rates for this anomaly were located in the UK. More directed action, particularly in the UK, is needed to address this public health concern.
- There was an *increasing* trend for the very rare anomaly **Complete absence of a limb**, with rates increasing on average by 7.8% per year to 0.22 per 10,000 births in 2009-2010. However this occurred in the context of a *decreasing* trend for **Upper limb reduction**. The data are being validated to make sure that this is not a classification problem.
- As in the previous report the three main chromosomal trisomy syndromes *increased* in prevalence. **Down syndrome/trisomy 21** increased on average by 1.1% per year to 22.38, **Patau syndrome/trisomy 13** by 2.4% per year to 2.09 and **Edward syndrome/trisomy 18** by 2.3% per year to 5.56 per 10,000 births in 2009-2010.

Following adjustment for maternal age these trends were no longer present, indicating that increases in trisomy syndromes in general are associated with rises in the proportion of women delaying child birth until later in life.

Clusters

Whilst the cluster analysis did not identify any clusters thought to be of immediate concern, a number (n=8) could not be explained by information held within the registries. The registries reported that these clusters, identified in the period 2009-2010, would remain under surveillance.

Conclusion

The statistical monitoring of trends and clusters is fundamental to the primary prevention of congenital anomalies, providing timely information on the stability and change in rates. Primary prevention of congenital anomalies continues to be a key objective of the EUROCAT network, and is reflected in the current ethos of the Joint Action between the European Union and Member States.

Annex 16: Data on medication using ATC codes up to 2010

	Registry	Comments
1.	Hainaut	Up to 2004
2.	Odense	Up to 2010
3.	Paris	Up to 2010
4.	Tuscany	Up to 2010
5.	Dublin	From 2005 to 2010 (some codes – mostly 3 digits)
6.	N Netherlands	Up to 2010
7.	Emilia Romagna	Up to 2010
8.	Strasbourg	Up to 2007 (behind in data transmission)
9.	Switzerland	Up to 2010
10.	Zagreb	Up to 2010
11.	Malta	Up to 2009 (behind in data transmission)
12.	S Portugal	From 2005 to 2010 (data seems poor – 3 digit codes only)
13.	Antwerp	Up to 2010
14.	Basque Country	From 2005 to 2010
15.	Saxony Anhalt	Up to 2010
16.	Mainz	Up to 2010
17.	Styria	No drugs before 2009. Some listed in 2009
18.	Cork & Kerry*	Up to 2009 (behind in data transmission)
19.	Wales	Up to 2010
20.	Norway	Up to 2010
21.	Ukraine	From 2005 to 2010. Quality never assessed
22.	Reunion	From 2006 to 2010. Quality never assessed
23.	Wielkopolska	Up to 2010
24.	Thames Valley	No drugs
25.	Wessex	No drugs
26.	E Midlands & S Yorkshire	No drugs
27.	Northern England	No drugs
28.	Hungary	No drugs
29.	SE Ireland	From 2005 to 2010. Quality never assessed.
30.	French West Indies	Up to 2010. Data looks very good
31.	South West England	No drugs
32.	Valencia	Up to 2010. Data quality never assessed