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 1-12

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 djecje 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 Nazional "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 Pubic 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 39 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 co-ordinated 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 first funding period of the current Joint Action contract: January to December 2011.

Workpackage progress

WP1: Coordination
• Registry Leaders Meeting held June 2011
• New financial management system created
• Election of new Steering Committee members June 2011

WP2: Dissemination
• Dissemination plan created
• Leaflet and newsletter distributed
• 11th European Symposium on Congenital Anomalies, Antwerp, June 17th 2011, with 232 participants from 25 countries
• Work has begun on establishing National EUROCAT Committees
• 20 peer reviewed publications and 28 conference presentations
• EUROCAT contributed factsheets to the launch of the International Federation for Spina Bifida and Bayer Healthcare Pharmaceutical's second report "Act against Europe's most common birth defects: one year on. Defining Neural Tube Defect prevention strategies in Europe".

WP3: Evaluation

Tender specification being created

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 33 registries updated to 2009, including 3 new registries (French West Indies, Valencia, SW England).
  - Prevalence data updated to 2006-8 for 6 registries
  - Data on proportion of cases prenatally diagnosed transmitted by 21 registries
- Revisions to EDMP/ECD software made, including to statistical monitoring module
- Registry Advisory Service
  - held workshop at Registry Leaders Meeting
  - developed applicant process flowchart for website
  - liaised with new and applicant registries (i.e. Valencia, Slovakia, Latvia)
- Statistical monitoring for trends and clusters over time conducted to include year 2009

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 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
- A pilot of proposed new variables for the EUROCAT dataset is in progress
- Revisions to data quality indicators have been proposed

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, and included in Annual Statistical Monitoring Report
- Task Force for Evaluation of Clusters set up and mandate agreed.
- A paper on vaccination policy for swine flu in European countries was published, and a systematic review of influenza and its association with congenital anomalies, and analysis of seasonality of congenital anomalies is ongoing (PhD project).

• Analysis of the implications of the rise in multiple births for congenital anomalies in Europe is ongoing (PhD project)
• Data files have been formally requested/ issued for investigation of gastroschisis and Hirschsprung disease
• A paper on trends in congenital heart disease has been submitted for publication
• A case-control study protocol for congenital heart disease has been submitted for funding
• A protocol for study of air pollution and congenital anomalies is under development, and the first pilot is ongoing
• A protocol for investigating pollution "hotspots" is under development

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.

• An inventory of primary prevention measures has been completed
• A questionnaire on folic acid policy in EU member states has been distributed to EUROCAT and EUCERD members
• A questionnaire on other primary prevention measures has been developed ready for distribution

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.

• Protocol submitted for analysis of EUROCAT database with regard to Down Syndrome and cardiac anomalies
• Epidemiological analyses of three syndromes: Beckwith Wiedemann, Oculo-auriculo-vertebral spectrum and Fraser presented at conferences or submitted as peer reviewed papers

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.

• Data quality evaluation on medication exposure is ongoing
• Pilot signal detection work is ongoing
• A study of SSRI exposure and congenital anomalies is ongoing (PhD project)
• The third update of a study of lamotrigine exposure and congenital anomalies was completed, and presented at a conference

Key epidemiologic surveillance results

Prevalence and prenatal diagnosis of EUROCAT congenital anomaly subgroups

For births 2005-9, the prevalence for of all congenital anomalies (registries combined) was 255.3 per 10,000 births.

- Chromosomal anomalies 14.2% of all anomalies
- Congenital heart defects 32.9% of all anomalies
- Neural tube defects 4.3% of all anomalise

Overall, 40% of non-chromosomal anomalies and 72% of chromosomal anomalies were prenatally diagnosed, varying by type of anomaly.

- Proportion of prenatal diagnosis varied by registry, from 17% to 59% for non-chromosomal anomalies, and from 8% to 90% for chromosomal anomalies
- The rate of TOPFA for all anomalies varied between registries from 0.42 to 10.26 per 1,000 births

Trends and clusters over time

A number of anomalies increased in prevalence over the period 2000-2009

- Gastroschisis increased by 29%, which requires investigation and action by national public health authorities
- Down Syndrome increased by 5%, mainly due to increasing maternal age
- Edward and Patau syndrome increased by 36% and 18% respectively, mainly due to increasing maternal age

A number of anomalies decreased in prevalence over the period 2000-2009

- Neural tube defects decreased by 10%
- Severe Congenital heart defects decreased by 19%

No new clusters of immediate concern were identified.

New exposures

A survey of H1N1 vaccination policies and their implementation in EU countries for pregnant women showed considerable variation in whether and when vaccination campaigns were initiated, and whether pregnant women in their first trimester, the sensitive period in case of unforeseen teratogenic effects, were included.

Syndrome prevalence

- Beckwith Wiedemann syndrome (BWS) is a rare congenital condition with prevalence of 1.45 per 100,000 or 1 in 69,930 births. As much as 2/3 of patients with BWS have associated major malformations. Most (86%) survive the first week of life.
- Oculoauriculovertebral spectrum (OAVS) is a phenotypically and genetically heterogeneous disorder grouping together different conditions thought to be caused by impaired development of the first and second branchial arches. We have established that the prevalence of the classical form of OAVS is 2.07 per 100 000 or 1 in 48,309 pregnancies. An excess of twinning and use of assisted reproductive techniques was observed among the analysed cases.
- Fraser syndrome is an ultra-rare autosomal recessive disorder with the prevalence of 0.20 per 100,000 or 1:495,633 births and high rate of consanguinity (27%). Most cases of Fraser syndrome (85%) are suspected prenatally often due to the presence of the association of renal agenesis and cryptophthalmos. In European population, a high proportion (82%) of pregnancies is terminated, thus reducing the live birth prevalence to a third of the total prevalence rate.

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	**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. 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.	**Process Indicators** Successful annual data transmission to Central registry from all Associate Partner Registries. **Output Indicators** Prevalence tables for 95 anomaly subgroups on the EUROCAT website, updated each year. **Outcome Indicators** Citations of EUROCAT prevalence information.	4, 5 and 6
2	**Network expansion and data quality improvement** - To co-ordinate the establishment of new registries throughout	**Process Indicators** Integration of Latvia, Slovenia and	4 and 5

	Europe collecting comparable, standardised data. The integration of new registries and countries allows the sharing of knowledge 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. 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.	Valencia as new Full Members of EUROCAT, with successful data transmission. Submission of revised ICD11 proposal to WHO. **Outcome Indicators** Improvement in Data Quality Indicators in two thirds of Registries.	
3	**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. 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.	**Process Indicators** Improvement in number of Registries meeting earliest data transmission deadline. **Output Indicators** Annual Statistical Monitoring Reports. Five in-depth investigations, including one by TEC and one of swine-flu impact. Environmental data linkage feasibility report. **Outcome Indicators** Generation and preliminary investigation of clusters/trends in each registry.	6
4	**Primary prevention policy** - To make recommendations for the inclusion of primary prevention of CA in national rare disease	**Output Indicators** Report on public health actions	7

	plans and to evaluate the effectiveness of existing primary prevention measures. A focus will be folic acid but this objective will 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. 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.	relevant to prevention of BD at EU MS level. Report on actions to prevent NTD by raising folic acid status at EU MS level. Report on potential consensus approach toward inclusion of primary prevention actions in national plans on RD.	
5	**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. Analysis of central database (enhanced with additional DS registry data) on genetic syndromes.	**Process Indicators** Integration of England and Wales NDSCR into central database. **Output Indicators** Expansion of prenatal diagnosis tables on EUROCAT website. **Outcome Indicators** Publication of 6 genetic syndrome papers.	8
6	**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. Analysis of medication exposure (ATC coded) in central database, prescription data linkage and protocol development.	**Process Indicators** 3 Workshops on quality of medication exposure data. Joint meeting with ISPE and ENTIS. **Output Indicators** 3 scientific papers. **Outcome Indicators** Protocol for early warning of drug-malformation associations.	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 - 26th EUROCAT Registry Leader's Meeting (RLM)	Milestone 3 of WP1	Month 6	Month 6	Meeting took place in Antwerp. Meeting minutes and presentations made available to network.		
	Activity 2 – Organisation of Project Management Committee Meetings		3 within reporting period	Months 1, 6, 11	3 meetings took place and meeting minutes were made available to network.		
	Activity 3 – Maintenance of EUROCAT website		Months 1-12	Months 1-12	Continuously reviewed and updated, currently relevant to the Joint Action with related improvements (i.e. new online Budget Management System for Associate Partners)		
	Activity 4 – Financial Management		Months 1-12	Months 1-12	Implementation of new online Budget Management System (EBS) to report budget for 1st reporting period	Minor logistical problems. 2 Associate Partners did not engage with EBS and therefore will not receive 2nd pre-payment	Logistical problems overcome with administrative support by coordinating partner. Coordinating partner will liaise with affected associate partners in an effort to prevent reoccurrence.
	Activity 5 – Reports to and liaison with Executive Agency and DGSanco	Milestone 1 of WP1 – 1st Interim Report	Months12	Month 17	1st Interim Report submitted	Date of achievement is anticipated to be after date foreseen as we have to delay until after the reporting period has been completed.	
	Activity 6 – Administrative support to all work packages		Months 1-12	Months 1-12	Met the needs of all WPs in reporting period		
	Activity 7 – Overall project management and co-ordination tasks		Months 1-12	Months 1-12	Met the needs of all WPs in reporting period	Delay in getting project manager in post	Project manager in post from Month 5
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,	Dissemination plan Milestone 5 of	Month 3 Month 3	Month 3 Month 3	Dissemination plan available and agreed by PMC.	Tracing dissemination of the Newsletter and Promotional Leaflet Detailed dissemination	

	contacts with media, promotional leaflet, use of website and newsletters (WP leader in discussion with Project Management Group). At the first meeting, a new promotional leaflet will be finalised.	WP2 (Promotional Leaflet)				list (i.e. emailing database) is still being 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				EUCERD Meeting (see WP5) and appointment of liaison officers		
	Activity 4 - Facilitation of national EUROCAT Committees or equivalent				Baseline survey complete		
	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	Tracing dissemination of the Newsletter and Promotional Leaflet Detailed dissemination list (i.e. emailing database) is still being finalised	
	Activity 7 - Organisation of European Symposium on Prevention of Congenital Anomalies - Antwerp 2011, Zagreb 2013	Milestone 4 of WP2 – 1st European Symposium	Month 6	Month 6	Meeting took place and evaluation complete and available on meeting website		
3	Evaluation WP						
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 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	Month 12	Month 12 (added to website Month 13)	Output indicator – annual statistical monitoring report Outcome indicator – generation and preliminary investigation of clusters/trends in each registry		
	Activity 3 - Develop statistical monitoring methods		Months 1-12	Months 1-12	Revised protocol, internally available		
	Activity 4 - Perinatal mortality						
	Activity 5 - Registry advisory service for new registries		Months 1-12	Months 1-12	Registry Advisory Service workshop held at registry leaders meeting, in addition to individual contact throughout the year with new and applicant registries		
5	Activity 1 - EUROCAT coding and classification Committee	Milestone 1 of WP5 - meetings	5 by Month 30	2 by Month 12	n/a		
	Activity 2 - ICD11			Month 10	ICD11 Chapter submission to Orphanet		
	Activity 3 - Surveillance of cases with multiple congenital anomalies						
	Activity 4 - Revision of Guide 1.3 to Guide 1.4						
	Activity 5 - Revision of Data Quality Indicators	Milestone 4 of WP5 – Publication of revised set of	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	

		DQI on website					
6	Activity 1 - Annual Statistical Monitoring	Milestone 1 of WP6 – Annual Statistical Monitoring Report	Month 12	Month 12 (added to website Month 13)	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)				Formed and mandate agreed (see Annex 10)		
	Activity 3 - Response to swine flu epidemic				Paper published (see Annex 6)		
	Activity 4 - Investigation of specific trends of - Hypospadias (UMCG) - Multiple births with congenital anomaly (UU) - Gastroschisis (ULEIC) - Hirschsprungs (UNEW)						
	Activity 5 - Investigation of Epidemiology of Congenital Heart Disease - Trends in prevalence of CHD (INSERMU953) - Epidemiology of selected CHD (Hospital Lillebaelt) - Case-control study protocol (UU)				Paper submitted Paper submitted Protocol submitted for funding		
	Activity 6 - Actions towards European environmental surveillance						
7	A To collect and review public health actions relevant to primary prevention of birth defects at level of A.1 pre- and peri-conceptional 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	Milestone 1 and 2 of WP7	Month 12		Achieved collection of public health actions relevant to prevention of birth defects Achieved collection of actions to prevent Neural Tube Defects by raising folic acid status	Reduction in personnel of WP leader associate partner, due to need to reduce the budget for this associate partner lead to some pressure on scheduling of WP7 activities.	

	counselling in collaboration with WP8; 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, 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. To do this a protocol needed to be written and the data formally requested from the registries	Protocol written			submitted to EUROCAT and approved		
	Activity 2. Prevalence of Down syndrome - To include the NDSCR data for England and Wales in EUROCAT website epidemiological tables						
	Activity 3. Prevalence of genetic syndromes	Data received from			Fraser paper submitted to the American Journal of		

		registries/Data cleaned and coded/Data analysed/Paper written			Medical Genetics		
	Activity 4. Review of prenatal diagnosis tables						
9	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 1 of WP9 – First annual workshop on ATC Coding	Month 6	Month 6	ATC workshop attended		
	2. Prescription data linkage - Identify national + regional available prescription data sources for use by registries (UMCG); Conduct + evaluate pilot linkage studies (UMCG).						
	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).				Protocol approved and pilot study underway Poster presentation at 20th World Congress of Neurology		
	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)						

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 one 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) and the President of the EUROCAT Association, as well as all work package leaders and the Project Manager detailed below.

Steering Committee
- Prof. Lorentz Irgens (Norway), President of the EUROCAT Association
- Prof. Eliza Calzolari (Emilia Romagna, Italy, IMER)
- Prof. Martin Haeusler (Styria, Austria, SFR) until June 2011
- Dr. Babak Khoshnood (Paris, France, INSERM U953)
- Dr. Vera Nelen (Antwerp, Belgium, PIH) until June 2011
- Dr. Diana Wellesley (Wessex, UK, SUHT)
- Prof. Ingeborg Barisic (Zagreb, Croatia, KDB) from June 2011

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 Lorentz Irgens) and elects four/five Steering Committee members.

Activity 1 - 26th EUROCAT Registry Leader's Meeting (RLM)

The 26th EUROCAT RLM was held in Antwerp, Belgium (14th - 16th June 2011) **and was the first milestone scheduled to be reached by WP1** (Month 6). Administrative support for the RLM was provided by both the main partner (UU) and the hosting partner (PIH). This meeting was attended by 37 RLs, by 29 local registry staff, by 9 Central Registry staff and doctoral students, and by 2 other external guests. Each associate partner was represented at the meeting. The participants list and agenda are detailed in Annex 1. The RLM was minuted and the minutes were made available to all associate partners through the member's only section of the EUROCAT website. During the 26th EUROCAT RLM the following workshops and committee meetings were held – Coding Committee Meeting, Air Pollution Meeting, Website Dissemination Committee Meeting, Medication During Pregnancy Meeting, Registry Advisory Workshop, ATC Coding Workshop, EDMP Clinic, EUROCAT Budget System workshop, EUROCAT Member's Forum Workshop, Statistical Monitoring Methods Subgroup Meeting.

Activity 2 – Organisation of Project Management Committee Meetings
The Project Management Committee (and separately the Steering Committee) met three times within the reporting period. Firstly on the 24th – 25th January 2011 (Luxembourg), then on the 15th June 2011 during the RLM (Antwerp, Belgium), and most recently on the 9th-10th November 2011 (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/symposium, management of PMC meeting arrangements, posting of relevant announcements which have included new publications, the RLM/Symposium, EUROCAT's central registries designation as a WHO Collaborating Centre as well as other dissemination announcements (i.e. inviting comment on the ICD11 proposal for developmental anomalies (relevant to WP5). A registration system for access to online tables has been in development during the reporting period for implementation in 2012.

Activity 4 – Financial Management
The main partner (UU) has implemented a secure, confidential and password protected online budget management system (EBS), accessible to members only through the EUROCAT website that enables 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 is making registries more aware of what they agreed to do for the contract and made 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. It is anticipated that it will be easier to distribute the interim payments – those who do not reply get their interim payments deferred until the final payment.

During the reporting period, one grant agreement amendment concerning a change of budget has been submitted to the Executive Agency. A decision is pending.

Associate partner 15 (ISS), WP7 leader, advised that a reduction in budget would be necessary. When the Italian National Centre for Rare Diseases (ISS) submitted the original version of WP7 (for the EU Commission), Prof. Garaci (President of the ISS) sent concurrently an official letter to the Italian Ministry of Health to obtain the co-funding in order to fully participate to the Joint Action EUROCAT 2011-2013. The Italian Ministry of Health could not provide sufficient funds to co-finance this project and ISS did not have the requested funds to co-finance the cost of the CNMR action plan and the related activities. As a result ISS asked for what they determined to be a sensible decrease of the total budget and a corresponding reduction in the amount due by the institution as a contribution.

The project manager based in the main partner institute (Rhonda Curran) attended an EHAC workshop on the Preparation of Final Payments on 14 November 2011.

Activity 5 – Reports to and liaison with Executive Agency and DGSanco
Compilation of the 1st 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
There was a delay in recruiting the Project Manager who was not in post until May 3rd 2011.
There was a delay in submission of the first 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 12 activities.
There were minor problems associated with the introduction of the EBS, including (i) associate partners putting up expenditure without attaching receipts – the policy has always been "no receipt no reimbursement", (ii) two associate partners did not engage at all with the EBS – Strasbourg and Poland, (iii) minor logistical problems – such as "bugs" on the system, putting expenditure into the wrong categories e.g. taxis in travel when they should have been in subsistence etc.
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.
For problems associated with WP7 leader budget reduction described above see WP7 report.

How were problems resolved
The Project Leader supported by Central Registry and the PMC adopted a Project Manager role until the Project Manager was in place. Procedures have been put in place to begin collation of report contributions earlier. We propose to amend date foreseen for delivery of 2nd Interim Report.

Associate partners that did not engage with the EBS have been made aware that their second pre-payment will be deferred. The coordinating partner will remain in communication with both partners involved to try and ensure this does not reoccur at the end of the second reporting period.

Activities planned for the next period
The next Registry Leaders Meeting (milestone 4 of WP1), in Budapest, Hungary, is planned for the 14-15th June 2012 (Month 18) with pre-meetings on the 13th 2012.

A PMC meeting has been scheduled for March 2012 (in Oxford) and in June 2012 (in Budapest). A third PMC meeting will be arranged (venue and Month still to be confirmed).

The second interim report with financial statements (Milestone 2 of WP1) is in planning for Month 24 (subject to change, see above in problems resolved).

As part of the website management activity it is planned to launch a new publication management system on the website within the next reporting period.

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 (please attach as Annex 2)**

Description of the activities undertaken

- stakeholder analysis / target group identification

We have identified different target groups that could benefit from the results of the EUROCAT Joint Action. The important group of stakeholders are health professionals with interest in congenital anomalies. Those are paediatricians, obstetricians, paediatric and foetal pathologists, medical geneticists, genetic counsellors and midwives, and other professionals actively involved in the care of children with congenital anomalies and/or pregnant women/families with risk for congenital disorders. Other important groups of stakeholders are public health professionals and those involved in health service planning at regional, national, EU and WHO levels. The deliverables of this Joint Action are also of special interest for governmental/public regulation agencies in different domains (industrial, air quality, environmental protection agencies, food and drug administration), patient organizations, scientific research community (area: epidemiology and public health, clinical genetics, embryology, etc.), politicians and policy makers.

- dissemination content

The key elements of the project content we plan to disseminate to each of the potential user groups identified are the main outcomes of WP4-9 of the EUROCAT Joint Action.

1) The availability of epidemiological information on congenital anomalies, including prevalence, birth outcomes, perinatal mortality and prenatal detection rates on the EUROCAT website (www.eurocat-network.eu)

2) The usefulness of the sustainable surveillance and prevention policy for congenital anomalies in Europe

3) The results of the investigation of clusters and trends in congenital anomaly prevalence during the EUROCAT Joint Action. Establishment of the Task Force for Evaluation of Clusters (TEC) for rapid response to public concern

4) The results of the investigation of new teratogenic exposures (swine flu, maternal illnesses)

5) Benefits of the linkage of registries of congenital anomalies with other electronic information systems in Europe (European pollution information system, prescription databases)

6) The importance of inclusion of the strategies for primary prevention for congenital anomalies in the National plans for rare diseases

7) Impact of delayed childbearing and changes in prenatal screening policies and techniques on congenital anomalies, especially on Down syndrome

8) Establishment of the pregnancy-related pharmacovigillance system in Europe (EUROmediCAT)

9) Importance of the congenital anomaly registries for public health planning and research

- dissemination means

1. Website – (See WP1, Activity 3 - Maintenance of the EUROCAT website). In addition, we have established a Website Dissemination Committee in order to improve the content and display of data on the website. The website tables have been totally redesigned during the reporting period and the new designs will be implemented in 2012.

Members of the Website Dissemination Committee

•Inbegorg Barisic (Chair)
•Elisa Calzolari
•Rhonda Curran
•Helen Dolk
•Ester Garne
•Ruth Greenlees
•Lorentz Irgens
•Babak Khoshnood
•Maria Loane
•Bob McDonnell
•Joan Morris
•Diana Wellesley

Committee Objectives: to improve the existing version of the EUROCAT webpage, to discuss changes, to co-ordinate the process and prepare final versions for presentation at PMC meetings.

2. Promotional leaflet – electronic version available for download on the EUROCAT website and a print version was produced (See Annex 3)

3. Newsletter – electronic version (See Annex 4)

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

5. Workshops (See WP1, Activity 1 and Annex 1)

6. 11th European Symposium on Congenital Anomalies, Antwerp, June 17th 2011

Together with the province of Antwerp, EUROCAT hosted successfully the 11th EUROCAT Symposium on Congenital Anomalies in Antwerp, Belgium, 17th June 2011. The objectives of the symposium were to share experiences in the prevention, registration and care of congenital anomalies. Main topics were preconceptional and prenatal care, environmental risks for congenital anomalies and long term outcome of children with a congenital anomaly. The symposium hosted a series of keynote presentations. Prof. Yves Jacquemyn of Antwerp University Hospital presented ways to improve prenatal diagnosis in the 21st century, Prof. Eric Steegers from Erasmus MC presented program on preconception care with highest priority given to ethnic minorities and couples with a low socioeconomic status. Dr. Gillian Hawthorne from Newcastle Primary Care Trust presented national strategy to improve the uptake and delivery of preconception care in diabetic women. Dr. Greet Schoeters of the University of Antwerp presented on biomarkers associated with prenatal chemical exposures

that could result in foetal damage. Dr. Christof Schaefer from the Universitätsmedizin Berlin presented on the preliminary results of the study on possible adverse pregnancy outcomes after swine flu vaccination. Dr. Bert Suys of the Congenital and Paediatric Cardiology University Hospital Leuven presented on lifelong medical care for grown-up patients with congenital heart disease, and Prof. Judith Rankin of the Institute of Health & Society, Newcastle University, presented estimates for survival for a range of congenital anomaly subtypes. Dr. Nasser Nadjmi of the Craniofacial Association Antwerp presented on therapy protocol and outcome of schisis patients in Antwerp. Abstracts of keynote presentations can be found on the EUROCAT website. Book of Abstracts is published as a supplement of the journal Facts, Views and Vision in ObGyn. All 40 abstracts can be found on the symposium website www.Eurocat2011.com. The symposium was attended by 232 participants from 25 countries. Participants came mainly from Belgium, the UK and the Netherlands but also from other European countries, Saudi Arabia and Canada.

7. Networking

Based on the aims of liaison with other networks (1. exploring possibilities of joint projects; 2. exchange of information, experience and expertise, 3. integration of Joint Action outcomes into the work of these bodies), UMCG partner (Marian Bakker) has proposed Liaison officer strategy with other networks, organisations and committees that was presented and adopted at the PMC Meeting, November 2011. For each network a tailor-made strategy was developed by the liaison officers, including e.g. invitations to RLMs, the organisation of joint symposia, presentations of EUROCAT studies at symposia organized by the networks, updates on network activities on PMC agenda 'news from other networks', exchange of newsletters etc. EUROCAT representatives met with EURORDIS and EUCERD representatives respectively during the reporting period (Domenica Taruscio in Amsterdam and Ester Garne - See WP5 report).

8. National EUROCAT Committees

During 2011 we have advocated the establishment of National EUROCAT Committees (NEC) or equivalent with representation from registries, Ministries of Health, patient groups and professional associations. The role of NECs is to advise and support EUROCAT registries in the achievement of their objectives through assistance in contacts with local key stakeholders and media and general presentation of EUROCAT Joint Action outcomes. At present we have collected information from 27/36 (75%) EUROCAT Joint Action associate partners. Of those, 13 (48%), mostly those from large countries, are part of the associations that can be considered as National Committees for congenital anomalies or rare diseases registries. Some of them are newly established for EUROCAT Joint Action purposes. Another 8 partners are in the process of forming National Committees (from Spain, Germany, and Croatia).

9. Conference Presentations and Posters

See full list in Annex 5.

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

See full list in Annex 6. It is important to note that some of the listed publications are continued dissemination of the last action's results, continued after submission of the final report.

In addition EUROCAT recently contributed to and was represented in Brussels on the 29th June 2011, at the launch of the International Federation for Spina Bifida and Bayer Healthcare Pharmaceutical's (in collaboration with EASPD, EFCNI, EURORDIS and MediClara) second

report “Act against Europe’s most common birth defects: one year on. Defining Neural Tube Defect prevention strategies in Europe”. EUROCAT authored a factsheet within the report entitled “Prevalence of Neural Tube Defects in Europe” and provided data for a second factsheet entitled “Terminating pregnancies is not prevention of Neural Tube Defects: With adequate maternal folate levels the same child may be born without a disability”. This report contributes to public policy debate and the European Commission has already uploaded the report on its website, under the rare diseases section. You can find the report here under the ‘latest updates’ at: http://ec.europa.eu/health/rare_diseases/policy/index_en.htm and a direct link is available at: http://ec.europa.eu/health/rare_diseases/docs/ntd_report_2011_en.pdf .

Problems encountered
There were delays in collecting updated information on activities from liaison officers and partners concerning networking and National EUROCAT Committees.
The full emailing database for dissemination is still being updated.
Difficulty in tracing dissemination of the newsletter and leaflet.

How were problems resolved
Periodical reports for PMC meetings are now required for these two activities.
The main partner is currently coordinating an update of the emailing database in conjunction with associate partners.

Activities planned for the next period
- During the June 2012 RLM we plan to organise a Workshop for the Website Dissemination Committee. Updating options for the website will be discussed.
- Collaboration with other networks will continue as planned in the strategy with regular reports on activities by liaisons officers at PMC meetings.
- At the next RLM we will encourage registries to take action for setting up NEC. It is planned that the Irish registry presents their experience at the general assembly. We will ask periodical reports for PMC meetings about a) establishment of new NECs b) activities of the existing NECs. We can expect that by the end of 2012 about 60% of the registries will have NEC.
- Organisation of the 12th European Symposium on Congenital Anomalies, Croatia 2013.
- New website table designs for perinatal mortality, prenatal diagnosis and indicators will be introduced.

WP3: Evaluation of the project

Evaluation plan available □ **no** □

Description of the activities undertaken
The Main Partner is currently developing a tender specification document for the University of Ulster’s procurement office.

Problems encountered

How were problems resolved

Activities planned for the next period
Initiation of the tender process and procurement of an independent evaluator (subcontracted).

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 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 is continually being 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. A new version of ECD was released in 2011 which automatically calculates EUROCAT Data Quality Indicators, increasing efficiency as these were manually calculated in the past. Also in 2011, a new development in ECD allows a case file of potentially multiple malformed cases (using EUROCAT algorithm) to be uploaded to a secure web-based system for review by a panel of geneticists. Only information necessary for the geneticists to reach a decision on each case is included in the data upload. The geneticists confirm or correct cases wrongly classified as "multiple" by the algorithm. Finally, in 2011, ECD and EDMP were amended to:

- allow 7 digit Anatomical Therapeutic Chemical (ATC) drug codes to be entered for cases born before 2005 (instead of the old EUROCAT 2-digit drug code)
- allow 5 drug codes to be entered for cases born before 2005 (the old version only allowed 3 drug codes to be entered)
- allow 2 ILLNESS BEFORE variables to be entered for cases born before 2005 (the old version only had 1 ILLNESS BEFORE variable).

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 March each year. In 2011, a new "summary" graph showing the average annual percentage change in prevalence for all anomaly subgroups at pan-Europe level was produced. Full details are found in the Statistical Monitoring Protocol http://www.eurocat-network.eu/content/Stat-Mon-Report-2009.pdf

3. Develop statistical monitoring methods

The statistical monitoring methodology continues to be refined. In 2011, we developed and tested statistical methods to allow for increases in maternal age and changes in prenatal screening for trisomy 18 and trisomy 13. We have provided new fetal loss up to 20 weeks gestational age and maternal age adjustments for both trisomies. These new developments will be implemented in year 2012. In addition, the graphs showing average annual percentage change in prevalence will be available by registry and by anomaly. The criteria for presenting an increasing or decreasing trend were altered; previously if there was a significant variation from a linear trend a significant trend was not reported; now if there is a monotonic increase of decrease in prevalence over the period then the significant trend will be reported despite the presence of significant variation from linearity. Finally, work is ongoing into the effect of incomplete data transmission and coding changes during the monitoring period which may affect the results generated by statistical monitoring.

4. Perinatal Mortality

Work has not yet begun on validating and analysing EUROCAT perinatal mortality data. A meeting with EURO-PERISTAT to discuss collaboration and conduct joint work on perinatal and infant mortality due to congenital anomalies is planned in March 2012.

5. Registry Advisory Service (RAS) for new registries

Organisation of workshop on EUROCAT methodology and coding held on June 15, 2011 in Antwerp, Belgium. The workshop was attended by 12 participants from different EU countries including new/ applicant members (Valencia, Slovakia and Latvia).
A one-year follow-up and evaluation of data collection was conducted for new applicant members Valencia, Hungary, Moldova and Slovenia (Collaborating Partner). Dr. Garne visited Valencia and evaluated the infrastructure and methodology. The reports have been discussed at the PMC meeting in Oxford 2011. Valencia and Hungary were granted full EUROCAT membership, while Moldova, Campania and Slovenia achieved Affiliate member status. Reports to Moldova and Campania have been sent with suggestions for improvement. Central Registry (R. Greenlees) has developed a Flowchart for the Applicant Process for achievement of Full or Associate EUROCAT member status. For inclusion as full EUROCAT member, a minimum prevalence for "all anomalies" was discussed at the PMC meeting in Oxford, October 2011. Contact with Latvia, Slovakia and Slovenia is ongoing and assistance with coding queries is provided by Central Registry and RAS members. The West Midlands registry in UK has expressed an interest in joining EUROCAT. National Centre for Disease Control and Public Health in Georgia has also expressed interest to collaborate with EUROCAT while setting up a birth defect registry in their country.

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-2009.pdf.

Coordination with other projects or activities
We are coordinating with EURO-PERISTAT 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.

Outcomes and deliverables achieved
1: Database related activities
Year 2009 data was uploaded to the website for the following 33 member registries: Styria (Austria); Antwerp, Hainaut (Belgium); Czech Republic; Zagreb (Croatia); Odense (Denmark); French West Indies, Ile de la Reunion, Paris, Rhone-Alpes, (France); Mainz, Saxony-Anhalt (Germany); Hungary; Dublin, SE Ireland (Ireland); Emilia Romagna, Tuscany (Italy); Malta; N Netherlands; Wielkopolska, Poland; South Portugal; Basque Country, Spain Hospital Network (Spain); Sweden; Vaud (Switzerland); Ukraine; East Midlands & South Yorkshire, Northern England, South West England, Thames Valley, Wales and Wessex (UK). Data up to year 2008 are available for the registries listed above and the following 2 registries Cork & Kerry (Ireland) and Norway. In addition, data up to year 2007 are available for Strasbourg (France), Barcelona and Valencia Region (Spain) and data up to year 2006 are available for Finland. Population coverage in 2010 is outlined in Annex 7.
In 2011, data was uploaded to the website for the first time for the following new registries: French West Indies (France), Valencia Region (Spain) and South West England. Hungary renewed data transmission after a lapse of several years.
For the 5 year time period 2005-2009, the prevalence of all congenital anomalies was 255.3 per 10,000 births and the prevalence of all non-chromosomal anomalies was 219.1 per 10,000 births. Congenital heart defects excluding chromosomal anomalies continues to account for almost one-third of these anomalies (32.9%), chromosomal anomalies accounted for 14.2% and neural tube defects (NTD) for 4.3% of all anomalies (see Annex 8).
Data on prenatal diagnosis (PD) 2005-2009 are available for the following 21 registries: Styria (Austria); Hainaut (Belgium); Zagreb (Croatia); Odense (Denmark); Ile de la Reunion, Paris (France); Mainz (Germany); SE Ireland; Emilia Romagna, Tuscany (Italy); Malta; N Netherlands; S Portugal; Basque Country (Spain); Vaud (Switzerland); Ukraine; East Midlands & South Yorkshire, Northern England, Thames Valley, Wales and Wessex (UK).
In summary:
- Overall, 40% of all non-chromosomal anomalies and 72% of chromosomal anomalies were prenatally diagnosed. The proportion prenatally diagnosed ranged from 43% of cases with transposition of great vessels to over 90% of anencephalus, gastroschisis and bilateral renal agenesis cases. Over 90% of trisomy 18 and 13 cases were prenatally diagnosed compared to 65% of trisomy 21 cases.
- The rates of prenatal diagnosis vary greatly between registries, ranging from 17% to 59% for all non-chromosomal anomalies and from 8% to 90% for chromosomal anomalies.
- The rate of TOPFA per 1,000 births for All Anomalies combined varied between registries from 0.43 – 10.26.

2: Statistical Monitoring

The EUROCAT Statistical Monitoring Report 2009 (http://www.eurocat-network.eu/content/Stat-Mon-Report-2009-Combined.pdf) describes statistical monitoring of both clusters and trends in Europe for the ten year period 2000-2009 (Annex 9). Key findings from the pan-Europe (all EUROCAT registries combined) analysis were:

- The prevalence of the abdominal wall defect gastroschisis increased by 29% from 2000-2001 to 2008-2009, with a consistently higher rate in the UK compared to the other European countries. Further studies are ongoing to investigate this phenomenon.
- Prevalence of chromosomal autosomal trisomies also increased over time:
  - Down syndrome/trisomy 21 increased by 5% from 2000-2001 to 2008-2009.
  - Edward syndrome/trisomy 18 increased by 36%
  - Patau syndrome/trisomy 13 increased by 18%

The increase in the prevalence of trisomy 21 was explained by the increase in older mothers giving birth. Work on maternal age and fetal loss adjustments into trisomies 18 and 13 are ongoing.

- Overall, the prevalence of all non-chromosomal anomalies decreased over time, with marked decreases found for the following congenital anomalies:
  - The prevalence of neural tube defects decreased by 10% and spina bifida by 19%
  - Severe congenital heart defects decreased by 19%

Problems encountered

Communication problems have been encountered with three of the collaborating partners (from Belarus, Cyprus, Russia).

How were problems resolved

The main partner will continue to try and re-establish contact. Each collaborating partner has been invited to attend the 2012 RLM to provide an update on their status as collaborating partners.

Activities planned for the next period

Implementation of new website tables

- In 2012, year 2010 data will be entered into the central database and uploaded to the website: http://www.eurocat-network.eu/accessprevalencedata/prevalencetables
- Upload Data Quality Indicators for years 2005-2009, in collaboration with WP5
- Update EUROCAT key public health indicator tables on website, in collaboration with WP2
- Conduct statistical monitoring 2001-2010 with data from registries that fulfil monitoring data criteria, in collaboration with WP6. Publish Statistical Monitoring Report 2010
- Continue to develop statistical monitoring methods i.e. develop robust methods of analysing data for a combination of registries
- Collaborate with EURO-PERISTAT to conduct joint work on perinatal and infant mortality due to congenital anomalies. Update perinatal mortality tables on website. A joint meeting with EURO-PERISTAT is planned for March 2012
- Continue to provide Registry Advisory Service to applicant members (Latvia, Slovenia and Slovakia) with the aim of becoming full members collecting and transmitting data by the end of 2013.
- Organise training workshops on EUROCAT methodology and coding at annual RLM meeting in Croatia
- Evaluate and report on the available infrastructure, methodology and data of applicant member

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
Members of Coding and Classification Committee
•Ester Garne (Chair)
•Ingeborg Barisic
•Elisa Calzolari
•Berenice Doray
•David Tucker
•Diana Wellesley
Committee Objectives: to improve coding and classification on congenital anomalies in Europe/EUROCAT and to ensure uniform coding of congenital anomalies in Europe/EUROCAT

Activity 1 - EUROCAT coding and classification Committee: Two meetings have been held in 2011: In Antwerp in June (½ day) and in Haarlem in September (1 day). At the June meeting several coding tips were written, a document with clinical definitions of the revised EUROCAT subgroups were approved and a table with prevalence of syndromes in Europe were discussed and agreed. At the Haarlem meeting a document with comments to the ICD11 proposal was discussed and written.
Coding queries from local registries have been answered throughout the year. After submission of data to Central Registry in February 2011 data from all registries were reviewed by Ester Garne. All registries received an email with comments and proposals for improving their coding of the congenital anomalies. The first dataset from Valencia received in autumn 2011 were reviewed and commented.

Activity 2 - ICD11: In July 2011 EUROCAT coding and classification committee received the first ICD11 draft for the chapter on developmental anomalies from Orphanet. Tasks for the review were distributed among the coding committee members and a meeting was held in Haarlem in September to discuss and write the response from EUROCAT. The final document was send to Orphanet on October 28th. Diana Wellesley and Ester Garne attended a meeting in Luxembourg on December 1st organised by EUCERD for discussion of the second draft of ICD11.

Activity 3 - Surveillance of cases with multiple congenital anomalies: a computer algorithm for classification of congenital anomalies followed by manual review of approx 10% of the cases has been developed. The task in this joint action is to implement the surveillance of multiple congenital anomalies using a website tool for manual classification of potential multiple cases and include the multiple cases as a subgroup in the statistical monitoring. The first output of cases was planned for month 3. Unfortunately this process has been delayed, see later

Activity 4 - Revision of Guide 1.3 to Guide 1.4: The variables in Guide 1.3 will be revised within this Joint Action. The first meeting in the Guide 1.4 committee was held in Haarlem in September. A list of new variables was agreed and revision of some of the existing variables was discussed. A pilot study of new variables has been carried out in six registries during the period of data collection for 2010. Results of the pilot study from the six registries have been received at Central Registry in February 2012.

Activity 5 - Revision of Data Quality Indicators: The DQI was developed in 2005. Over the years there have been many changes in the clinical world, which has outdated some of the existing DQI. A document describing the current status of the DQI and proposals for changes has been written by Ruth Greenlees and Ester Garne in summer 2011. This document was discussed at the PMC meeting in November and a revised set of DQI was agreed. The final document was ready in February 2012.

Methodology applied as planned
Yes, although the website tool for review of potential multiple anomalies is not in use yet.
Involvement of partners and target groups
The Coding and Classification committee has performed the first 2 tasks.
The Guide 1.4 Working Group is responsible for the work with the new variables
The surveillance of multiples and the revision of DQI have been done in collaboration between UU and Hospital Lillebaelt

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 first review of multiple malformed cases has been delayed (month 3)

Problems encountered
Programming for the website review of multiple congenital anomalies began in 2010 as planned and was presented at a subgroup meeting at the RLM in Dublin 2010 for comments. Changes were recommended. There was a delay in implementing the changes and piloting of the improved software as the programmer responsible for this task changed jobs and priority was given to other programming tasks i.e. automating the DQI, changes to the statistical monitoring and development of new drug variables. The software is now in place for surveillance of isolated and multiple anomalies

How were problems resolved - Please see above under problems

Activities planned for the next period
Coding Committee: meeting in March 2012 for comments on the third ICD11 draft. A meeting is planned at the RLM in June (multiple anomalies, exclusion of genetic cases in the statistical surveillance, and Guide 1.4 variables on classification)
ICD11: comments to be send to Orphanet on the third ICD11 draft and for further revisions send out in 2012. Ester Garne will attend a EUCERD workshop in September 2012 on coding of rare diseases
Surveillance of multiples: The 2010 cases with potential multiple anomalies will be uploaded for web review in April 2012. Uploading of the 2009 cases planned in autumn 2012 in order to be able to do surveillance over 3 years in spring 2013 after the 2011 data is received and reviewed.
Guide 1.4: the Guide 1.4 proposal to be discussed at the PMC in spring 2012 and presented at the RLM in June.
DQI: the first set of DQI after the revision will be made public at the RLM in June (this is the usual procedure of the annual versions of the DQI)

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

Description of the activities

Activity 1: Annual Statistical Monitoring

Trends and clusters are investigated by registries and reported on at the annual Registry Leaders Meeting, and an annual Statistical Monitoring Report is produced.

Investigation of clusters in the last 2 years (2008-2009) identified no clusters of immediate public health concern. The recently established Task Force for Evaluation of Clusters (TEC) under WP6 was involved in the evaluation of registry investigation reports into the clusters and trends identified by Statistical Monitoring.

Individual investigations are ongoing following creation of the statistical monitoring report. See WP4 report section 2.

Activity 2: Task Force for Evaluation of Clusters (TEC)
The task force convened for its first meeting in Bergen 12-13 May 2011.
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)

Telephone conferences were organized on 29 August 2011 and 19 October 2011.
The following issues were on the agenda of these meetings:
1 Mandate of the TEC. A mandate was discussed and adopted (See Annex 10).
2 An evaluation of the most recent output of the routinely conducted EUROCAT surveillance: The 2008 Report.
3 An in depth evaluation of clusters reported in the 2008 Report.

TEC will be involved in the evaluation of future EUROCAT surveillance reports and, on request, in ad hoc incidents related to potential clusters or potentially harmful exposure.

Activity 3: Response to swine flu epidemic
The 2010 births data for analysis of the swine flu epidemic will be transmitted to Central Registry in February 2012. Preparations were made for analysing these data by conducting a survey of vaccination policy in EU countries published as a paper in 2011 (See Annex ?), a systematic literature review of the association between influenza and congenital anomalies,

and by conducting an analysis of seasonality of congenital anomaly prevalence. All remaining parts will be submitted as scientific papers during 2012.

Activity 4: Investigation of specific trends of:
1. Hypospadias (UMCG)
We will investigate the trends prevalence of hypospadias in Europe, taking into account the type of hypospadias and the presence of associated anomalies. We plan to start with the study in the second half of 2012 and complete the study in the first half of 2013.

2. Multiple births with CA (UU)
A paper describing the public health implications of the rise in multiple births in Europe in terms of congenital anomalies was drafted and circulated to all participating EUROCAT registries for approval. It should be submitted for publication in early 2012. Analysis of data on Down Syndrome, including integration of data from the England and Wales (NDSCR) register was also conducted for submission for publication in mid 2012.

3. Gastroschisis (ULEIC)
This task is currently applying for access to the data from the EUROCAT registries for the gastroschisis study. Analyses will be undertaken in 2012.

4. Hirschprung (UNEW)
This project has begun and data has been received from the participating registers. The analysis will be undertaken in March/April 2012 and a paper will be submitted for publication later in 2012.

Activity 5: Investigation of Epidemiology of Congenital Heart Disease
1. Trends in prevalence of CHD (INSERM U953)
A paper on the trends in CHD was submitted to Journal of Pediatrics and is currently under revision. For the future, it is planned to follow-up on this analysis with a more specific trends analysis for certain individual CHD.

2. Epidemiology of selected CHD (Hospital Lillebaelt)
A paper on the epidemiology of Atrioventricular septal defects among infants in Europe has been submitted for publication (Christensen N, et al. "Atrioventricular septal defects among infants in Europe; A population based study of prevalence, associated anomalies and survival").

3. Case-control study protocol (UU)
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. Extra (charity) funding was applied for to implement this protocol with result due in April 2012.

Activity 6: Actions towards European environmental surveillance
During 2011 this task has been working on establishing protocols for the air pollution pilot study, and on carrying out a pilot study in the Barcelona area. 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., 2011). The group of registries interested in contributing to the pilot study (ASPB, CSISP, IFC-CNR, PIH, UNEW) met on 14th June 2011 in Antwerp to discuss feasibilities in each region. A first draft protocol was circulated on 13 December 2011

and will be further refined during 2012. The pilot study 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. The pilot report will detail these problems. In Barcelona the methodology for obtaining spatial and temporal estimates of air pollution and linking these to congenital anomaly cases and control births is currently being tested and a report of this will become available in 2012 for use in the other regions. In 2012 we will start the pilot study in the other regions.
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.

References
Vrijheid M, Martinez D, Manzanares S, Dadvand P, Schembari A, Rankin J, Nieuwenhuijsen M. Ambient air pollution and risk of congenital anomalies: a systematic review and meta-analysis. Environ Health Perspect. 2011 May;119(5):598-606. Epub 2010 Dec 3. Review.

Methodology applied as planned
Yes

Involvement of partners and target groups
See above

Outcomes and deliverables achieved

Annual statistical monitoring report (Milestone 1 of WP6), including indepth evaluation of clusters (outcome indicator).
Paper submissions and preparations described above.

Activities planned for the next period

Hypospadias Task 6.4.1. (See above)
Gastroschisis Task 6.4.3. (See above)

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).

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 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

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 given to investment in research on CA and 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 these goals, WP7 has 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.

PRELIMINARY PHASE (From February to May 2011)

1. Identification of general ISSUES related to primary prevention of CA: folic acid, maternal lifestyles, maternal diseases, medications, environmental, home and working exposures, genetic risks.
2. Reaching consensus on above listed ISSUES among all WP7 partners, the main partners and the coordinator of the JA (see next paragraph for details)
3. Establishing Working Groups (WGs) working on the identified ISSUES.

The selection of participants has been on the basis of specific expertise and interest (see next paragraph for details)

From September to October 2011:

The WGs prepared specific questions to be considered for their inclusion in the Questionnaires; questions were related to the following topics:

- Law, regulation, decree (national as well as local)
- Guidelines
- Recommendation
- Training for health professional
- Health educational initiatives, public campaign
- Governmental support, incentives

- CA primary prevention plan/strategy

Two questionnaires have been finalized:
- the first questionnaire (**Title: Policies for primary prevention of Neural Tube Defects (NTD) with Folic acid and folate**) aims to collect national policies and actions on FA and Folates (November 2011)
- the second questionnaire (**Title: Public Health Actions on Primary Prevention of CA**) aims to collect policies and actions related to other CA risk factors related to maternal lifestyles, infectious diseases, chronic diseases, medications, environmental, home and working conditions (December 2001).

The advanced draft of the "FA and folate" questionnaire has been sent by e-mail to all WP7 collaborating partners for reviews and comments (July 14, 2011). Contents and design of this questionnaire were discussed during September 2011. The final version of was approved in October 2011. We adapted Survey monkey to our needs (November 2011). We sent invitations (by e-mail) to participate in this survey to:
a) complete membership list of EUROCAT (68)
b) all EUCERD members (108).

The Survey was launched on November 8, 2011. The deadline was December 15, 2011.

From November to December 2011:
a first draft of the second questionnaire has been developed, collecting the contributions sent by each WG. The draft has been sent to all WP7 partners and to the coordinator of the JA for reviews and comments (December 2011).

Involvement of partners and target groups (Activity A)
An important role of the WP7 activities is to reinforce the construction of a network in EU Countries to exchange experiences regarding the activities, initiatives and best practices for the primary prevention of CA.

The final aim is to include CA primary prevention in National plans/strategies on Rare Diseases which should be in place by the end of 2013.

We facilitated the process of networking by
- developing the European survey;
- implementing the contents of the two questionnaires;
- involving EUROCAT Members
- involving EUCERD Members

The first phase of activities were the organization of specific Working Groups (WG) among WP7 partners, on the basis of their declaration of interest.

Seven specific ISSUES (to CA primary prevention) for seven WG were defined:

WG1 - Folic acid and related nutritional aspects
Domenica Taruscio (ISS) – WG Coordinator
Elisa Calzolari (IMER)
María Luisa Martínez-Frías (ASEREMAC)
Miriam Gatt (MCAR DHIR)
Anna Latos-Bielenska (PUMS)

WG2 - Maternal lifestyles
Coordinator Elisa Calzolari (IMER) – WG Coordinator
María Luisa Martínez-Frías (ASEREMAC)
Miriam Gatt (MCAR DHIR)
Berenice Doray (UDS)

WG3 - Chronic and infectious maternal conditions
Domenica Taruscio (ISS) - WG Coordinator

WG4 - Environment, home and workplace
Fabrizio Bianchi (IFC-CNR) - WG Coordinator
Domenica Taruscio (ISS)

WG5 - Drugs
Marian Bakker (UMCG) - WG Coordinator
Giocacchino Scarano (AO "G Rummo"),

WG6 - food safety
Domenica Taruscio (ISS) - WG Coordinator
Alberto Mantovani (ISS) - external scientific expert
Stefania Ruggeri (INRAN) - external scientific expert

WG 7 - Genetic factors and genetic counselling
Elisa Calzolari (IMER), WG Coordinator
Fabrizio Bianchi (IFC-CNR)
Giocacchino Scarano (AO "G Rummo")
Ingeborg Barisic (KDB)
Anna Latos -Bielenska (PUMS)
Berenice Doray (UDS)
Borut Peterlin (UMCL)

Coordination with other projects or activities (Activity A)
In collaboration with EUROPLAN project (www.europlanproject.eu), WP7 is highlighting CA primary prevention as an essential component of national plans/strategies for Rare Diseases in the EU – MS. Moreover, starting from March 2012 WP7, jointly with EUROPLAN activities, will facilitate this inclusion process.

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 2 preliminary results
Data on "FA and folate" has been collected from 18 UE MS and 4 non EU-MS. For some countries there was more than one respondent. Details are showed in Annex 9. Preliminary results show that 18 out of 22 countries have a recommendation on supplementation of FA in

the peri-conceptional period (Annex 10). 14 out of 22 countries have a recommendation elaborated by (or in collaboration with) Regional/National Governmental Body (Annex 11) . Details on "Recommendations on FA supplementation" reported by respondents are shown in Annex 10 and 11.

Problems encountered (Activity A)
The elaboration and finalization of the two questionnaires has been very laborious and quite complex.

Other operative problems encountered were:
1. First questionnaire: in the following countries Croatia, Czech Republic Germany, The Netherlands, United Kingdom and Spain, more than one respondent answered to the questionnaire.
This was an enriching resource for our survey as well as useful for quality control of collected data. However, we received divergent answers from the same Country.
2. Second questionnaire: the first draft of questionnaire has been considered too complex to be filled by a unique respondent in a country. In fact, according to WP7 partners, the respondent would have to spend many days to collect all information to respond rigorously to all proposed questions.

The WP leader associate partner also required a reduction in budget. When the Italian National Centre for Rare Diseases (ISS) submitted the original version of WP7 (for the EU Commission), Prof. Garaci (President of the ISS) sent concurrently an official letter to our Ministry of Health to obtain the co-funding in order to fully participate in the Joint Action EUROCAT 2011-2013. The Italian Ministry of Health could not provide sufficient funds to co-finance this project and ISS did not have the requested funds to co-finance the cost of the CNMR action plan and the related activities. Thereby, ISS asked a sensible decrease of the total budget that implies a corresponding reduction in the amount due by ISS as a contribution.

Description of ISS budget reduction
The budget was amended so that:
1. the staff were reduced from 5 to 2 public officials;
2. the contribution to travel and subsistence fixed cost for public officials was reduced consequently;
3. all costs for the staff become ISS contribution and all travel and subsistence costs becoming a EUROCAT expense.
Therefore, ISS is supporting the project costs through two public officials: 1 Director of Research and 1 Researcher.
Operation of WP7 activities was impacted slightly by reduction of personnel. In particular we have experienced delays in respect of our activities scheduled.
From the current perspective, we are working to achieve on time the WP7 milestones and deliverables planned in the project timetable.

How were problems resolved (Activity A)
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. Actually we are finalizing the second questionnaire and we are planning to launch this questionnaire by the end of March.
1. First questionnaire: in order to clarify the reasons for divergent answers, we are studying in depth the questionnaire evidences and references, as provided by respondents.

Following this experience, for the second questionnaire we agreed to identify only one respondent per country, who is willing to take the effort to contact others potential respondents.
2. Second questionnaire: we will perform a pilot study in March 2012; we will send the questionnaire to selected Countries (Italy, Spain, The Netherland and UK (pilot study).

Activities planned for the next period (Activity A)
The data collected with the first questionnaire will be validated and analyzed by M13. We are finalizing the second questionnaire and we will start the pilot study. We are evaluating several aspects of the process (see point 1 and 2 of previous paragraph) which need to be addressed before launching the second questionnaire. Starting from March 2012 jointly with EUROPLAN, we will facilitate the process to include CA primary prevention as an important part of national plans/strategies for Rare Diseases in the EU – MS.

Description of activity B
The actions on prevention of NTD by raising FA 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
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 folic acid intake and folate status in all European countries up to the end of 2011.
B.2 track prevalence rates of NTD through the registries through analysis of trends in the prevalence of NTD in Europe, 1991-2009.
B.3 approaches to assess knowledge and attitude toward FA of women in childbearing age
Knowledge and awareness toward folic acid were approached through a standardized questionnaire specifically developed to interview women during pregnancy or early after delivery. The questionnaire has been used in Tuscany region to perform a survey in 2002 and in 2010. The questionnaire includes items on source of information on folic acid,
folic acid in medical counselling, time of folic acid consumption, type of folic acid consumed, reasons of folic acid consumption, scientific knowledge on folic acid and other vitamins, knowledge on food rich of folic acid, knowledge on folic acid and congenital anomalies, knowledge on other risk factor for congenital anomalies, knowledge on recommendation of folic acid, information on present and previous pregnancies, personal data.

B.4 appraisal of strategies to monitor population folate status
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.
The main deliverable of the project will be a report including
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 and

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 an (pilot) implementation in the EUROCAT region NNL.
The report will be based on a review of the applicable scientific and policy literature and consultations with an expert advisory team.

Methodology applied as planned
B.1 Questionnaires in Activity A. The questionnaire was designed to update and expand upon the previous data reported in earlier official documents produced by EUROCAT and EFSA.
B.2. Analysis of trends in total and live birth prevalence of NTD for cases not associated with chromosomal anomalies. Separate analyses for anencephaly and spina bifida. Random-effects poisson models to take into account heterogeneity across registries. Use of splines to look at trends over different time intervals.
B.3. Analysis before/after a trend to check the changes of knowledge and awareness variables over time, registry by registry. The methodology will be similar to that used in Tuscany study: a standardized questionnaire specifically developed to interview women during pregnancy or early after delivery. It is suggested that the Registry partners largely follow the main points of the methodology and the questionnaire proposed, though adapting these to their own circumstances, realities and specific situation of country. Once this is done, in your own language, we will need you to send to us at the working group an English translation of all the elements you have adapted/ modified: it is very important that we centralise this information, so that we can share it to all the partners, and take it into account in any of the analyses and comparisons we will be undertaking.
B.4. Work planned to be conducted in second half of 2012 according to project plan

Involvement of partners and target groups
B.1. To develop and finalize the questionnaire we are involving all wp7 EUROCAT Members. To collect data by European countries we sent invitations to participate in this survey at complete membership list of EUROCAT (68) and all EUCERD members (108). A draft report with results of the survey will be circulated to all respondents that have participate the survey to confirm/validate data and information reported.
B.2. Team in charge of completing the task: Babak Khoshnood (INSERM), Maria Loane (UU), Helen Dolk (UU)- in collaboration with Hermien De Walle (UMCG)
B.3. Full and Associated EUROCAT members will be involved to define main topics of methodology and questionnaire in order to assess knowledge and attitude toward folic acid of women in childbearing age, country by country.
B.4. The draft report will be circulated to experts of a selected number (maximum five) of EUROCAT registries for initial comments on essential differences between countries/regions with respect to the conditions and prerequisites for implementation.

Outcomes and deliverables achieved
Presentation of preliminary analysis – EUROCAT Annual Meeting, Antwerp June 2012
The “folic acid and folate survey” results reflect the participation of 22 European countries (18 EU Member States a and 4 non EU Member States). For some countries there was more than one respondent (Croatia, Czech Republic, Germany, The Netherlands, United Kingdom and Spain). Contributions from EUROCAT Special Report (Prevention of NTD by periconceptional folic acid supplementation in Europe - Update version December 2009) refers to 21 European countries (17 EU Member States and 4 non EU Member States).

The EFSA Report (ESCO Report Prepared by EFSA Scientific Cooperation Working Group on Analysis of Risks and benefits of Fortification of Food with Folic Acid - Issued on 6th October 2009) presents a summary on recommendations for folic acid supplementation in 11 European countries (9 EU Member States and 2 non EU Member States). Integrating and comparing such data sets we performed in 26 European countries (9 EU Member States and 2 non EU Member States) an overview on the current practices and policies for congenital anomaly prevention with folic acid and folate.

Problems encountered
None.

Activities planned for the next period
Completion of analysis and presentation of final results at the EUROCAT Annual Meeting in Budapest, 2012
Completion of analysis of data collected by folic acid and folate survey.
Draft of the final report part 1 "Report on actions to prevent neural tube defetcs by raising folic acid status at EU MS level" will be circulated to all respondents that have participate to the survey to confirm/validate data and information reported.
MedicClara expects to finish the project within the next reporting period. The activities will include the formation of an advisory team, literature search and reviewing, consultations of the advisory team, draft reporting, EUROCAT consultation, final reporting.

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

1. DS and Cardiac anomalies: Protocol written and submitted for approval
2. Prevalence of Down syndrome: Preliminary plan for integration of England and Wales NDSCR into website tables
3. Prevalence of genetic syndromes
4. Review of prenatal diagnosis tables

Methodology applied as planned

Yes

Involvement of partners and target groups

Yes partners involved

Coordination with other projects or activities

Coordinated with WP4

Outcomes and deliverables achieved

1. Protocol submitted for DS & Cardiac Anomalies
2. Prevalence of Down syndrome: No deliverables due yet
3. Genetic syndromes: First results on the Beckwith Wiedeman syndrome analysis were presented at the general Registry Leaders meeting, 15th June 2011 in Antwerpen, and as a poster presentation at the European Society of Human Genetics Conference in Amsterdam. Beckwith Wiedemann syndrome (BWS) is a rare congenital condition with prevalence of 1.45 per 100,000 or 1 in 69,930 births. As much as 2/3 of patients with BWS have associated major malformations. Most (86%) survive the first week of life. Data on prenatal diagnosis of Oculo-auriculo-vertebral spectrum (OAVS) were presented at the 11th EUROCAT Symposium on Congenital Anomalies in Antwerpen (see WP2 report). OAVS is a phenotypically and genetically heterogeneous disorder grouping together different conditions thought to be caused by impaired development of the first and second branchial arches. We have established that the prevalence of the classical form of OAVS is 2.07 per 100 000 or 1 in 48,309 pregnancies. An excess of twinning and use of assisted reproductive techniques was observed among the analysed cases. Paper: Fraser Syndrome: Epidemiological Study in a European Population has been submitted to the American Journal of Medical Genetics. Fraser syndrome is an ultra-rare autosomal recessive disorder with the prevalence of 0.20 per 100,000 or 1:495,633 births and high rate of consanguinity (27%). Most cases of Fraser syndrome (85%) are suspected prenatally often due to the presence of the association of renal agenesis and cryptophthalmos. In European population, a high proportion (82%) of pregnancies is terminated, thus reducing the live birth prevalence to a third of the total prevalence rate.
4. Review of prenatal diagnosis: New variable being trialled to see if it can be collected. No deliverables due yet

Problems encountered Delays over new prenatal diagnosis and Down syndrome website tables due to needing to revise other website tables first

How were problems resolved Other website tables have now been revised

Activities planned for the next period

1. DS and Cardiac Anomalies: data to be cleaned and analysed and paper written within 12 months of receipt of data
2. Prevalence of Down syndrome: Website tables including NDSCR data to be decided on and implemented on website within 12 months
3. Prevalence of genetic syndromes
4. Review of prenatal diagnosis: New variable to be collected by all registers
   Revised website tables to be decided and implemented on website within 12 months

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) + antidiabetics (RUG); compile report on information sources on maternal medication used by registries (RUG). At the Registry Leaders Meeting in Antwerp (June 2011) UMCG presented the evaluation of the data quality on medication use. Data from 21 registries were included. There was a high variability in the prevalence of medication use in pregnancy. Also a workshop on ATC coding was organized, in which the ATC system was explained and how to find the appropriate ATC code for the drug. To improve the data quality a new variable to clarify better whether the mother used medication in the first trimester is currently being piloted for Guide 1.4: First trimester medication use: yes / no / unknown. Following the results of the pilot testing a decision will be taken on this new variable, and whether or not to include an explanation on the usual sources consulted. In the new version of EDMP (issued Febr 2012) the possibility to add more than 5 medications was added.

A proposal for new DQI was discussed at the PMC meeting in November and 2 new DQI will be implemented on medication use:
1) Proportion of cases with first trimester medication use (compared to average)
2) Proportion of cases with unknown first trimester medication use (if this is a high % then we know that the registry will probably collect incomplete data)

Activity 2 - Prescription data linkage - Identify national + regional available prescription data sources for use by registries (UMCG); Conduct + evaluate pilot linkage studies (UMCG). A protocol for prescription data linkage is being developed under the EUROmediCAT project (FP7). As soon as this has finished and a software module has been developed, other registries will be asked if there are prescription databases in their country or region that could be linked to congenital anomaly registers, using this new software module.

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 are currently piloting a signal detection method in which they try 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.

3.1 SSRI study (UU)
The study protocol was presented at the 2010 RLM in Dublin. After the approval of the protocol by the PMC drug exposure data spanning 1990-2007 held at the Central Registry were evaluated and 12 registries meeting specified criteria for specific birth years were invited to participate in the study. Consent was received from these 12 registries. Preliminary results

presented at the 2011 RLM in Antwerp. In order to ascertain the sources of information for drug exposure among the women to the registries, and to understand the coding of drug exposure data by the registries, a questionnaire was designed and sent to the registries. Eleven out of the twelve registries had already responded to this questionnaire. When the last registry responded to the questionnaire the responses will be collated. Final results are planned to be presented at the 2012 RLM in Budapest.

3.2 Lamotrigine (RUG)

Lamotrigine 3rd update report is ready. Comments were received from the advisory board on the 3rd updated report. RUG is currently working on the answer to these replies. A poster on the signal of lamotrigine and clubfoot was presented by Jan Mejnartowicz at the 20th World Congress of Neurology in Morocco. RUG has worked on the protocol for descriptive study on clubfoot and lamotrigine, has been send for approval to the UMCG.

Two abstracts (lamotrigine use and risk of club foot, lamotrigine use and risk of oral clefts) using 3rd update data have been submitted to the International Conference on PharmacoEpidemiology (ICPE, 23-26 August 2012 in Barcelona).

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) UMCG has submitted a symposium abstract to the International Conference on PharmacoEpidemiology (ICPE, 23-26 August 2012 in Barcelona), together with ENTIS, for a symposium on Bias and Confounding in Studies on Medication Use in Pregnancy.

Methodology applied as planned

Yes

Involvement of partners and target groups

Data on medication use up to 2010 have been provided by 12 registries, 11 registries have provided data on medication use but not up to 2010, or not for all medications. 8 registries have not sent data on medication use in pregnancy. See Table 9.1.

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 AED and SSRIs

Outcomes and deliverables achieved

The ATC workshop was organized in Antwerp (June 2011).
The updated report on sources of medication use was not written yet, but is planned for the next period. This report will be written by UMCG, RUG and UU. The reason for the delay is that we want to combine the description of the sources of medication data with the new DQI used on the new dataset. This report will be written by UMCG, RUG and UU.

Problems encountered

How were problems resolved

Activities planned for the next period

• Organize workshop on improving data and not so much on the use of ATC codes at the RLM in Budapest.
• Make inventory among registries on how medication use is collected and registered
• Apply the DQI on the new dataset with updated info on medication use, combine with updated report on sources of information on medication use used in registries providing medication information.
• Use updated dataset to evaluate data on antiasthmatics (LIL) and antidiabetics (RUG)

4. Annexes

Annex 1 – RLM Agenda and Participant List

Programme for 26th Registry Leaders' Meeting
Antwerp, Belgium
14-16 June 2011

Tuesday 14th (Closed Sessions)

17.00-21.00 **Coding Meeting** (Attendees: Ester Garne, Elisa Calzolari, Ingeborg Barisic, Diana Wellesley, Berenice Doray and David Tucker)

18.00-21.00 **Air Pollution Meeting** (Attendees: Martine Vrijhied, Fabrizio Bianchi, Vera Nelen, Guy Thys, Judith Rankin, Larraitz Arriola, Deiene Urcelay and Carmen Martos)

Wednesday 15th (Open Sessions)

Session 1 (Chair: Lorentz Irgens, Co-Chair: Vera Nelen)

08.30-08.35 **Welcome and apologies (Vera Nelen)**

08.35-08.40 **Approval of Minutes from Last Meeting**

08.40-09.35 **WP1: *Co-ordination of the Joint Action***

News from the Rare Diseases Programme of DG Sanco (Karl Freese / 15 mins)
The EUROCAT Joint Action Overview (Helen Dolk / 15 mins)
The EUROCAT Joint Action Budget (Georgios Margetidis or Karl Freese / 15 mins)
Discussion (Lead by Lorentz Irgens / 10 mins)

09.35-11.15 **WP2: *Dissemination of the Joint Action* and WP8: *Prenatal Screening, Down Syndrome and Genetic Syndromes***

Introduction and Key Public Health Indicator Tables (Ingeborg Barisic)
New Prevalence Tables (Joan Morris and Anna Springett)
New Prenatal Diagnosis Tables (Diana Wellesley)
Perinatal Mortality Tables (Ingeborg Barisic)
Single Disease Registers (Joan Morris)
Dissemination Structure and Discussion (Lead by Ingeborg Barisic)

11.15-11.40 **Tea/Coffee**

Session 2 (Chair: Elisa Calzolari, Co-Chair: Martine Vrijheid)

11.40-12.50 **WP4: *Central Database and Surveillance* and WP6*: Investigation of Trends, Clusters and New Exposures***

Statistical Monitoring

Cluster Detection and Investigation (Maria Loane / 5 mins)
HYDROCEPHALY cluster, Tuscany (Anna Pierini / Fabrizio Bianchi 5 mins)
ANORECTAL ATRESIA, Odense (Ester Garne / 5 mins)
DUODENAL ATRESIA cluster, NorCAS (Judith Rankin / Mary Bythell 5 mins)
ASD cluster, Antwerp (Vera Nelen / 5 mins)
Central Registry/Ukraine clusters (Nichola McCullough / 5 mins)
5 clusters in Ukraine (Wladimir Wertelecki / 10 mins)

- Arhinencephaly/holoprosencephaly
- Severe CHD
- VSD
- Tetralogy of Fallot
- Pulmonary valve stenosis

12.50-14.00 Lunch

Session 3 (Chair: Diana Wellesley, Co-Chair: Martin Haeulser)

14.00-15.00 WP7: *Primary Prevention of Congenital Anomalies*

WP7 State of art (Domenica Taruscio / 10 mins)
Surveillance experience in Italy on folic acid preventable BD: an activity coordinating by Tuscany Registry of Congenital Defects (Fabrizio Bianchi / 10 mins)
Surveillance strategy for monitoring folate-sensitive birth defects in Europe (Babak Khoshnood / 10 mins)
Folic acid knowledge and attitude in women: an operative model in Tuscany Registry of Congenital Defects (Fabrizio Bianchi / 10 mins)
Appraisal of strategy to monitor population folate status (Denhard de Smit / 10 mins)
Discussion (10 mins)

15.00-16.00 WP5*: Registration, Coding and Classification, Data Quality*

DQI Present Situation and Plan
Report from Coding Committee Meeting (14th June)
Guide 1.4 Information

16.00-18.00 PMC Meeting (Closed Meeting)

Evening Welcome in City Hall

Thursday 16th (Open Sessions)

Session 1 (Chair: Ingeborg Barisic, Co-Chair: Marian Bakker)

09.00-10.25 WP4: *Central Database and Surveillance* and WP6: *Investigation of Trends, Clusters and New Exposures* (cont'd)

Statistical Monitoring: Increasing Trends
Overview and Trisomies (Maria Loane / 5 mins)
Cystic-Lung (Diana Wellesley / 5 mins)
Gastroschisis (Hanitra Randrianaivo / 5 mins)
Discussion (5/10 mins)

Statistical Monitoring: Decreasing Trends
Overview, Anophthalmos/Microphthalmos and Arthrogryposis Multiplexa Congenita (Nichola McCullough / 10 mins)
Atresia of Bile Ducts (Ester Garne / 5 mins)
NTD (Babak Khoshnood / 10 mins)
CHD (Babak Khoshnood /10 mins)
Severe CHD and AVSD (Individual Registry Wielkopolska / 5 mins)
Cleft Palate and Limb reduction (Joan Morris / 5 mins)
Partial Data (Nichola McCullough / 10 mins)
Statistical Explorations (Joan Morris / 10 mins)

10.25-10.40 WP6: ***Investigation of Trends, Clusters and New Exposures***
Swine flu (Michiel Luteijn /10 mins)
Hirsprungs Disease Study Protocol (Judith Rankin / 5 Mins)

10.40-10.50 News from New and Applicant Registries
Slovakia (5 mins)
Macedonia (5 mins)

10.50-11.00 New Online EUROCAT Budget System (Helen Dolk/Rhonda Curran)

11.10-12.10 Website Dissemination Committee Meeting (Attendees: Joan Morris, Deiene Urcelay, Babak Khoshnood, Ester Garne, Ingeborg Barisic, Lorentz Irgens, Barbara Norton, Ruth Greenlees, Maria Loane, Elisa Calzolari, Helen Dolk, Rhonda Curran)

11.00-12.10 Tea/Coffee & Networking Session

12.10-12.40 WP8: ***Prenatal Screening, Down Syndrome and Genetic Syndromes***

Overview and Contacting Registries regarding DS and CHD next year (Joan Morris / 5 mins)
Beckwith Wiedeman Syndrome (Ingeborg Barisic / 10 mins)
Discussion (15 mins)

12.40-13.40 Lunch

Session 2 (Chair: Babak Khoshnood, Co-Chair: Joan Morris)

13.40-14.40 Parallel Sessions			
WP9: ***Medication During Pregnancy*** (organised by Marian Bakker) Contents of WP9 Development of DQI for drug variables Update ongoing studies ▪ SSRIs (Anthony Wemakor/10 min) ▪ Lamotrigine (Lolkje de Jong-van den Berg/10 min)	**Registry Advisory Service** (Ingeborg Barisic, Attendees: representatives from Valencia, Macedonia, Latvia, Slovakia) **See documents needed list** Coding Workshop and Discussion with New and Applicant Registries - Introduction (Ingeborg Barisic) • EUROCAT organization • Application for membership and membership criteria • Guidelines for Registration • Data quality indicators - Coding of malformations (Ester Garne) - Coding Exercise (Ester Garne) - Questions and closing remarks	**EDMP Clinic*** (James Densem, Ruth Greenlees and Maria Loane) One to one opportunities to speak about use of the EUROCAT Data Management Programme. Leaders will have the EDMP loaded on their computers. If you wish, bring data with you. **Session 1** Session 1. A short presentation on: <u>Confirming Data on the test website</u> • From .csv file to test website • Prevalence data and prenatal diagnosis data • Using reporting function to check numbers Following this, Ruth and James will be available to discuss any other EDMP queries.	**Demonstration of EUROCAT Member's Forum** (Barbara Norton, Rhonda Curran) An opportunity to familiarise yourself further with the benefits of using the EUROCAT Members Forum

14.40-16.10 Parallel Sessions			
Statistical Monitoring Methods Subgroup (**Closed Meeting**, Attendees: Diana Wellesley, Elisa Calzolari, Ester Garne, Ingeborg Barisic, Joan Morris, Lorentz Irgens, Vera Nelen, Babak Khoshnood, Martin Haeusler, Helen Dolk, Nichola McCullough, Maria Loane)	**ATC Coding Workshop** An interactive session on registration of medication use in pregnancy using the ATC coding system. Tips for using ATC codes will be presented, difficulties in using ATC codes can be discussed. (Linda de Jonge, Marian Bakker)	**EDMP Clinic*** (James Densem and Ruth Greenlees) One to one opportunities to speak about use of the EUROCAT Data Management Programme. Leaders will have the EDMP loaded on their computers. If you wish, bring data with you **Session 2.** A short presentation on: <u>Statistical Monitoring</u> • How to run statistical monitoring from EDMP • Running reports to help complete templates sent by Central Registry	**New Online EUROCAT Budget System** Rolling presentation (Rhonda Curran) Q & A Session (Barbara Norton, Rhonda Curran)

*If the EDMP Clinic Sessions are not suitable you may also arrange to meet with James, Ruth or Maria at any time during the RLM Meeting.

16.10-16.20 2012 RLM Budapest (Judit Beres)

16.10-16.40 Tea/coffee

16.40-17.40 EUROCAT Association Meeting (Closed Meeting, Attendees: Registry Leaders Only**)**

Evening Conference dinner in Hotel

Documents to bring with you:
All Registry Leaders please bring the following documents with you (available at http://www.eurocat-network.eu/default.aspx, may be password protected and logging in as a EUROCAT member may be required):
RLM Programme
List of Participants
Minutes of last RLM 2010 in Dublin
Contract Deliverables and Work packages
EUROCAT Guide 1.3
Statistical Monitoring Protocol
Summary of all Clusters (Anomaly and Centre)
Summary of 10 yr trends (Anomaly and Centre)
List of Detected Clusters (2005-2009)
Pan Europe Trends (2000-2009)
ICD10-BPA
Syndrome Guide
Project Status Report (projects using database)
Publication List (2010-2011)

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

Annex

Registry Advisory Service
Thursday 16th June 2011, 13.40pm-14.40pm
Antwerp, Belgium

Invitation

Registry Advisory Service is a service created 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. Training workshop will be organized at annual RLM meetings, but contacts by e-mail and via webpage will be also available in future.
This year we have prepared a short presentation of the most important EUROCAT documents and coding exercise but your questions are welcomed as well

Introduction (Ingeborg Barisic)

- EUROCAT organization
- Application for membership and membership criteria
- Guidelines for Registration
- Data quality indicators

Coding of malformations (Ester Garne)
Coding Exercise (Ester Garne)
Questions and closing remarks

If interested in attending the workshop, please email Rhonda Curran [r.curran1@ulster.ac.uk] before 6st June 2011.
Please bring the following essential documents to the 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

Country	Registry	Name
Austria	Styria	Haeusler, Martin
Belgium	Antwerp	Coenen, Machteld D'Hooge, Kristien Lommaert, Marie-Paule Nelen, Vera Thys, Guy
Belgium	Hainaut	Mols, Myriam Verellen-Dumoulin, Christine
Croatia	Zagreb	Barisic, Ingeborg Odak, Ljubica
Denmark	Odense	Garne, Ester
EU Office	Luxembourg	Freese, Karl
Finland	Finland	Ritvanen, Annukka
France	Paris	Khoshnood, Babak
France	Strasbourg	Doray, Berenice
Germany	Mainz	Wiesel, Awi
Germany	Saxony-Anhalt	Rissmann, Anke
Hungary	Hungary	Balku, Eszter Beres, Judit Foldvari, Anett Valek, Andrea
Ireland	Cork & Kerry	O'Mahony, Mary Ryan, Maria
Ireland	Dublin	McDonnell, Bob
Ireland	South East Ireland	Costigan, Johanna Mullaney, Carmel
Italy	Emilia Romagna	Elisa Calzolari
Italy	Tuscany	Bianchi, Fabrizio Pierini, Anna
Latvia	Children's Hospital	Grinfelde, Ieva
Malta	Malta	Gatt, Miriam
Netherlands	North Netherlands	Bakker, Marian De Jong, Linda De Walle, Hermien Siemensma-Muhlenberg, Nicole Wang, Hao
Netherlands	Pharmacy	De Jong-van den Berg, Lolkje
Norway	Norway	Gunnar Tufta, Jon Irgens, Lorentz Klungsoyr, Kari
Poland	Poland	Latos-Bielenska, Anna Materna-Kiryluk, Anna Mejnartowicz, Jan
Portugal	South Portugal	Braz, Paula Matias Dias, Carlos
Saudi Arabia	Saudi Arabia	Al Hashem, Amal
Slovakia	Slovakia	Szabova, Elena
Slovenia	Slovenia	Peterlin, Borut
Spain	Basque Country	Arriola, Larraitz Urcelay, Deiene
Spain	CREAL	Vrijheid, Martine
Spain	ECEMC	Bermejo, Eva
Spain	Valencia	Cavero, Clara Martos, Carmen Zurriaga, Oscar
Sweden	Sweden	Kallen, Kari
Ukraine	Ukraine	Wertelecki, Wladimir
UK	Bio-Medical Computing Ltd	Densem, James
UK	Central Registry	Boyle, Breidge, Curran, Rhonda, Dolk, Helen Greenlees, Ruth, Loane, Maria, Luteijn, Michiel McCullough, Nichola, Norton, Barbara Wemakor, Anthony
UK	E Mids & S Yorks	Berry, Laura Budd, Judith
UK	Northern England	Bythell, Mary Rankin, Judith
UK	NDSCR	Morris, Joan Springett, Anna
UK	Thames Valley	Boyd, Patricia Rounding, Cath
UK	Wales	Tucker, David
UK	Wessex	Wellesley, Diana

Annex 2: 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 periconcepitonal 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 pharmacovigillance 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 Taruscio
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 3: EUROCAT Joint Action Promotional Leaflet

Annex 4: EUROCAT Newsletter

Annex 5: Conference Oral and Poster Presentations (excluding internal meetings, RLM and symposia

Annex 6: Peer-reviewed Collaborative Publications (involving more than one registry)

Bermejo E, Cuevas L, Amar E, Bakker M, Bianca S, Bianchi F, Canfield M, Castilla E, Clementi M, Cocchi G, Feldkamp M, Landau D, Leoncini E, Li Z, Lowry B, Mastroiacovo P, Mutchinick O, Rissmann A, Ritvanen A, Scarano G, Siffel C, Szabova E and Martinez-Frias M-L (2011). Amelia: A multi-center descriptive epidemiologic study in a large dataset from the International Clearinghouse for Birth Defects Surveillance and Research, and overview of the literature. American Journal of Medical Genetics Part C (Seminars in Medical Genetics). 157: 288-304.

Botto L, Feldkamp M, Amar E, Carey J, Castilla E, Clementi M, Cocchi G, de Walle H, Halliday J, Leoncini E, Li Z, Lowry B, Marengo L, Martinez-Frias M-L, Merlob P, Morgan M, Luna-Munoz L, Rissmann A, Ritvanen A, Scarano G and Mastroiacovo P (2011). Acardia: Epidemiologic findings and literature review from the International Clearinghouse for Birth Defects Surveillance and Research. American Journal of Medical Genetics Part C (Seminars in Medical Genetics). 157: (262) 273.

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.

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, 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.

Crijns H, Jentink J, Garne E, Gispen-de Wied C, Straus S, de Jong-van den Berg L and EUROCAT Working Group (2011). The distribution of congenital anomalies within the VACTERL association among tumor necrosis factor antagonist-exposed pregnancies is similar to the general population. Journal of Rheumatology. 38: (9). 1871-1874.

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.

Feldkamp M, Botto L, Amar E, Bakker M, Bermejo E, Bianca S, Canfield M, Castilla E, Clementi M, Csaky-Szunyogh M, Leoncini E, Li Z, Lowry B, Mastroiacovo P, Merlob P, Morgan M, Mutchinick O, Rissmann A, Ritvanen A, Siffel C and Carey J (2011). Cloacal Exstrophy: An epidemiologic study from the International Clearinghouse for Birth Defects Surveillance and Research. American Journal of Medical Genetics Part C (Seminars in Medical Genetics). 157: 333-343.

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.

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.

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Annex 7: Coverage of the European Population, Birth Year 2010, by EUROCAT Full or Associate

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)			1,586,789	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	116,626	116,626	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	10,626		
	Dublin	1980	27,815		
	South East	1997	7,969		
	Total		46,410	73,720	63.0
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	55,055		
	Total		178,249	482,885	36.9
France	French West Indies	2009	10,456		
	Isle de la Reunion	2002	14,543		
	Paris	1981	27,400		
	Rhone-Alpes[2]	2006	59,069		
	Strasbourg	1982	13,239		
	Total		124,707	834,559	14.9
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			90,129	90,129	100.0
Malta	Malta[3]	1986	3,978	3,978	100.0
Netherlands	Northern	1981	17,569	183,982	9.5
Austria	Styria	1985	10,235	78,728	13.0
Poland	Wielkopolska	1999	40,396		
	Rest of Poland[2, 3]	1999	371,811		
	Total		412,207	412,207	100.0
Portugal	South	1990	18,270	101,058	18.1
Romania				212,476	0.0
Slovenia				22,312	0.0
Slovakia				60,217	0.0
Finland	Finland[2]	1993	61,006	61,006	100.0
Sweden	Sweden[2, 3]	2001	114,890	114,890	100.0
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					
Candidate countries in EUROCAT					
Croatia	Zagreb	1983	9,181	43,372	21.2
EFTA countries in EUROCAT					
Norway	Norway	1980	61,213	61,213	100.0
Switzerland	Vaud	1989	8,169	80,194	10.2
Ukraine	Ukraine[4]	2005	31,710	494,408	6.4

[1] Source: 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 EUROSTAT

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

Annex 8: Prevalence rates (including and excluding chromosomal cases) for all EUROCAT anomaly subgroups, 2005-2009, all full member registries

						Excluding Chromosomal	
Anomaly	**LB N**	**FD N**	**TOPFA N**	**LB+FD+TOPFA N**	**LB+FD+TOPFA Rate**	**LB+FD+TOPFA N**	**LB+FD+TOPFA Rate**
All Anomalies	82483	1814	16034	100331	255.28	86100	219.07
Nervous system	4756	385	4556	9697	24.67	8833	22.47
Neural Tube Defects	980	162	2686	3828	9.74	3676	9.35
Anencephalus and similar	127	93	1192	1412	3.59	1379	3.51
Encephalocele	129	21	308	458	1.17	435	1.11
Spina Bifida	724	48	1186	1958	4.98	1862	4.74
Hydrocephaly	1238	102	954	2294	5.84	2086	5.31
Microcephaly	897	43	71	1011	2.58	928	2.37
Arhinencephaly/holoprosencephaly	116	30	359	505	1.28	335	0.85
Eye	1514	11	96	1621	4.12	1485	3.78
Anophthalmos/micropthalmos	342	5	59	406	1.03	339	0.86
Anophthalmos	60	2	22	84	0.21	76	0.19
Congenital cataract	461	0	4	465	1.18	449	1.14
Congenital glaucoma	145	0	0	145	0.37	142	0.36
Ear, face and neck	743	19	190	952	2.42	763	1.94
Anotia	131	1	12	144	0.37	133	0.34
Congenital heart defects (CHD)	28784	470	2432	31686	80.62	28312	72.04
Severe CHD	6338	210	1371	7919	20.15	6619	16.84
Common arterial truncus	213	9	85	307	0.78	267	0.68
Transposition of great vessels	1203	13	112	1328	3.38	1292	3.29
Single ventricle	177	13	103	293	0.75	275	0.7
Ventricular septal defect	12718	134	628	13480	34.3	12203	31.05
Atrial septal defect	9141	46	154	9341	23.77	8484	21.59
Atrioventricular septal defect	1092	68	348	1508	3.84	654	1.66
Tetralogy of Fallot	1100	21	145	1266	3.22	1121	2.85
Tricuspid atresia and stenosis	177	9	39	225	0.57	214	0.54

						Excluding Chromosomal	
Anomaly	**LB N**	**FD N**	**TOPFA N**	**LB+FD+TOPFA N**	**LB+FD+TOPFA Rate**	**LB+FD+TOPFA N**	**LB+FD+TOPFA Rate**
Ebstein's anomaly	133	18	28	179	0.46	174	0.44
Pulmonary valve stenosis	1517	2	37	1556	3.96	1504	3.83
Pulmonary valve atresia	264	4	69	337	0.86	313	0.8
Aortic valve atresia/stenosis	437	7	31	475	1.21	459	1.17
Hypoplastic left heart	602	41	436	1079	2.75	998	2.54
Hypoplastic right heart	122	9	58	189	0.48	174	0.44
Coarctation of aorta	1301	17	81	1399	3.56	1265	3.22
Total anomalous pulm venous return	220	1	14	235	0.6	221	0.56
Respiratory	1787	124	536	2447	6.23	2158	5.49
Choanal atresia	325	5	12	342	0.87	310	0.79
Cystic adenomatous malf of lung	272	4	37	313	0.8	310	0.79
Oro-facial clefts	5341	89	606	6036	15.36	5590	14.22
Cleft lip with or without palate	3177	62	458	3697	9.41	3393	8.63
Cleft palate	2164	27	148	2339	5.95	2197	5.59
Digestive system	5817	167	805	6789	17.27	6147	15.64
Oesophageal atresia with or without tracheo-oesophageal fistula	838	33	63	934	2.38	856	2.18
Duodenal atresia or stenosis	459	21	26	506	1.29	361	0.92
Atresia or stenosis of other parts of small intestine	338	3	10	351	0.89	347	0.88
Ano-rectal atresia and stenosis	941	26	213	1180	3	1096	2.79
Hirschsprung's disease	479	0	2	481	1.22	433	1.1
Atresia of bile ducts	102	0	2	104	0.26	104	0.26
Annular pancreas	55	0	6	61	0.16	48	0.12
Diaphragmatic hernia	817	46	204	1067	2.71	969	2.47
Abdominal wall defects	1447	110	927	2484	6.32	2135	5.43
Gastroschisis	916	38	174	1128	2.87	1110	2.82
Omphalocele	452	68	624	1144	2.91	828	2.11
Urinary	11644	234	1644	13522	34.41	12916	32.86

						Excluding Chromosomal	
Anomaly	**LB N**	**FD N**	**TOPFA N**	**LB+FD+TOPFA N**	**LB+FD+TOPFA Rate**	**LB+FD+TOPFA N**	**LB+FD+TOPFA Rate**
Bilateral renal agenesis including Potter syndrome	113	39	314	466	1.19	454	1.16
Renal dysplasia	1251	39	328	1618	4.12	1546	3.93
Congenital hydronephrosis	3890	34	197	4121	10.49	3964	10.09
Bladder exstrophy and/or epispadia	213	5	50	268	0.68	263	0.67
Posterior urethral valve and/or prune belly	264	3	89	356	0.91	343	0.87
Genital	8337	54	235	8626	21.95	8432	21.45
Hypospadias	6896	15	41	6952	17.69	6882	17.51
Indeterminate sex	194	16	54	264	0.67	231	0.59
Limb	14589	307	1483	16379	41.67	15539	39.54
Limb reduction	1486	101	553	2140	5.45	1983	5.05
Upper limb reduction	1075	71	367	1513	3.85	1397	3.55
Lower limb reduction	496	43	277	816	2.08	762	1.94
Complete absence of a limb	17	7	54	78	0.2	78	0.2
Club foot - talipes equinovarus	3721	98	417	4236	10.78	4051	10.31
Hip dislocation and/or dysplasia	2873	3	4	2880	7.33	2851	7.25
Polydactyly	3368	41	199	3608	9.18	3416	8.69
Syndactyly	2005	49	118	2172	5.53	2054	5.23
Arthrogryposis multiplex congenita	140	9	77	226	0.58	220	0.56
Musculo-skeletal	2349	132	1003	3484	8.86	3247	8.26
Thanatophoric dwarfism	24	7	100	131	0.33	131	0.33
Jeunes syndrome	16	1	20	37	0.09	37	0.09
Achondroplasia	121	5	36	162	0.41	160	0.41
Craniosynostosis	711	9	42	762	1.94	703	1.79
Congenital constriction bands/amniotic band	92	27	99	218	0.55	212	0.54
Other malformations	2311	127	647	3085	7.85	2859	7.27
Asplenia	35	3	30	68	0.17	61	0.16

						Excluding Chromosomal	
Anomaly	**LB N**	**FD N**	**TOPFA N**	**LB+FD+TOPFA N**	**LB+FD+TOPFA Rate**	**LB+FD+TOPFA N**	**LB+FD+TOPFA Rate**
Situs inversus	195	3	48	246	0.63	240	0.61
Conjoined twins	13	8	56	77	0.2	77	0.2
Disorders of skin	556	7	37	600	1.53	561	1.43
Teratogenic syndromes with malformations	402	19	82	503	1.28	499	1.27
Fetal alcohol syndrome	180	2	4	186	0.47	185	0.47
Valproate syndrome	35	0	2	37	0.09	36	0.09
Warfarin syndrome	1	0	1	2	0.01	2	0.01
Maternal infections resulting in malformations	146	12	64	222	0.56	220	0.56
Genetic syndromes + microdeletions	1819	50	304	2173	5.53	2092	5.32
Chromosomal	5912	557	7762	14231	36.21	0	0
Down Syndrome	3872	193	4155	8220	20.91	0	0
Patau syndrome/trisomy 13	151	39	584	774	1.97	0	0
Edward syndrome/trisomy 18	317	150	1461	1928	4.91	0	0
Turner's syndrome	250	61	549	860	2.19	0	0
Klinefelter syndrome	194	8	113	315	0.8	0	0
Cri-du-chat syndrome	30	1	14	45	0.11	0	0
Wolf-Hirschhorn syndrome	25	1	18	44	0.11	0	0

LB= Livebirth
FD= Fetal death from 20 weeks gestation
TOPFA= Termination of Pregnancy following prenatal diagnosis of a congenital anomaly

Annex 9: Executive Summary of Statistical Monitoring Report

Annex 10: Taskforce for the Evaluation of Clusters Mandate

TEC Mandate proposal (Version 2 29th August 2011)

1 TEC (Taskforce for Evaluation of Clusters) is a committee reporting to the EUROCAT Project Management Committee and established in connection with the EU financed project EUROCAT: Surveillance of Congenital Anomalies in Europe as an activity under Work Package 6: 6.2:.Investigation of Trends, Clusters and New Exposures.

2 TEC has the following functions:

- **2.1.** On request by the PMC to comment on the output of cluster investigations conducted by EUROCAT including its presentation and possible uses.
- **2.2.** Serve as a consulting unit in cases of clusters, commissioned by EUROCAT or individual member registries.
- **2.3.** In the assessment of a cluster the TEC may:
  - **2.3.1.** Correspond and get written information and data from the registers involved
  - **2.3.2.** Pay site visits for meetings with the registries involved and, if considered expedient, with other parties.
  - **2.3.3.** Propose and advise on ad hoc studies aiming at clarification of a cluster.

3 TEC members are:
Lorentz M Irgens (EUROCAT Bergen, Chair)
Ingeborg Barisic (EUROCAT, Zagreb)
Petter Kristensen (Oslo)
Rolv Terje Lie (Bergen)
Nichola McCullough (EUROCAT Central Registry, secretary)
Vera Nelen (EUROCAT Antwerp)
Helen Dolk (EUROCAT Project Leader, ad hoc member)

Additional members may be appointed by TEC in ad hoc situations according to needs for further expertise in relevant specialities.

Annex 11: FA Survey: Countries and number of respondents per country

Countries	n. resp	Countries	n. resp	Countries	n. resp
UE COUNTRIES					
Austria	1	Hungary	1	Slovak Republic	0
Belgium	1	Ireland	1	Slovenia	1
Bulgaria	0	Italy	1	Spain	4
Cyprus	0	Latvia	1	Sweden	0
Czech Republic	2	Lithuania	1	United Kingdom	3
Denmark	1	Luxembourg	0		
Estonia	1	Malta	1	**NON EU COUNTRIES**	
Finland	1	Netherlands	2	Croatia	2
France	0	Poland	0	Norway	1
Germany	3	Portugal	1	Republic of Moldova	1
Greece	0	Romania	0	Ukraine	1

Annex 12: Countries and recommendations on FA supplementation for primary prevention of CA *(Yes/No – 18/4)*

Austria	**No**	Hungary	**Yes**	Portugal	**Yes**
Belgium	**Yes**	Ireland	**Yes**	Republic of Moldova	**Yes**
Croatia*	**No**	Italy	**Yes**	Slovenia	**Yes**
Czech Republic	**Yes**	Latvia	**Yes**	Spain	**Yes**
Denmark	**Yes**	Lithuania	**Yes**	UK	**Yes**
Estonia	**No**	Malta	**No**	Ukraine	**Yes**
Finland	**Yes**	Netherlands	**Yes**		
Germany	**Yes**	Norway	**Yes**		

Annex 13: Type of Institution/organization/association who developed the recommendation on FA supplementation (Governmental/ Non Governmental - 14/4)

Austria	NA	Hungary	**Gov**	Portugal	**Gov**
Belgium	**Non Gov**	Ireland	**Gov**	Republic Of Moldova	**Gov**
Croatia	NA	Italy	**Gov**	Slovenia	**Non Gov**
Czech Republic	**Gov**	Latvia	**Non Gov**	Spain	**Gov**
Denmark	**Gov**	Lithuania	**Gov**	UK	**Gov**
Estonia	NA	Malta	NA	Ukraine	**Gov**
Finland	**Gov**	Netherlands	**Gov**		
Germany	**Non Gov**	Norway	**Gov**		

Notes: In grey the countries for whom the questions are "Not applicable" (NA), in fact they have not got a recommendation.

Annex 14: Status of ATC codes in database for years 2005-2010 (9th March 2012)

Registry	Comments
1. Hainaut	No
2. Odense	Up to 2010
3. Paris	Up to 2010
4. Tuscany	Up to 2010
5. Dublin	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	Up to 2009 (data seems poor)
13. Antwerp	Up to 2010
14. Basque Country	Up to 2010
15. Saxony Anhalt	Up to 2010
16. Mainz	Up to 2010
17. Barcelona	No drugs
18. Styria	Some listed in 2009
19. Cork & Kerry*	Up to 2009
20. Wales	Up to 2010
21. Norway	Up to 2008 (behind in data transmission)
22. Ukraine	Up to 2009. Quality never assessed
23. Reunion	Up to 2009. Quality never assessed
24. Wielkopolska	Up to 2009 (behind in data transmission)
25. Thames Valley	No drugs
26. Wessex	No drugs
27. E Midlands & S Yorkshire	No drugs
28. Northern England	No drugs
29. Hungary	No drugs
30. SE Ireland	Up to 2009 (behind in data transmission)
31. French West Indies	Up to 2009. Data looks very good
32. South West England	No drugs
33. Valencia	Year 2007 only. Data quality never assessed

Cork & Kerry have sent data up to 2006, and have sent their 2008-09 data. We have not yet received their 2007 data, but we will get it when it is ready.