Health Programme 2008-2013
Together for Health

EU HEALTH PROGRAMME

Call for Proposals 2008-2013

FINAL REPORT

for Joint Actions & Projects

Executive Agency for Health and Consumers

SECTION I

Declaration by the scientific representative of the project coordinator

I, as scientific representative of the coordinator of this project and in line with the obligations stated in the Grant Agreement declare that:

✓ **The attached periodic report represents an accurate description of the work carried out in this project for this reporting period;**

The project (tick as appropriate) :

□ **has fully achieved its objectives and technical goals for the period;**

✓ **has achieved most of its objectives and technical goals for the period with relatively minor deviations.**

□ **has failed to achieve critical objectives and/or is not at all on schedule.**

The public website, if applicable,

✓ **is up to date**

□ **is not up to date**

✓ **To my best knowledge, the financial statements that are being submitted as part of this report are in line with the actual work carried out and are consistent with the report on the resources used for the project and, if applicable, with the certificate of the financial statement.**

✓ **All beneficiaries, in particular non-profit public bodies, have declared to have verified their legal status. Any changes have been reported under section wp1 Coordination and project management, in accordance with the requirements of the Grant Agreement.**

Name of the scientific representative of the project Coordinator:

Prof. Helen Dolk

……

Date: 31/ 07/ 2014

SECTION II

Checklist

Please see the separate checklist (Checklist final payment.xls).

Please read the checklist and answer all respective questions in it.

x the checklist has been filled, answered and printed. An printout is annexed to this report. An electronic copy is enclosed.

SECTION III

Specification of the project

Proposal title: European Surveillance of Congenital Anomalies

Acronym: EUROCAT

Starting date: 01/01/2011

Duration (in months): 36

EC co-funding: 1,106,302 EURO

Priority area: 3.3 Promote Health

Sub-action: 3.3.2 Promote healthier ways of life and reduce major diseases and injuries by tackling health determinants

Action: Rare diseases – European Surveillance on Congenital Anomalies (EUROCAT) network

Main partner information and contact person:

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Associated partner information and contact person:

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List 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. Institute of Care of Mother and Child (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)

FOREWORD

Please describe in this section the following:

- What this report is about
The following report details EUROCAT: European Surveillance of Congenital Anomalies Network activity that has been funded (January 2011-December 2013) as a Joint Action (JA) of the EU and Member States (MS) through the DG Sanco Public Health Programme (2008-2013).

- Why the project is important
Congenital anomalies are a major cause of perinatal mortality, childhood morbidity and disability. EUROCAT' s mission is to support the primary prevention of congenital anomalies and the provision of appropriate services to pregnant women, affected children and their families by the ongoing collection, analysis, interpretation and dissemination of population-based epidemiologic data. Epidemiological surveillance should inform policies and interventions to reduce the size of, and inequalities in, the public health burden of congenital anomalies.

- What the key findings are
By April 2013, EUROCAT website data (for 89 congenital anomaly subgroups) was updated to birth year 2011. EUROCAT's Coding and Classification committee worked with WHO's International Classification of Diseases Rare Disease group on the revision of the malformation chapter. EUROCAT contributed to the global burden of disease process. EUROCAT evaluated the impact of primary prevention policies and interventions, and developed recommendations on policies to be considered for primary prevention of congenital anomalies in national plans and strategies on Rare Diseases. Annual statistical monitoring enabled the detection, investigation and reporting of clusters and trends in congenital anomalies that may indicate new or changing teratogenic exposures and improve capacity for rapid response (i.e. response to swine flu pandemic). EUROCAT (with EUROmediCAT, a FP7 funded project 2011-15) has taken innovative measures to build a European pharmacovigilance database for evaluation of safety of medication use in pregnancy in relation to risk of CA. Epidemiological studies of rare chromosomal abnormalities and rare genetic syndromes were made possible due to the unique value of pooled population-based EUROCAT data. A JA report on "Actions towards European Environmental Surveillance: Feasibility of Environmental Linkage" explored a number of issues relevant to the development of systematic and continuous monitoring of CA prevalence in relation to potential pollution sources.

- who might benefit from the outputs/outcomes
Epidemiological surveillance continues beyond any project. The JA finished in 2013 and was a continuation of European projects since 1979. The outputs, outcomes and their potential impact in part relate to dissemination done in previous contracts, and in part relate to impact still to come. EUROCAT results are mainly published in scientific journals (25 papers from the JA) and become part of the evidence base. EUROCAT will continue to track the impact and benefits that result from the JA outputs and outcomes, whilst continuing to serve as a reference centre in Europe for questions on prevalence, coding and classification of CA.

- what the target group (s) should do differently as a result
There is a need for reinforced public health action to promote adequate periconceptional folic acid levels for pregnant women. Some EU countries are under-represented in EUROCAT and a change in the funding situation in those countries could contribute to the goal of EU-wide surveillance.

ACKNOWLEDGEMENTS

"We thank the many people throughout Europe involved in providing and processing information, including affected families, clinicians, health professionals, medical record clerks, and registry staff."

Keywords (using Mesh terms)
1. Congenital anomalies
2. Epidemiological surveillance and registers
3. Rare diseases
4. Pharmacovigilance
5. Prevention and risk factors

SECTION IV

Final Publishable Executive Summary.

This is a comprehensive summary of your project. It should be formatted to be printed as a stand alone paper document - extending to a maximum of three pages- to reach a wide audience, including the general public. Kindly ensure that it is of suitable quality to enable direct publication by the EAHC.

Please structure your executive summary as follows:

- A summary description of the project scope and objectives (general and specific).

- A description of the work achieved including methods and means.

- The final results in terms of outputs and outcomes, and their potential impact and use by the target group (including benefits).

- The strategic relevance and contribution to the Health Programme.

- Conclusions and recommendations.

Please include available diagrams or photos illustrating the work of the project.

EUROCAT Joint Action: Executive Summary

Project scope and objectives (general and specific)
EUROCAT, in existence since 1979, is a European network of geographically defined population-based registries (representing the unselected experience of all who live in the population) for epidemiologic surveillance of congenital anomalies (CA). EUROCAT currently surveys over 1.7 million births per year in Europe (31% of the EU birth population), via 37 registries in 21 countries. EUROCAT activity has been funded (2011-2013) as a Joint Action (JA) of the EU and Member States (MS) through the DG Sanco Public Health Programme (2008-2013).

CA are a major cause of perinatal mortality, childhood morbidity and disability, with a total prevalence of 2.5% of births. Most CA are Rare Diseases (RD) (<5 per 10,000 population). The live birth prevalence of rare CA in 2010 was 96.2 per 10,000 births, extrapolating to approx 4.7M affected persons in the EU, 12-15% of the total estimated persons affected by RD.

EUROCAT' s mission is to support the primary prevention of CA and the provision of appropriate services to pregnant women, affected children and their families by the collection, analysis, interpretation and dissemination of population-based epidemiologic data. Epidemiological surveillance should inform policies and interventions to reduce the size of, and inequalities in, the public health burden of CA.

The specific objectives of the EUROCAT JA Project 2011-2013 were:

1. Prevalence Information
EUROCAT JA aimed to provide essential comprehensive epidemiologic information on prevalence of CA in Europe updated to 2011. This was needed for several other objectives of the JA, in particular assessment of the impact of policies for primary prevention and prenatal diagnosis of CA, and the role of old and emerging risk factors i.e. swine flu.

2. Network expansion and data quality improvement

EUROCAT values collaboration and mutual interdependence. All registries make a valuable contribution to, and derive benefit from, the European network irrespective of disciplinary, geographic, institutional or other origin. The JA aimed to establish new member registries in Europe collecting comparable, standardised data toenable the sharing of knowledge and expertise and a widening contribution to public health planning. EUROCAT invests considerable effort in assuring high quality data, and transparency regarding data quality deficiencies. Data quality monitoring and improvement were essential prerequisites for other objectives using EUROCAT data, and for effective comparison between countries.

3. Early warning
The importance of rapid response to emerging health threats and clusters of CA has been illustrated by major safety concerns (i.e. thalidomide). The JA aimed to continue as the only organisation annually monitoring, on an EU, country and regional basis, trends and clusters of CA in time to detect signals of new and increasing teratogenic exposure that may require public health action. EUROCAT JA aimed to monitor and respond to emerging health threats and exposures in a timely manner, and communicate the results to public health authorities.

4. Primary prevention policy
Many CA are potentially preventable (eg. periconceptional folic acid to prevent neural tube defects) but total prevalence has not declined in recent decades. EUROCAT uses epidemiologic data to raise awareness of the need and potential to accelerate the slow progress towards reducing the number of affected live births, perinatal deaths and terminations. Many risk factors for CA are increasing: delayed childbearing, diabetes, obesity, assisted reproduction, use of medications, recreational drugs, and alcohol and smoking in some countries. EUROCAT surveillance is needed to measure the impact of these and measures taken to alleviate them. The JA aimed to make recommendations for the inclusion of primary prevention of CA in national RD Plans and to evaluate effectiveness of existing primary prevention measures.

5. Prenatal screening information
Prenatal screening, diagnosis technology and policy are constantly changing, and unequally implemented across health systems and countries. EUROCAT population-based data on prenatal diagnosis are of great value in evaluating these changes for individual types of CA, including changes in pregnancy outcomes. EUROCAT JA aimed to assess the impact of developments in prenatal screening, diagnosis and policy at population level, in particular for Down Syndrome.

6. Postmarketing drug surveillance
Despite the thalidomide epidemic, there is still no effective postmarketing surveillance of drug use in pregnancy. The safety of most medications for use in early pregnancy is unknown, yet women, particularly those with chronic diseases, need safety information to guide treatment choices. The JA aimed to develop a European postmarketing surveillance tool in relation to medication use in pregnancy and risk of CA by analysing a population-based database of worldwide importance, and by exploiting new possibilities for linkage with prescription data.

A description of the work involved including methods and means
Through the network of high quality multiple source population-based CA registries ascertaining live births, still births/fetal deaths, and terminations of pregnancy following prenatal diagnosis of CA, the JA enabled provision and dissemination of accessible and updated epidemiological information, including prevalence, prenatal diagnosis and perinatal mortality data, and the pooling of population-based data on monogenic syndromes and rare chromosomal abnormalities. Registries sent anonymised individual case data or summary data to a Central Database at EUROCAT Central Registry.

The final results in terms of outputs and outcomes, and their potential impact and use by the target group (including benefits)

The EUROCAT website allows visitors to interrogate anonymous aggregate prevalence data (updated biannually), by registry, year and 89 CA subgroups of interest ie. Spina bifida, Down syndrome. In April 2013, data was updated to birth year 2011.

The Coding and Classification committee worked with WHO's International Classification of Diseases RD group to impart expertise for revision of the malformation chapter.

EUROCAT contributed to the global burden of disease process helping to put CA in the context of other diseases worldwide and to place CA firmly on the public health agenda.

EUROCAT evaluated the impact of Primary Prevention policies and interventions, and developed Recommendations on Policies to be considered for Primary Prevention of CA in National Plans and Strategies on RD. EUROCAT is liaising with EUROPLAN to discuss measures to monitor the inclusion, implementation and impact (across MS) of the recommendations.

Annual statistical monitoring enabled the detection, investigation and reporting of clusters and trends in CA that may indicate new or changing teratogenic exposures and improve capacity for rapid response. No new clusters of immediate concern were detected during the JA. The final statistical monitoring report of the JA covering births from 2002-2011 demonstrated a moderate decline in neural tube defects (mostly preventable by raising the folate status of women periconceptionally) suggesting folic acid supplementation has not been an effective strategy for prevention in Europe. There is a need for reinforced public health action to promote adequate periconceptional folic acid levels for pregnant women.

EUROCAT (with EUROmediCAT, a FP7 funded project 2011-15) has taken innovative measures to build a European pharmacovigilance database for evaluation of safety of medication use in pregnancy in relation to risk of CA. This is now one of the largest data sources on CA with medication exposure in 1st trimester pregnancy worldwide, facilitating collaboration among MS for effective organisation by developing protocols and databases for signal detection and evaluation relating to medication exposure in early pregnancy.

Epidemiological studies of rare chromosomal abnormalities and rare genetic syndromes are limited, as they require analyses of large populations and a well-organised diagnostic network, such as EUROCAT, demonstrating the unique value of EUROCAT data. Pooling population-based data (with case review by medical geneticists) enabled EUROCAT to provide baseline prevalence figures to guide health service planning for management and care of people affected by rare chromosomal abnormalities, prevalence data on 44 selected monogenic syndromes in Europe and comprehensive epidemiologic studies on specific syndromes (ie. Fraser, Meckel-Gruber).

Other epidemiological studies were carried out to address specific hypotheses ie. a descriptive epidemiological study on atrioventricular septal defects (a congenital heart defect), where 993 cases were registered over 2000–2008, with a total prevalence of 5.3 per 10,000 births. Another study on multiple births with CA showed that within the European population studied, there was approx a 50% rise in the multiple birth rate from 1984-2007 and with it a rise in multiple births affected by CA. A case-malformed control analysis showed there remains no evidence of an association between orofacial clefts and lamotrigine monotherapy (an anti-epileptic drug) in the first trimester of pregnancy relative to other malformations.

A JA report on "Actions towards European Environmental Surveillance: Feasibility of Environmental Linkage" explored a number of issues relevant to the development of systematic and continuous monitoring of CA prevalence in relation to potential

pollution sources. The existence of exposure databases and CA registry data in many regions of Europe provides great potential for the environmental surveillance and epidemiological research of CA. The report identified that it is feasible to link EUROCAT registry data to small-scale and hot-spot pollution maps but highlighted the urgent need for collaborative structures involving, in each country, environmental scientists and specialists in epidemiology and surveillance of CA.

Epidemiological surveillance continues beyond any project. The JA finished in 2013 and was a continuation of European projects since 1979. The outputs, outcomes and their potential impact in part relate to dissemination done in previous contracts, and in part relate to impact still to come. EUROCAT results are mainly published in scientific journals (25 papers from the JA) and become part of the evidence base. EUROCAT will continue to track the impact that results from the JA outputs and outcomes, whilst continuing to serve as a reference centre in Europe for questions on prevalence, coding and classification of CA.

The Strategic Relevance and Contribution to the Health Programme
EUROCAT is active in areas prioritized by the Health Programme ie. Generating and Disseminating Health Information. EUROCAT contributes to surveillance of non-communicable diseases (NCD) by improving timeliness, comparability, analysis and reporting of health data by efficient, well-established mechanisms for the collection of data and information, to produce scientific evidence and provide stakeholders with information to take decisions on issues affecting individual and collective health. EUROCAT highlights geographical inequalities in Europe in relation to prevention, screening and need for treatment and care.

EUROCAT has EU added value concerning EU-level action in areas where national action is not feasible or effective, specifically for RD. The Council Recommendation 2009 on an action in the field of RD and the Commission Communication on RD: Europe's Challenges 2008, recognise the need for registries and databases co-ordinated at European level. Through a RD platform the EC aims to support and sustain registries/networks - key instruments in increasing knowledge of RD, in developing clinical research and the only way to pool data in order to achieve a sufficient sample size for epidemiological and/or clinical research. EUROCAT achieves EU added value through: • Pooling of data • Comparison of data between countries • Sharing of expertise/resources • Joint approach to European public health questions.

EUROCAT is equipped to improve and reinforce public health emergency preparedness and planning to respond to potential risks. EUROCAT is focused on primary prevention of CA. The Health Programme prioritises effective prevention of NCD (including RD) by taking action on common risk factors. Adequate public understanding of risk factors can help reduce the burden of ill health from NCD. EUROCAT focuses on the pregnancy/fetal component in support of MS efforts to motivate action on healthy nutrition and other health promotion actions (ie. obesity).

Conclusions and Recommendations
EUROCAT provides a ready collaborative network and infrastructure for research related to causes and prevention of CA and treatment and care of affected children. Post 2014, EUROCAT will be moving to the EU Joint Research Centre at ISPRA in Italy, as part of the new Public Health Unit of the Institute for Health and Consumer Protection. This is a considerable success for EUROCAT in achieving a long term sustainable future. Moving forward, some EU countries are under-represented in EUROCAT and a change in the funding situation in those countries could contribute to the goal of EU-wide surveillance.

SECTION V

Technical aspects of the project

Background and project scope

EUROCAT is a European network of population-based registries for epidemiologic surveillance of congenital anomalies, in existence since 1979. EUROCAT currently surveys over 1.7 million births per year in Europe (31% of the EU birth population), via 37 registries in 21 countries. High quality multiple source registries ascertaining still births/fetal deaths, terminations of pregnancy following prenatal diagnosis of congenital anomaly and live births, enables provision of prevalence, prenatal diagnosis and perinatal mortality data. Member registries send anonymised individual case data (full members) or summary data (associate members) to the EUROCAT Central Registry database, also a WHO Collaborating Centre for the Surveillance of Congenital Anomalies. EUROCAT activity has been funded from January 2011 to December 2013 as a Joint Action of the EU and Member States through the DG Sanco Public Health Programme (2008-2013), relating to European Action on Rare Diseases.

Congenital anomalies are a major cause of perinatal mortality, childhood morbidity and disability. According to EUROCAT Report 9, more than 115,000 babies are affected by major congenital anomaly in the EU each year. 1.8% of live births have major congenital anomalies, of which more than half have surgery and need specialist services during childhood and adulthood. 0.9% of babies in the EU have a major congenital anomaly prenatally diagnosed of which 0.4% result in termination of pregnancy. Perinatal mortality relating to congenital anomaly affects 1 in every 1,000 births.

Most congenital anomalies are Rare Diseases (<5 per 10,000 population). The live birth prevalence of rare congenital anomalies in 2010 was 96.2 per 10,000 births. This extrapolates to approximately 4.7M affected persons in the EU, 12-15% of the total estimated persons affected by Rare Diseases.

Many congenital anomalies are potentially preventable but total prevalence has not declined in recent decades. For example, neural tube defects, mostly preventable by raising the folic acid status of women periconceptionally, have not declined substantially. A number of risk factors for congenital anomalies are moreover increasing: delayed childbearing, diabetes, obesity, assisted reproduction. EUROCAT surveillance is needed to measure the impact of these changes and measures taken to alleviate them.

The safety of most medications for use in early pregnancy is unknown, yet women particularly with chronic diseases need safety information through population-based registry-based postmarketing surveillance to guide treatment choices.

The importance of rapid response to emerging health threats and clusters of congenital anomaly has been illustrated by major safety concerns (eg thalidomide, Chernobyl, early invasive prenatal tests, swine flu). EUROCAT is the only organisation annually monitoring (on an EU and country basis) for trends and clusters of congenital anomaly in time to detect signals of new and increasing teratogenic exposure that may require public health action.

Prenatal screening and diagnosis technology and policy are constantly changing and unequally implemented across health systems and countries. EUROCAT population-based data on prenatal diagnosis are of great value in evaluating these changes.

EUROCAT is an established, authoritative source of information with effective dissemination channels.

EUROCAT' s mission is to support the primary prevention of congenital anomalies

and the provision of appropriate services to pregnant women, affected children and their families by the ongoing collection, analysis, interpretation and dissemination of population-based epidemiologic data i.e. by epidemiologic surveillance. Surveillance should inform policies and interventions to reduce the size of, and inequalities in, the public health burden of congenital anomalies.

The values that guide EUROCAT's strategic definition of aim and objectives:

- POPULATION-BASED: We collect epidemiological data in geographically defined populations to represent the unselected experience of all who live in the population.

- REDUCTION OF INEQUALITIES: We highlight the preventive and service needs for a group of individually mainly rare conditions which together constitute a significant but neglected public health problem; highlight differences between countries and identify high risk groups; work to improve data on socioeconomic inequalities; expand capacity for registries across EU.

- EARLY WARNING: We aim to monitor and respond to emerging health threats and exposures in a timely manner, and communicate the results to public health authorities.

- ACCURACY: We invest considerable effort in assuring high quality data, and transparency regarding data quality deficiencies

- PRIMARY PREVENTION AS THE ULTIMATE GOAL: We use epidemiologic data to raise awareness of the need and potential to accelerate the very slow progress in recent decades towards reducing the number of affected livebirths, perinatal deaths and terminations of pregnancy. We also provide primary prevention recommendations for rare disease plans.

-TRANSPARENCY: We make all our information available to health care professionals, researchers, policy makers and the public.

- COLLABORATION AND MUTUAL INTERDEPENDENCE: all members make a valuable contribution to, and derive benefit from, the European network irrespective of disciplinary, geographic, institutional or other origin

- SUSTAINABILITY AND EFFICIENCY: We design data systems to ensure the efficiency and sustainability of the network.

General objective of the project

The aim of the EUROCAT Joint Action is the epidemiologic surveillance of congenital anomalies (CA) through the EUROCAT Network of population-based CA registries. This supports the reduction of the public health burden of CA by promotion of health; reduction of teratogenic risks preconceptionally and in early pregnancy; high quality diagnostics, treatment and counselling prenatally and postnatally; and minimising inequalities in the experience of prevention and care.

The objectives of EUROCAT are:
1. To provide essential epidemiologic information on CA in Europe
2. To facilitate early warning of new teratogenic exposures
3. To evaluate the effectiveness of primary prevention
4. To assess the impact of changes in prenatal screening
5. To act as an information and resource centre for the population, health professionals and policy makers regarding clusters, exposures and risk factors of concern
6. To provide a ready collaborative network and infrastructure for research related to

causes and prevention of CA and treatment and care of affected children
7. To act as catalyst for the setting up of new registries in Europe collecting comparable, standardised data

Specific objective(s) of the project

	Title and Description	Link to the WPs	Link to the deliverables	Level of achievement (measured by the indicators specified in WP3)
1	**Prevalence information** – To provide comprehensive epidemiologic information on prevalence of congenital anomalies in Europe.	WP4 Registration, Central Database, and Surveillance	D4 – Website Epidemiological Tables updated to 2011	**Process Indicator - Successful annual data transmission to Central registry from all Associate Partner Registries.** Regarding the Process Indicator – the majority of Associate Partner registries successfully transmitted data to EUROCAT Central Registry each year of the EUROCAT Joint Action (see full detail in WP4 report). **Output Indicator - Prevalence tables for 95 anomaly subgroups on the EUROCAT website, updated each year.** Regarding the Output Indicator – Prevalence tables for the entire list of EUROCAT anomaly subgroups (which had since changed from 95 to 89) have been updated each year of the EUROCAT Joint Action (see full detail in WP4 report). **Outcome Indicator - Citations of EUROCAT prevalence information.** Regarding the outcome indicator – citations of EUROCAT prevalence information, collectively website registrations to use the prevalence tables available on the EUROCAT

				website (detailed in Section C of Part B), the results of the web-based evaluation survey (detailed in Section F of Part B), the log of external enquiries (detailed in Section D of Part B) and the results of the Independent Evaluation (detailed in Section H of Part B) all confirm that EUROCAT prevalence information is used widely. See also Section A of Part B for examples of citations of prevalence tables.
2	**Network expansion and data quality improvement** – To coordinate the establishment of new registries throughout Europe collecting comparable, standardised data and continue to monitor and improve data quality in all registries.	WP4 Registration, Central Database, and Surveillance WP5 Coding, Classification, Data Quality	D6 – ICD11 Coding Revision Submission	**Process Indicator 2 -** Integration of Latvia, Slovenia and Valencia as new Full Members of EUROCAT, with successful data transmission **Process Indicator 2 – Submission of revised ICD11 to WHO** Regarding the first Process Indicator – Latvia and Slovenia have progressed to Affiliate membership level and Valencia has become a Full Member registry (see full detail in WP4 report) Regarding the second Process Indicator – Revised ICD11 proposals were submitted to WHO (see full detail in WP5 report). **Outcome Indicator 1 – Improvement in Data Quality in 2/3 of registries** Regarding the Outcome Indicator – Data Quality Indicators were improved

				in two thirds of registries (see full detail in WP5 report).
3	**Early warning** – To coordinate 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.	WP4 Registration, Central Database, and Surveillance And WP6 Investigation of Trends, Clusters and New Exposures	D7 – Investigation Reports 3 Annual Statistical Monitoring Reports Part B (Months 12, 24 and 36). Report of the Taskforce for the Evaluation of Clusters (Month 20). Report of Environmental Pollution Data Linkage (Month 36) and protocols. 5 Epidemiological papers (Months 24 and 36).☐	**Process Indicator - Improvement in number of registries meeting earliest data transmission deadline** Regarding the Process Indicator – There was in improvement in the number of registries meeting the earliest data transmission deadline (see full detail in WP4 report). **Output Indicator 1 - Annual Statistical Monitoring Reports** **Output Indicator 2 - Five in-depth investigations, including one by the Taskforce for the Evaluation of Clusters and one of swine flu impact** **Output Indicator 3 - Environmental data linkage feasibility report** Regarding the Output Indicators – 3 annual statistical monitoring reports were been created (see full detail in WP4 and WP6 report). More than five in-depth investigations were conducted within WP6. The TEC investigation did not happen, alternatively resources were diverted to expand the in-depth investigation of the impact of swine-flu (see full detail in WP6 report). The environmental data linkage feasibility report was created as part of WP6 (see full detail in WP6 report).

				Outcome Indicator - Generation and preliminary investigation of clusters/trends in each registry Regarding the Outcome Indicator – Generation of clusters/trends in each participating registry, and subsequent preliminary investigation by affected registries, happened as part of each year's annual statistical monitoring process (see full detail in WP4 and WP6 report).
4	**Primary prevention policy –** To make recommendations for the inclusion of primary prevention of congenital anomalies in national rare disease plans and to evaluate the effectiveness of existing primary prevention measures including folic acid.	WP7 Primary Prevention of Congenital Anomalies	D8 Report on Primary Prevention of Congenital Anomalies	**Output Indicator -** **Report on public health actions 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.** This output indicator was delayed. The three part report has been delayed until May 2014 (see explanation in WP7 report).
5	**Prenatal screening information –** To assess the impact of developments in prenatal screening at a population level, with particular reference to Down	WP8 Prenatal Screening, Down Syndrome and	D9 – Set of 6 Scientific Down Syndrome and other Genetic Syndrome Papers	**Process Indicator – Integration of England and Wales National Down Syndrome Cytogenic Register data into**

	Syndrome.	Genetic Syndromes And WP4 Registration, Central Database, and Surveillance And WP5 Coding, Classification, Data Quality		**EUROCAT Central Database** Regarding the Process Indicator – Data were not incorporated into the EUROCAT Central Database as planned (see explanation in WP8 report). Alternatively England and Welsh National Down Syndrome Cytogenic Registry data were incorporated into the EUROCAT website as part of the prenatal diagnosis epidemiological tables. **Output Indicator 1 – Expansion of prenatal diagnosis tables on the EUROCAT website** Regarding the Output Indicator – Prenatal diagnosis tables were expanded on the EUROCAT website (see full detail in WP4 and WP5 report). **Outcome Indicator – Publication of 6 genetic syndrome papers** Regarding the Outcome Indicator – 3 papers have been published, one has been submitted (outcome pending) and 2 are to be submitted (see detail in WP8 report).
6	**Postmarketing drug surveillance –** To develop EUROmediCAT as an effective postmarketing surveillance tool in relation to medication use in pregnancy and risk of congenital anomaly.	WP9 Medication During Pregnancy	D10 – EUROmediCAT papers	**Process Indicator 1 – 3 workshops on quality of medication use exposure data** **Process Indicator 2 – Joint Meeting with ISPE and ENTIS**

				Regarding the Process Indicators – workshops were held at each annual Registry Leaders' Meeting and a Joint meeting with ISPE and ENTIS took place (see full detail in WP9 report). **Output Indicator - 3 scientific papers** Regarding the Output Indicator – One report has been generated (to be converted to scientific paper in 2014), one paper has been published and one paper has been finalised for submission in 2014 (see full detail in WP9 report). **Outcome Indicator – Protocol for early warning of drug malformation associations** Regarding the Outcome Indicator – This protocol is now alternatively being developed as part of the FP7 funded EUROmediCAT project (see full detail in WP9 report).

Overview of the workpage and deliverables:

	WP Title	Deliverables	Description	Confidentiality	Expected month of delivery	Actual delivery month	Justification for the delay (if applicable)
1	Coordination of the Joint Action	D1 – Final Report	Final Report to Executive Agency/DG Sanco (Month 36), and Interim Reports at Months 12 and 24	Public	36	April 2014	The EUROCAT Project Manager was on maternity leave Months 32-36.
2	Dissemination of the Joint Action	D2 – Two European Symposia	Two 1-day European Scientific Symposia on Prevention of Congenital Anomalies, Antwerp (Month 6) and Zagreb (Month 30)	Public	30	30	na
3	Evaluation of the Joint Action	D3 – Evaluation Report	Evaluation Report	Public	36	June 2014	The EUROCAT Project Manager was on maternity leave Months 32-36.
4	Registration, Central Database and Surveillance	D4 – Website Epidemiological Tables Updated to 2011	Website tables updated annually to birth year 2011, for 95 congenital anomaly subgroups, by registry, year and pregnancy outcome, on prevalence, perinatal mortality	Public	28	28	

			and prenatal diagnosis, with data quality indicators (Months 4, 16 and 28) 3 Annual Statistical Monitoring Reports (Part A) on the detection of clusters and trends (Months 12, 24 and 36)				
		D5 – Statistical Monitoring Reports Part A		Public	36	36	
5	Coding and Classification, Data Quality	D6 – ICD11 Coding Revision Submission	Revised submission to ICD11 for congenital anomaly coding revision	Confidential	18	Submissions made in M10 and M16 and further submissions throughout 2013	na
6	Investigation of Trends, Clusters and New Exposures	D7 – Investigation Reports	3 Annual Statistical Monitoring Reports Part B (Months 12, 24 and 36). Report of the Taskforce for the Evaluation of Clusters (Month 20). Report of Environmental Pollution Data Linkage (Month 36) and protocols. 5 Epidemiological papers (Months 24 and 36)	Public	36	3 Annual Statistical Monitoring Reports Part B by M36 TEC Report no longer a planned output of D7 Environmental Pollution Data Linkage Report, provided with final report in June 2014 10 epidemiological papers have been created as a result of	Na (see WP6 report for full detail)

						activity undertaken in WP6, 6 of which have been accepted for publication or fully published by M36, one of which has been accepted for publication in Feb 2014 and 3 of which are to be submitted within 2014.	
7	Primary Prevention of Congenital Anomalies	D8 – Report on Primary Prevention of Congenital Anomalies	A 3-part report : I. Public Health Actions (Month 24) II. Prevention of Neural Tube Defects with folic acid (Month 24) III. National plans (Month 36)	Public	36	Dealyed	See explanation in WP7 report
8	Prenatal Screening, Down Syndrome and Genetic Syndromes	D9 – Set of 6 Scientific Down Syndrome and other Genetic Syndrome Papers	2 scientific papers on Down Syndrome (Months 18 and 36). 4 papers on other genetic syndromes (Months 9, 18, 27 and 36)	Public	36	2 scientific papers on Down syndrome, one submitted in M11 and subsequently published, and one to be submitted in early 2014 (draft ready). 4 papers on genetic syndromes, one published in M27, one published in January 2014, one submitted in	Submission of one of the Down Syndrome papers was delayed to early 2014, due to time delays in acquiring permissions to use data from participant EUROCAT registries. Fraser syndrome

						February 2014 and one to be submitted in early 2014 (draft in preparation).	paper delayed due to requests for change from the American Journal of Human Genetics editorial team. For other syndrome papers see WP8 report
9	Medication During Pregnancy	D10 - EUROmediCAT Papers	3 scientific papers on risks of specific medications and pharmacovigilance methodology	Public	36	More than 3 scientific papers will be produced as a result of the activity undertaken in WP9 Paper 1 – report version published on website in 2014 to be converted to paper in 2014 (Annexed in Section VII) Paper 2 – published M35 (Annexed in Section VII) Paper 3 – to be submitted to scientific journal in 2014 (Abstract and Tables Annexed in	Paper 1 has been prepared initially as a report for publication on the EUROCAT website and is now being converted to a scientific paper. Production of the report and subsequent paper were delayed due to maternity leave of one of the key researchers. Paper 3 – see WP9 report Paper 4 – is an additional

						Section VII) Paper 4 – to be submitted to scientific journal in 2014 (Annexed in Section VII) Papers 5 and 6 - further related papers on lamotrigine use and risk of club foot and on lamotrigine use and risk of oral clefts to be submitted in 2014	unplanned paper, due to follow up studies conducted as a result of research undertaken in activity 3.1

Main activities carried out including methods and means.

MAIN ACTIVITIES IN TERMS OF EUROCAT OUTPUT AND VALUE (see Dissemination section for further information on Dissemination activities)

-provision and dissemination of accessible and updated epidemiological information: prevalence of CA (in live births, stillbirths, terminations of pregnancy), prenatal diagnosis, and perinatal mortality; including geographic inequalities and trends.

-Detection, investigation and reporting of clusters/trends in CA (through statistical monitoring and surveillance) that may indicate new or changing teratogenic exposures (e.g. medication, environmental pollutants) and improving the capacity for rapid response.

-Assessing teratogenic risks of new/changing environmental exposures and addressing environmental incidents involving exposure of pregnant women – past examples include Chernobyl, dioxin food contamination; swine flu pandemic - with appropriate dissemination.

-Evaluating the impact of primary preventive policies and interventions eg tracking neural tube defect prevalence in relation to prevention by folic acid supplementation and related measures, collaborating with ECDC on congenital rubella; disseminating findings to policymakers.

-Developing and Monitoring EUROCAT/EUROPLAN Recommendations on policies to be considered for the primary prevention of congenital anomalies in National Plans and Strategies on Rare Diseases.

-Evaluating impact on prevalence of CA of demographic/societal changes eg of increasing maternal age in Europe for prevalence of Down Syndrome and of the rise in multiple births for prevalence of CA. Currently investigating diabetes, obesity and assisted reproduction.

-Evaluating impact of changes in prenatal screening policy and practice by tracking trends and geographic inequalities in the proportion of cases prenatally diagnosed, the proportion first detected by different screening tests, gestational age at diagnosis, outcome of prenatally diagnosed cases (including termination).

-Assessing impact of termination of pregnancy for fetal anomaly on live birth prevalence of CA and on perinatal mortality.

-Building and analysing EUROCAT's pharmacovigilance database, now one of the largest data sources on CA with medication exposure in 1st trimester pregnancy worldwide; liaising with EncePP and EUROmediCAT (EUROCAT daughter FP7 funded project) and disseminating findings to date concerning antiepileptic and antidepressant medication exposures.

-Pooling of population-based data on monogenic syndromes and rare chromosomal abnormalities.

-Improved coding and classification of CA through training and contribution to revision of the WHO's ICD10 to ICD11.

-Expansion of the EUROCAT network - supporting new registries, providing expertise, guidelines, software.

-Organisation of European Symposia on the Prevention of CA, every two years in a different country, to share results and knowledge.

Target groups

The information provided by the Joint Action will be targeted to:

-Health professionals eg. 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.

-Public health professionals and those involved in health service planning at regional, national, EU, and WHO levels

-Organisations and networks working in the area of Rare Diseases

-Governmental/public regulation agencies in several domains (industrial, air quality, environmental protection agencies, food, medications)

-Patient organisations

-Scientific research community (in epidemiology, public health, clinical genetics, embryology etc.)

-Scientific research community (in epidemiology, public health, clinical genetics etc and international research networks including Global Burden of Disease study which makes extensive use of EUROCAT data, and International Clearinghouse).

-Politicians/policy makers

-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 congenital anomalies, 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.

Evaluation of the degree of achievement of the objectives and discussion based on the project's indicators as outlined in your evaluation plan/ WP3.

See Full Evaluation Report Annexed in Section VII under WP3.

Results and key findings

Please discuss the results achieved in terms of outputs and (actual or expected) outcomes and their potential impact and use by the target group (including the socio-economic impact, the wider societal implications of the project and contribution to the policy development at all levels of governance (EU, MS, Regional and local).

Epidemiological surveillance is longer than any JA term. EUROCAT JA 2011-13 is a continuation of European funds since 1979. The outcomes and surveillance in part relate to previous dissemination done in previous contracts and are being continued through the JA e.g. in relation to folic acid to see if primary prevention measures are having an effect. We have also observed that there was no decrease in prevalence of CA during the 80's and 90's but now for the first time we are seeing a decline suggesting an improved environment. EUROCAT results are mainly published in scientific journals and become part of the evidence base. Progress in the coding of CA through EUROCAT is also transmitted to the revision process of ICD10 to ICD11 which will have global use. EUROCAT also contributed to the global burden of disease

process. EUROCAT has become a reference centre in Europe for questions on prevalence, coding and classification of CA.

EUROCAT provides a degree of reassurance that no major clusters of concern have been detected in the general population. We identify areas of improvement and areas that need addressing in relation to detecting downward and upward trends. Epidemiological data are needed to set the agenda in terms of the public health importance of CA and their prevention and to have information on prevalence, risk factors and to bring prevention to the fore.

The setting up of a pharmacovigilance system in relation to medication use in pregnancy - the first results in relation to anti-epileptic drug exposure have been important evidence contributing to the guidelines for optimal treatment of epilepsy.

Through the EUROCAT/EUROPLAN Recommendations on policies to be considered for the primary prevention of congenital anomalies in National Plans and Strategies on RD (developed as part of the EUROCAT JA), EUROCAT has endeavoured to make primary prevention part of the RD national plans. EUROCAT is already liaising with EUROPLAN to discuss measures to monitor the inclusion, implementation and impact (across Member States) of the EUROCAT/EUROPLAN Recommendations.

Another important benefit is that EUROCAT is population-based and not related to specific centres of excellence. We have also been able to compare different prenatal screening policies and compare outcomes to inform EU MS policy.

In general terms, policy makers at all levels need information on prevalence of CA for service planning, and on the impact on prevalence and perinatal mortality of health service interventions. EUROCAT provides this in the area of CA, and is the leading provider within the RD field for comprehensive information of this type. EUROCAT's surveillance can help policy makers put into perspective local concerns about suspected clusters or increases in CA with high quality data – lack of data of this type would be very quickly felt as local health authorities would be unable to respond to questions.

Results concerning prenatal screening and diagnosis are used to inform policy in MS.

The results of the EUROCAT JA were also used to facilitate the setting up and maintenance of surveillance registries in some of the participating countries in order to be part of the EUROCAT network and conform to EUROCAT methodology.

The EUROCAT Joint Action was just completed in December 2013. As with previous rounds of funding EUROCAT will aim to track where possible the subsequent impact of the EUROCAT Joint Action.

Coordination with other projects or activities at European, National and International level

EUROCAT was represented on the European Expert Committee on Rare Diseases (EUCERD) by the Chair of the EUROCAT Coding and Classification Committee (Dr Ester Garne) and a member of the EUROCAT Steering Committee (Dr Velen Nelen) as well as the EUROCAT President who represents Croatia (Dr Ingeborg Barisic).

European Project for Rare Diseases National Plans Development (EUROPLAN) - EUROPLAN is supporting the mechanisms that will facilitate Member States to incorporate EUROCAT's recommendations for Primary Prevention of Congenital Anoamlies in their National Plans for Rare Diseases, and will facilitate exchange of experience among Member States, in collaboration with EUROCAT.

EUROCAT contributes to the European Platform for Rare Diseases Registries (EPIRARE).

World Health Organisation (WHO)

- For ICD11 revision - The International Coding and Classification System for Diseases (ICD10) has been in use since 1994. WHO plan to release the next version (ICD11) in 2015. The EUROCAT Coding and Classification Committee have been involved (in collaboration with Orphanet) in the development of the malformation chapter for ICD11.

- As a WHO Collaborating Centre for the Surveillance of Congenital Anomalies - EUROCAT Central Registry re-designated May 2011 for 4 years. In this capacity EUROCAT is assisting the WHO in implementing the resolution WHA63.17 of the 63rd World Health Assembly (2010) on birth defects at both a European and global level. EUROCAT is also assisting the WHO in implementing its strategy for the prevention & control of non-communicable diseases (NCDs action plan 2008-2013).

EUROCAT exchanges information and has a liaison officer for:

- International Clearing House for Birth Defects (ICBDSR) – 17 EUROCAT registries are members

- The Voice of Rare Disease Patients in Europe (EURORDIS)

- European Network Teratology Information Services (ENTIS)

- Better statistics for better health for pregnant women and their babies (EUROPERISTAT)

- Surveillance of Cerebral Palsy in Europe (SCPE)

- European Society of Human Genetics (ESHG)

- European Network of Centres for Pharmacoepidemiology (ENCePP)

- European Centre for Disease Prevention and Control (ECDC) e.g. joint work on congenital rubella

EUROCAT is working with SCPE and EUROPERISTAT for improved recording of socio economic status for analysis of inequalities

Strategic relevance, contribution to the Health Programme, EU added value and level of innovation.

EU action in the area of public health is designed to support and complement Member States' (MS) action in improving public health. EUROCAT is a network active in areas corresponding to all 3 priority objectives of the health programme's 2013 Workplan; Improve Citizens Health Security, Promote Health, Generate and Disseminate Health Information. EUROCAT activity contributes to integrated surveillance of non-communicable diseases (NCD) (WP2013 4.2.4.2) by improving timeliness, comparability, analysis and reporting of health data (WP2013 4.3.1.1) by efficient, well-established mechanisms for the collection of data and information, to produce scientific evidence and to provide citizens, stakeholders and policy-makers with information to take decisions on a range of issues affecting individual and collective health. EUROCAT also highlights geographical inequalities in Europe in relation to prevention, screening and need for treatment and care services. EUROCAT activity has EU added value concerning EU-level action in areas where national action is not feasible or effective, specifically for rare diseases (RD) (eg.

Improving coding and classification, evaluation of primary preventive measures). The Council Recommendation 2009 on an action in the field of RD and the Commission Communication on RD: Europe's Challenges 2008, recognise the need for registries and databases co-ordinated at European level. The WP2013 aims to support RD registries and networks (this includes Congenital Anomaly registries and networks) with a view to their sustainability, to set up a sustainable platform to coordinate and maintain registries and networks on RD. Registries and networks are key instruments in increasing knowledge of RD and in developing clinical research. They are the only way to pool data in order to achieve a sufficient sample size for epidemiological and/or clinical research (WP2013 4.2.4.4). EUROCAT achieves EU added value through: • Pooling of data • Comparison of data • Sharing of expertise and resources • Joint approach to European public health questions

EUROCAT is equipped to improve and reinforce public health emergency preparedness and planning to respond to potential risks (WP2013 4.1.2) e.g., it has responded to issues such as swine flu and Chernobyl. Through epidemiological surveillance, pharmacovigilance and annual monitoring for trends and clusters in time EUROCAT can detect signals of new or increasing teratogenic exposure that may require public health action. EUROCAT has activity focused on primary prevention (PP) of congenital anomalies (CA) (e.g. EUROCAT Recommendations on policies considered for PP of CA in MS National Plans and Strategies on RD). The WP2013 prioritises effective prevention of NCD (at any stage of the life cycle including chronic conditions and RD) by taking action on common risk factors (WP2013 4.2.1.1). Adequate public understanding of risk factors can help reduce the burden of ill health from NCD on health systems. EUROCAT focuses on the pregnancy/fetal health component in support of MS efforts to motivate action on healthy nutrition and other EU health promotion actions (obesity, tobacco, alcohol consumption) to improve health of EU citizens, in line with the Strategy for Europe on Nutrition, Overweight and Obesity-related Health Issues (WP2013 4.2.3). EUROCAT registries exchange experience in E Health on use of e records and data linkage for registries (WP2013 4.2.2.5). EUROCAT is taking innovative measures to build on the EUROCAT Joint Action 2011-2013 and EUROCAT's daughter project, FP7 funded EUROmediCAT (2011-15), by building a European pharmacovigilance system for evaluation of safety of medication use in pregnancy in relation to risk of CA (WP2013 4.1.5.2). EUROCAT's pharmacovigilance activity facilitates collaboration among MS for effective/optimal organisation by developing protocols and databases for signal detection and signal evaluation relating to medication exposure in early pregnancy.

Effectiveness of the dissemination

As part of EUROCAT joint action proposal a dissemination plan was developed with the purpose of:

- dissemination of expected outcomes of the the EUROCAT-Joint Action project
- raising the profile of the EUROCAT network
- raising awareness on the importance of registries and databases on congenital anomalies (CA) coordinated at European level
- gaining wider support for setting up registries for CA across Europe

The information provided by the JA was targeted to:

-Health professionals eg. 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.

-Public health professionals and those involved in health service planning at regional,

national, EU, and WHO levels

-Organisations and networks working in the area of Rare Diseases

-Governmental/public regulation agencies in several domains (industrial, air quality, environmental protection agencies, food, medications)

-Patient organisations

-Scientific research community (in epidemiology, public health, clinical genetics, embryology etc.)

-Scientific research community (in epidemiology, public health, clinical genetics etc and international research networks including Global Burden of Disease study which makes extensive use of EUROCAT data, and International Clearinghouse).

-Politicians/policy makers

-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.

Dissemination methods included a EUROCAT promotional leaflet (copies provided to the EAHC, to Registry Leaders and brough to conferences etc for further dissemination), 3 EUROCAT Newsletters (sent to the EUROCAT Central Registry global emailing database, and further disseminated via member's own emailing databases), the EUROCAT website (both a public and internal interface), 3 Registry Leaders' Meetings, 2 European Symposia on CA, workshops and conferences, publications (reports, peer-reviewed credible high impact scientific papers, press releases etc.), networking with and contribution of results and expertise to other networks, organizations and committees (i.e. EURORDIS, EUCERD, EUROPLAN), EUROCAT Central Registry's designation and activity as a WHO Collaborating Centre for the surveillance of CA and the setting up of National EUROCAT Committees (now involving approx. 2/3rds of registries).

EUROCAT updates prevalence tables twice a year, making data available globally within 6 weeks of receiving it- http://www.eurocat-network.eu/accessprevalencedata/prevalencetables. Through dissemination EUROCAT has become an increasingly recognised framework, applied broadly for the coding and classification of congenital anomalies and is recognised as having expertise in the setting up of registries, databases and interpretation of data.

Numbers can be assigned to some of EUROCAT's Central Registry activity (i.e. the no. of individuals in the EUROCAT Central Registry emailing database). Thereafter EUROCAT Member Registries also disseminate widely (i.e forwarding e-newsletter circulations further to their own mailing lists, taking the promotional leaflets to their own meetings and conferences etc.). Putting a numerical value on such reaching of stakeholders was impossible due to the scale and structure of the EUROCAT JA.

Over the period of the JA (Jan 2011 to Dec 2013) there were 70,670 visitors to the EUROCAT website (from 182 different countries globally), 38,763 unique visitors and 207,221 page views. 54.2% of visitors were new to the website and 45.8% were returning visitors.

Since registration to obtain website prevalence data from the website was initiated in

March 2012, 564 individuals from 54 different countries and diverse roles (spanning the entire range of EUROCAT's target audience) have registered to use EUROCAT's interactive website prevalence tables.

EUROCAT Central Registry continues to respond to a variety of external enquiries received by email from a diverse array of individuals spanning the full spectrum of EUROCAT's target audience i.e. Parents of affected individuals, patient organisations, pharmacists, clinicians, registry leaders, epidemiologists, pharma industry, students, government officials, public health officials, reporters etc. A special enquiry form has been developed to deal with increasing demand for information on medication exposure.

232 participants from 25 different countries attended the first EUROCAT symposium of the Joint Action on the prevention of congenital anomalies, and ? participants from ? countries attended the second.

Approx. 2500 people are on the EUROCAT Central Registry emailing database.

EUROCAT aimed to obtain constructive feedback (relating to the EUROCAT JA January 2013 through December 2013) about its website and other outputs via a web-based evaluation survey tool (upon visiting the EUROCAT website). 133 respondents from 33 different countries responded. Respondents represented the full spectrum of EUROCAT's target audience.

As part of the EUROCAT JA Evaluation activity a questionnaire (created by an external subcontractor and accessed via an online survey tool) was employed to focus on perception of "value" of the EUROCAT outputs/outcomes by targeted end-users. 93 individuals (from 33 different countries) responded to the EUROCAT Independent Evaluation Questionnaire Survey. 22 of those respondents identified themselves as Registry Leaders, all other respondents represented other target end users, i.e. Public Health Authority, Paediatrician or Paediatric Surgeon, Obstetrician, Nurse or Midwife, Medical Geneticist, Other Healthcare Professional, Patient or Patient's Family, Patient Organisation, Academic or Researcher, Regional/National Department of Health, European Commission, WHO or Other International Organisation.

For a full decscription of feedback from EUROCAT's target audience, obtained through the evaluation process, see the full Evaluation Report Annexed in Section VII as part of WP3.

Conclusions and recommendations, sustainability of the project (after EC co-funding) and lessons learned.

EUROCAT provides a ready collaborative network and infrastructure for research related to causes and prevention of CA and treatment and care of affected children. Post 2014, the co-ordination of EUROCAT will be moving to the EU Joint Research Centre at ISPRA in Italy, as part of the new Public Health Unit of the Institute for Health and Consumer Protection. This is a considerable success for EUROCAT in achieving a long term sustainable future. Moving forward, some EU countries are under-represented in EUROCAT and a change in the funding situation in those countries could contribute to the goal of EU-wide surveillance.

SECTION VI

Horizontal Work packages

Work package title : Coordination of the Joint Action
Work package Number : 1
Work package Leader : Prof. Helen Dolk (Main Partner and Project Leader)
Number of associated partners involved : Main partner plus 13 associates
UU, SFR, PIH, KDB, Lillebaelt, INSERM U953, NCHAI, IMER, ISS, UMCG, FHI, CREAL, QMUL, Oxford
Number of person/ days of this work package:

1,197.77

Total budget of this work package:

Total Cost	EU funded	Contribution
609,345.00	447,305.00	162,040.00

Starting Date : 01/01/2011 **Ending date :** 31/12/2013

Project management

Management Plan **yes**
The EUROCAT Association is the association of EUROCAT Member Registries (Full and Associate), which has a constitution & is independent of funding modes and of EUROCAT Central Registry. The Association elects a President (2 years) and 5 further Steering Committee (SC) members (4 years). The SC, including also the Director of Central Registry (Project Leader), are responsible for decision making regarding the EUROCAT Network, data and processes. The EUROCAT Project Management Committee, comprising of the SC, the Project Manager and Activity Leaders, were responsible for delivering the EUROCAT Joint Action funded work programme.

Sustainability plan available, describing the measures taken to ensure the continuation of the action after the end of the EC funding **yes**
Post 2014, the co-ordination of EUROCAT will be moving to the EU Joint Research Centre at ISPRA in Italy, as part of the new Public Health Unit of the Institute for Health and Consumer Protection. This is a considerable success for EUROCAT in achieving a long term sustainable future. Further detail can be obtained from Jaroslaw Waligora (EAHC) as part of the Rare Disease Platform development.

Partnership Internal Agreement **yes**
The Main Partner and those associate/collaborating partners that are members of the EUROCAT Network comply with the EUROCAT Association Constitution.

Description of the work package:

Activities undertaken to ensure the coordination and management of the project and the partnership and to ensure that the activities are implemented as planned.

WP1 was supported by a management/governance structure that included a EUROCAT Project Management Committee (PMC), a EUROCAT Project Manager (Dr. Rhonda Curran, UU, UK) and a EUROCAT Project Administrator (Barbara Norton, UU, UK).

Please note the EUROCAT Project Manager was not appointed until Month 5 and was absent months 32-36 (maternity leave), but returned to finalise the Final Report of the EUROCAT Joint Action. There was no cross funding (applies to the EUROCAT

Administrator and the EUROCAT Project Manager) between the EUROCAT Joint Action and the EUROCAT Operating Grant (which commenced January 2014).

The PMC consisted of;
(i) the Project Leader (Prof. Helen Dolk (UU, UK) also Director of EUROCAT Central Registry)
(ii) the President of the EUROCAT Association (the association of EUROCAT member registries (Full and Associate), which has a constitution and is independent of funding modes and of EUROCAT Central Registry)
(iii) a Steering Committee of elected registry leaders from Full EUROCAT member registries
(iv) the Work Package Leaders
(v) the Project Manager

The President of the EUROCAT Association was Prof. Lorentz Irgens (FHI, NO, *until June 2012*), who was then proceeded by Prof. Ingeborg Barisic (KDB, HR, *until present*).

The Steering Committee (SC) included;
- Prof. Lorentz Irgens (FHI, NO) *until June 2013*
- Prof. Eliza Calzolari (IMER, IT) *until June 2013*
- Dr. Babak Khoshnood (INSERM U953, FR)
- Dr. Vera Nelen (PIH, BE) *until June 2011, reinstated June 2012*
- Dr. Diana Wellesley (SUHT, UK)
- Prof. Ingeborg Barisic (KDB, HR) *since June 2011*
- Prof. Martin Haeusler (SFR, AT) *until June 2011*
- Dr. Ester Garne (Hospital Lillebaelt, DK) *since June 2013*
- Dr. Fabrizio Bianchi (IFC-CNR, IT) *since June 2013*

The Work Package Leaders included;
WP1 Prof. Helen Dolk (UU, UK)
WP2 Prof. Ingeborg Barisic (KDB, HR)
WP3 Prof. Helen Dolk (UU, UK)
WP4 Ms. Maria Loane (UU, UK)
WP5 Dr. Ester Garne (Hospital Lillebaelt, DK)
WP6 Dr. Martine Vrijheid (CREAL, ES) *until June 2013*
WP7 Dr. Domenica Taruscio (ISS, IT)
WP8 Prof. Joan Morris (QMUL, UK)
WP9 Dr. Marian Bakker (UMCG, NL) *until June 2013*

WP1 was also supported by an internal communication process. EUROCAT Central Registry was responsible for the management, administration and provision of the associate partner's information-exchange infrastructure. In addition to use of the website (described below), ad hoc email, telephone and fax correspondence, EUROCAT Central Registry communicated with associate partners on an approximate fortnightly basis via emailed EUROCAT Communications to bring issues relating to EUROCAT's Joint Action to the attention of associate partners, i.e. deadlines for EUROCAT member registries to give permission for their data to be used in planned Joint Action research projects, published EUROCAT papers and reports, to bring attention to updated or new documents on the EUROCAT website. All associate partners were able to supply information to be added to the website or email Communications, via the EUROCAT Central Registry Administrator.

Activity 1 – 26th – 28th EUROCAT Registry Leader's Meetings (RLMs)

Administrative support for each RLM was provided by both the main partner (UU, UK) and the respective hosting partner. RLM agendas, meeting documents, participant lists and subsequent minutes were made available to all associate partners through the member's only section of the EUROCAT website.

The 26th EUROCAT RLM was held in Antwerp (PIH, BE) on the14th-16th June 2011. Attended by 37 EUROCAT Registry Leaders, 29 local EUROCAT Registry staff, 9 EUROCAT Central Registry staff and doctoral students, and 2 external guests. All associate partners were represented.

The 27th EUROCAT RLM was held in Budapest (NCHAI, HU) on the 14th-15th June 2012. Attended by 74 participants from 23 countries, including 30 EUROCAT Registry Leaders, 32 local EUROCAT Registry staff, 8 EUROCAT Central Registry staff and doctoral students, and 4 external guests. 32 of 36 associate partners were represented.

The 28th EUROCAT RLM was held in Zagreb (KDB, HR) on the 12th–13th June 2013. Attended by 85 participants from 22 countries, including 34 EUROCAT Registry Leaders, 35 local EUROCAT Registry staff, 8 EUROCAT Central Registry staff and doctoral students, and 8 external guests. 30 of 36 associate partners were represented.

Activity 2 – Organisation of PMC Meetings

In addition to meeting at each RLM, the PMC (and separately the SC) met at other times. Physical meetings included the 24th–25th January 2011 (Luxembourg), the 9th-10th November 2011 (Oxford, UK), the 28th–29th March 2012 (Oxford, UK), the 12th-13th December 2012 (Oxford, UK), and the 27th-28th November 2013. The PMC (and separately the SC) also utilised frequent ad hoc teleconference meetings. All meetings were minuted and the minutes were made available to all associate partners through the member's only section of the EUROCAT website and have been annexed in Section VII.

Activity 3 – Maintenance of EUROCAT website

Throughout the project, the EUROCAT website www.eurocat-network.eu has been a main management tool for EUROCAT as well as the main portal of external and internal dissemination.

EUROCAT Central Registry has administrative control of the EUROCAT website with both a public and member's only interface. The public website holds much of the information necessary to members: Central Registry staff and member registry contact details; website tables; documents describing the EUROCAT network, guidelines and processes; announcements; reports; press releases, bibliography, newsletters; data request documentation. Additional information for members only includes the member's forum, the online budget management system, meeting documents, minutes of all Association, Steering/Project Management Committee/Registry Leaders meetings, archived Communication emails, research project protocols, draft reports and tables.

The EUROCAT administrator, Project Manager and Website Dissemination Committee (formed in 2011 for the EUROCAT Joint Action) have been responsible for updating the website, which also now features an overview of the Joint Action http://www.eurocat-network.eu/aboutus/jointactioneurocat. The Website Dissemination Committee met during the RLM in 2012 and 2013 and minutes of the meetings were made available to EUROCAT members internally on the EUROCAT website.

The Website Dissemination Committee includes;

Prof. Inbegorg Barisic (Chair) (KDB, HR)
Prof. Elisa Calzolari (IMER, IT) *until June 2013*
Hermien de Walle (NL) *since June 2013*
Prof. Helen Dolk (UU, UK)
Dr. Ester Garne (Hospital Lillebaelt, DK)

Ruth Greenlees (UU, UK)
Prof. Lorentz Irgens (NO) *until June 2013*
Dr. Babak Khoshnood (INSERM U953, FR)
Maria Loane (UU, UK)
Dr. Bob McDonnell (HSE, IE)
Prof. Joan Morris (QMUL, UK)
Dr. Diana Wellesley (SUHT, UK)

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

Specific applications of the website relating to WP1 activities included providing a portal to link associate partners to registration for the RLMs/symposiums, providing an online budget management system to all associate partners and management of PMC/SC meeting arrangements.

Other WP activities have made specific use of the EUROCAT website. This has included the provision of website data related to WP4, use of the website to invite comment on the ICD11 proposal for developmental anomalies (relevant to WP5) and review of multiple malformation cases (also relevant to WP5).

A registration system for non-member access to online tables was developed during 2011 and piloted and launched during 2012 (see evaluation of this system in WP3 report).

Activity 4 – Financial Management

In 2011 the main partner (UU, UK) implemented a secure, confidential and password protected online budget management system (EBS), accessible to EUROCAT members only through the EUROCAT website. Workshops to describe, demonstrate and train associate partners on how to use the EBS were held at annual RLM meetings. The EBS enabled associate partners to maintain their accounts, submit timesheets, and upload invoices and receipts. As well as maintaining the main partner accounts, administrator access to the online budget management system enabled the co-ordinating partner to monitor expenditure throughout the project. The system made associate partners more aware of what they agreed to do for the contract and made them more aware of the amount of money they were receiving from the EU. As associate partners were more aware it was easier for the coordinating partner to produce yearly expenditure summaries and identify who was underspent and who was overspent.

The EUROCAT Project Manager and the EUROCAT Administrator attended an EAHC workshop on the Preparation of Final Payments on the 14th November 2011 and the 24th November (2013) respectively.

The subcontracting rules applied and the process for implementing the public procurement (E5 subcontracting cost), were in accordance with guidelines issued by the EAHC and for funds held by EUROCAT Central Registry, also complied with constraints imposed by the Main Partner hosting organisation – the University of Ulster. UU required that subcontracting costs in excess of £5000 (GBP) go to tender via the University of Ulster Procurement Office, unless a case is provided to support the need to go with one particular subcontractor, thus avoiding tender. This process was adopted to secure the services of BioMedical Computing Ltd thus ensuring essential continuity of a subcontractor that has detailed knowledge and experience of EUROCAT. Bio-Medical Computing has worked closely with EUROCAT for the last 3 periods of European Union funding (since 2000).

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

The first and second interim reports of the EUROCAT Joint Action were submitted to the EAHC.

EUROCAT Central Registry liaised with the EAHC Health Unit to provide information for the Joint Action brochure 2008-2011 which has been published on the EAHC website:
http://ec.europa.eu/eahc/publications/publications_for_health_programme.html.

Karl Freese of DG Sanco attended the RLM in 2011 and 2012. Jaroslaw Waligora of DG Sanco attended the RLM in 2013.

See EAHC workshops attended in Activity 4.

EUROCAT Central Registry responded to a request from DG Sanco (from both Karl Freese and Jaroslaw Waligora) for expert information that would help them formulate a response to a written question received from the European Parliament – "Does the commission not think that a positive screening result for down syndrome would increase the numbers of abortions or does it think that this would be a way for families to make informed decisions"?

EUROCAT Central Registry has been liaising with Jaroslaw Waligora of the EAHC in an effort to determine how to make EUROCAT and relevant EUROCAT topics (i.e. congenital anomalies, preconceptional care etc.) more visible on the EU Health Portal.

Activity 6 – Administrative support to all work packages

Administrative support has been provided throughout the reporting period by both the EUROCAT Administrator and the EUROCAT Project Manager, based at EUROCAT Central Registry.

Activity 7 – Overall project management and co-ordination tasks

Corresponds to Activities 1-6 combined. In addition, the PMC and/or SC were responsible for the management and coordination of project planning, organisation, assuring quality of implementation of project activities, identifying and overcoming obstacles and verifying that stated objectives (process/output indicators, milestones and deliverables) were met (see Process Evaluation in WP3 report).

Additional Information

On the 9th April 2013, the Project Leader and EUROCAT Administrator informed the EAHC (by letter) about a number of requested grant amendments (relevant budget transfer forms were also submitted), a number of changes in partnership and a number of changes to the legal status of some of the beneficiaries (Latvian and Hungarian partner).

Deviation from planned milestones
The first interim report, reports on project activity spanning Months 1-12, and the second interim report, reports on project activity spanning Months 13-24. A deliverable date of Months 12 and 24 were originally anticipated for each respective report. WP leaders preferred to wait until each reporting period had been fully completed so that they could provide comprehensive information for the interim reports. Thus a delay was necessary to bring this information together following the reporting period and it was therefore no longer possible to provide each interim report immediately at the end of each reporting period. This delay in submission of interim reports did not impact on the project.

List of deliverable(s) linked to this work package

Deliverable

	Title
1	**D1 – Final Report** Final Report to Executive Agency/DG Sanco (Month 36), and Interim Reports at Months 12 and 24.

Milestones reached by this WP

	Milestone title	Month of achievement
1	Interim Report	Expected M12 Achieved M17
2	Interim Report	Expected M24 Achieved M31
3	Registry Leader's Meeting in Antwerp (June 2011)	Expected M6 Achieved M6
4	Registry Leader's Meeting in Budapest (June 2012)	Expected M18 Achieved M18
5	Registry Leader's Meeting in Zagreb (June 2013)	Expected M30 Achieved M30

Horizontal Work packages

Work package title : Dissemination of the Joint Action
Work package Number : 2
Work package Leader: Prof. Ingeborg Barisic (Associate Partner No. 4 (KDB) and President of EUROCAT Association)
Number of associated partners involved : Main Partner plus 17 associates
KDB, UU, SFR, PIH, Lillebaelt, INSERM U953, IMER, ISS, UMCG, FHI, CREAL, QMUL, Oxford, THL, HSE, IFC-CNR, UMCL, NCHAI
Number of person/ days of this work package:

132.00

Total budget of this work package:

Total Cost	EU funded	Contribution
56,435.00	36,367.00	20,068.00

Starting Date : 01/01/2011 **Ending date :** 31/12/2013

Dissemination plan available yes
Project leaflet/brochure/newsletters submitted to EAHC yes
Project website: www.eurocat-network.eu
The EU funding disclaim and EU logo are visible in the project website and public presentations yes

Description of the work package

Description of the activities undertaken
See target groups outlined in Section V.
See Dissemination Plan Annexed in Section VII under WP2.
Dissemination methods and relevant outputs
Website
See WP1 report.
Promotional leaflet (Milestone 5 of WP2) – an electronic version has been made available for download on the EUROCAT website (http://www.eurocat-network.eu/content/EUROCAT-Leaflet.pdf) (M10) (Annexed in Section VII under WP2) and a print version was produced and copies for distribution were sent to all EUROCAT Registry Leaders and to the EAHC (M16). The promotional leaflet was further distributed on an ad hoc basis (i.e. when visitors were present at EUROCAT Central Registry, at the EUROCAT Symposiums, or when EUROCAT representatives were attending relevant meetings/conferences). EUROCAT Central Registry has difficulty tracing dissemination of hard copies of the EUROCAT promotional leaflet. EUROCAT member registries do not always report or log where and when they distribute the leaflet.
Production of the EUROCAT Promotional Leaflet was due to a number of factors, delayed appointment of the EUROCAT Project Manager (appointed in M5), and delays in printing and posting the final product by the Italian partner responsible for printing.
Newsletter (Milestone 1, 2 and 3 of WP2)

Three EUROCAT Joint Action Newsletters have been published online on the EUROCAT website (M15, M27 and March 2014),

2011 Newsletter http://www.eurocat-network.eu/content/EUROCAT-Newsletter-5.pdf

2012 Newsletter http://www.eurocat-network.eu/content/EUROCAT-Newsletter-6.pdf

2013 Newsletter http://www.eurocat-network.eu/content/EUROCAT-Newsletter-Dec-2013.pdf

and also distributed to the EUROCAT Central Registry emailing database (a dynamic list, in constant revision, currently approx. 2500 globally distributed recipients). All three newsletters are annexed in Section VII under WP2.

Collation of information from WP leaders for inclusion in the EUROCAT Newsletters took longer than expected. Due to this each EUROCAT Newsletter was delayed by 3 months. This did not have any impact on other activities within the WP or on allocated resources.

EUROCAT Central Registry encourages member registries to further disseminate the EUROCAT Newsletter to their respective relevant mailing lists. We know from informal internal communication that many member registries elect to do this but EUROCAT Central Registry finds it difficult to trace this further dissemination.

Registry Leaders Meeting (RLM)

For information in Annual Registry Leaders' Meetings see WP1 report.

Workshops

WP leaders utilised workshops during the annual RLMs, described where applicable in each respective WP report (in Section XI).

EUROCAT Symposiums (Milestone 4 of WP2 and Deliverable 2 of the EUROCAT Joint Action)

For the outcome of the evaluation of each EUROCAT symposium see WP3 report.

See both Abstract books including programmes annexed under Deliverable 2 in Section VII.

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

Together with the province of Antwerp, EUROCAT successfully hosted 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. The 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 a 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 a 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 fetal 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 the keynote presentations can be found on the EUROCAT website. A Book of Abstracts was 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.

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

The 12th international EUROCAT symposium took place on 14th of June in Zagreb, Croatia. The main topics of the symposium were the marking of the 50th anniversary of the thalidomide tragedy, public health policies in the field of rare diseases, research on genetic and environmental risk factors for congenital anomalies, the use of drugs in pregnancy and evaluation of pre-implantation and prenatal diagnosis. The symposium hosted distinguished keynote speakers from different European countries. Prof Patricia Boyd from the National Perinatal Epidemiology Unit of the University of Oxford presented how thalidomide accident led to the development of registries for surveillance of congenital anomalies and to further investigation of possible teratogenic effects of new drugs and procedures such as assisted reproductive technology. Dr Eva Bermejo Sanchez and Prof Maria-Luisa Martinez-Frías from the Institute for Rare Diseases Research and Research Centre for Congenital anomalies of the University of Madrid presented clinical manifestations of thalidomide embryopathy and how the thalidomide tragedy led to the development of preventive measures such as strict regulation of marketing and categorization of drugs. Prof Stephen Lynn and Prof Kate Bushby presented EUCERD Joint Action activities in supporting the implementation of plans and strategies for rare diseases across Member States. Prof Dian Donnai from the Manchester Centre for Genomic Medicine of the University of Manchester presented advances in genetic testing for children with congenital anomalies and developmental disorders, and Prof Albert Schinzel from the Institute of Medical Genetics of the University of Zürich spoke about the impact of twin pregnancies on the development of congenital anomalies. Lolkje de Jong-van den Berg, Emeritus Prof in Pharmacoepidemiology from the University of Groningen presented different study designs for signal detection and signal evaluation to identify teratogenic risks of medicines used in pregnancy. Prof Borut Peterlin from the Clinical Institute of Medical Genetics of the University Medical Centre Ljubljana presented experiences of his centre in preimplantation genetic diagnosis. Prof Ivan Malcic from the Department of Paediatric Cardiology of the Zagreb University Hospital Centre presented Croatian registry of congenital heart disease. There were 19 oral and 57 poster presentations. Book of abstracts can be found on the EUROCAT website

http://www.eurocat-network.eu/aboutus/publications/eurocatsymposiaandworkshops/zagrebsymposium2013

Networking

In M11 the EUROCAT PMC agreed to adopt a Liaison Officer strategy to facilitate liaison with other networks, organisations and committees. Through liaison with other networks EUROCAT aimed to;

1. Explore the potential of joint projects
2. Exchange information, experience and expertise
3. Integrate Joint Action outcomes with related activity of other networks

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 the PMC agenda 'news from other networks', exchange of newsletters etc.

An overview of EUROCAT's liaisons with other networks, organisations and committees during the time of the EUROCAT Joint Action is annexed in Section VII under WP2.

Regarding liaison with the Rare Disease Community:

EUROCAT activity has EU added value concerning EU-level action in areas where national action is not feasible or effective. This particularly applies for Rare Diseases (RD) (eg. Improving coding and classification, evaluation of primary preventive measures). The Council Recommendation 2009 on an action in the field of RD and the Commission Communication on RD: Europe's Challenges 2008, recognise the need for registries and databases co-ordinated at European level. The WP2013 of the Health Programme aims to support RD registries and networks (this includes Congenital Anomaly registries and networks) with a view to their sustainability, to set up a sustainable platform to coordinate and maintain registries and networks on RD. Registries and networks are key instruments in increasing knowledge of RD and in developing clinical research. They are the only way to pool data in order to achieve a sufficient sample size for epidemiological and/or clinical research. EUROCAT has taken steps throughout the timeframe of the Joint Action to promote this message through liaison with the wider Rare Disease Community.

In particular via creation of a:

Special report for the attention of Orphanet.

The report includes a comparison of EUROCAT and Orphanet prevalence data per EUROCAT congenital anomaly subgroup and for very rare monogenic syndromes and details the contribution of congenital anomalies to RD.

EUROCAT (2013): A potential source of prevalence data for Orphanet (Annexed in Section VII under WP8). Also available at http://www.eurocat-network.eu/content/EUROCAT-Report-Potential-Source-of-Data-for-Orphanet.pdf

Segolene Ayme (Director of International Affairs at Orphanet, Chair of the EU Committee of Experts of Rare Diseases, Chair of the Topic Advisory Group on Rare Diseases at WHO, Project leader of Support IRDiRC, Editor in chief of the OJRD) provided feedback indicating that Orphanet *"always consider the EUROCAT database as the best source of information on epidemiology data for congenital anomalies".*

Special Report for the wider Rare Disease Community.

This report details the contribution of congenital anomalies to RD and the Contribution of EUROCAT to European Action on RD.

EUROCAT (2012). EUROCAT Special Report: Congenital Anomalies are a Major Group of Mainly Rare Diseases (Annexed in Section VII under WP8). Also available at http://www.eurocat-network.eu/content/Special-Report-Major-Group-of-Mainly-Rare-Diseases.pdf

Liaison relating to Primary Prevention of Congenital Anomalies:

EUROCAT contributed to and was represented in Brussels (by Dr. Rhonda Curran EUROCAT Project Manager) 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 uploaded the report on its website, under the RD section. The report can be accessed via http://www.ifglobal.org/images/2nd-report-ntdprevention.pdf

EUROCAT (represented by Dr. Rhonda Curran, the EUROCAT Project Manager) was also present to deliver a presentation (Birth Defect Surveillance with a View to Prevention) and be represented on an expert panel at "The challenges of health inequalities in the treatment and prevention of birth defects in Europe: An information workshop for MEPs and NGOs" at the European Parliament, Brussels, 9th October 2012.

Dr. Curran also provided slides in relation to Primary Prevention to Prof Peter Mossey (Director of WHO Collaborating Centre for Public Health Issues on Congenital Anomalies and Technology Transfer) for the purposes of chairing a Prevention Task Force at the International Craniofacial meeting in Orlando in May 2013.

For further information on the liaison with EUROPLAN and EUCERD in relation to the development of EUROCAT's Recommendations on policies to be considered for the primary prevention of congenital anomalies in National Plans and Strategies on Rare Diseases, see WP7 (Primary Prevention of Congenital Anomalies) report.

National EUROCAT Committees

During 2011 the EUROCAT PMC advocated (to the EUROCAT Network) the establishment of National EUROCAT Committees (NEC) or equivalent with representation from registries, Ministries of Health, patient groups and professional associations. The proposed role of NECs was 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 the 2nd Annual RLM in Budapest in June 2012, registries were further encouraged to pursue the establishment of NECs. A representative from one of EUROCAT's three Irish member registries presented their experience of setting up a NEC to other EUROCAT members.

By the end of 2013 we have collected information from 32/36 (89%) EUROCAT Joint Action associate partners. Of those, 20/32 (62.5%), 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.

The British Isles Network of Congenital Anomaly Registers (BINOCAR) is working closely with Public Health England (PHE) to secure a national surveillance system involving CARs in every region in England. In 2012 annual general meeting was held at the University of Oxford hosted by CAROBB. BINOCAR data was used in a number of research projects. Two BINOCAR representatives sit on the newly configured National Congenital Anomaly Group chaired by Dr Jem Rashbass of PHE. A national committee established in the Netherlands met on June 5, 2012. Their role is to advise the Ministry of Health on aspects associated with registration of congenital anomalies, to monitor the relation with other perinatal registrations and to stay in contact with the National Board for Perinatal Care. Members are representative from the relevant health professions, gynaecologists, midwives, pathologists, paediatricians, geneticists etc. In 2013 the Committee expanded with representatives of the National Centre for Population Screening which hold the prenatal screening database. During 2012, the Irish National Congenital Anomaly Committee enabled progress in improving data capture, particularly in relation to a national NTD prevalence study. The results of this study, carried out by

the three Irish EUROCAT registries, are being analysed, and presented in 2013. The Spanish Registries included in EUROCAT are working jointly for a research project (IRDiRC Consortium) called SpainRDR (Spanish Rare Diseases Registries Research Network), EUROCAT registries are now full members of this consortium which constitutes a sort of National Committee for registries of congenital anomalies, although it is not recognized as such. The Italian Central Coordination Committee on CA established at the Italian National Centre of Rare Diseases (CNMR) is composed by the Director and experts of CNMR, leaders of regional registries, members of the Italian Ministry of Health and of Italian National Institute of Statistics. In this contest, the CNMR is promoting also the EUROCAT Joint Action activities at national level. ISTISAN (National Health Institute in Rome) recently published a chapter on the situation in Italy regarding CA registries proposing to create a national network of regional registries that would cover the whole country. In Croatia an unofficial National Committee including neonatologist, paediatric surgeon, patient representative, public health professional and clinical geneticist was established in November 2013. The Swedish Register of Congenital Malformations is run by the Swedish National Board of Health and Welfare. For births, it is a sub register of the Swedish Medical Birth Register. The terminations, however, are reported to a special register under strict regulations concerning anonymity of data. Sweden do not have a formal National EUROCAT Committee, but they have an advisory committee regarding congenital malformations, with representation from different professions (obstetricians, neonatologists, child cardiologists, clinical geneticists, midwifes, and epidemiologists), and from different parts of the country.
In Germany there has been initiative at regional level (Saxony-Anhalt) to establish EUROCAT Committee. The Malformation Monitoring Centre Saxony-Anhalt organized in 2013 several meetings for doctors and health care professionals in Saxony-Anhalt to discuss data together - and benefiting from the EUROCAT surveillance activities.
This advisory committee actually plays the role of the National Committee. In Norway and Hungary there is an interest in setting up a National Committee, but no action so far.
In France there is at present no National EUROCAT Committee, but the registry leaders meet regularly with colleagues at the in VS (French National Institute of Health Surveillance) who follow and evaluate the activities of the registries of congenital anomalies at the national level. In Belgium there is no "National EUROCAT Committee". The Antwerp registry has a steering committee with members from the University of Antwerp.
There have been initiatives similar to National Committees but including other types of registries. For example, in Finland there is a general advisory committee covering all Reproductive Registries (Malformation Register, Medical Birth Register, Register on Very Small Babies, Register on Abortions and Sterilisations and IVF statistics) with participants from the Ministry of Health, from other governmental authorities, from related professionals: clinicians, hospitals and hospital districts, from associations of doctors with certain specialities, Association of Midwives etc. In some countries (e.g. Finland, Denmark, Austria, Slovenia, Malta) there will be difficulties in setting up a National EUROCAT Committees, either because of the organisation of the health care system or because of the small size of country.
Conference Presentations and Posters
Conferences were identified as an important method of disseminating information about EUROCAT activities to stakeholders. The EUROCAT PMC aimed to present results of the EUROCAT Joint Action at academic conferences as well as to audience present at special interest conferences (e.g. Rare Diseases Conference). A full list of instances where EUROCAT members have attended scientific meetings and contributed by presenting (either orally or by way of a poster) as representatives/advocates of EUROCAT has been annexed to Section VII under WP2 (this list relies on notification to EUROCAT Central Registry by EUROCAT member registries). Where possible (when provided by EUROCAT members) EUROCAT Central Registry tries to make these presentations available to the

wider network on the member's only section of the EUROCAT website.

EUROCAT publications

Papers providing information on the EUROCAT Joint Action and its outputs have been submitted to peer-reviewed academic journals to maximize the visibility of the project in the scientific community. 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. A full list of relevant publications is annexed in Section VII (see related citation profiling WP3 report). This also includes non-peer-reviewed publications added to the EUROCAT website that were produced as a result of EUROCAT activity within the Joint Action timeframe.

For a full back catalogue of EUROCAT publications, both collaborative and single registry publications (including outputs not related to the Joint Action) access an interactive publications search facility on the EUROCAT website http://www.eurocat-network.eu/aboutus/publications/publications.

Other publication types

EUROCAT contributed to and was represented in Brussels on the 29th June 2011 (M6), 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 uploaded the report available at: http://ifglobal.org/images/2nd-report-ntdprevention.pdf

Press Releases

When appropriate the work package teams have prepared press releases to be sent to relevant media. Some of these press releases are also posted on the EUROCAT website at http://www.eurocat-network.eu/aboutus/publications/eurocatpressreleases (combined into one pdf and annexed in Section VII under WP2). For an evaluation of media interest in EUROCAT activity see WP3.

Other Dissemination

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

A description of the EUROCAT Joint Action was included in EAHCs report "The EU support for key public health initiatives 2008-2011". Available at http://ec.europa.eu/eahc/documents/health/leaflet/EAHC-Joint-Action.pdf

EUROCAT Central Registry responded to a request from The Health and Consumers Directorate General of the European Commission to provide a poster on the EUROCAT Joint Action for the purposes of showcasing a number of co-financed projects at the Gastein Conference in Austria (held in October 2012) and later on at the EUPHA/ASPHER conference in Malta (held in November 2012) – and also at other similar occasions. The poster is annexed in Section VII under WP2.

Overview table showing the distribution and target for all project deliverables

	Title	Distribution Channel	Target audience
1	Final Report	DG Sanco	DG Sanco and EAHC
2	Two European Symposia	Conference	Policy makers and researchers
3	Evaluation Report	DG Sanco	DG Sanco and EAHC
4	Website Epidemiological Tables update to 2011	Website (open access)	Policy makers, health professionals, patient organisations
5	Statistical Monitoring Reports Part A	Website (open access)	Public health officials
6	ICD11 Coding Revision Submission	WHO ICD11 committees	WHO ICD11 committees
7	Investigation Reports	Scientific peer-reviewed journals and website (open access)	Scientific/clinical research community
8	Report on Primary Prevention of Congenital Anomalies	Website (open access)	Policy makers and public health officials
9	Set of 6 Scientific Down Syndrome and othee Genetic Syndrome Papers	Scientific peer-reviewed journals	Scientific/clinical research community
10	EUROmediCAT Papers	Scientific peer-reviewed journals	Scientific/clinical research community

List of deliverable(s) linked to this work package

Deliverable

	Title
1	**D2 – Two European Symposia** Two 1-day European Symposia on Prevention of Congenital Anomalies, Antwerp (Month 6) and Zagreb (Month 30)

Milestones reached by this WP

	Milestone title	Month of achievement
1	Newsletter 1	Planned M12 Achieved M15
2	Newsletter 2	Planned M24 Achieved M27
3	Newsletter 3	Planned M36 Achieved March 2014
4	1st European Symposium	Planned M6 Achieved M6
5	Promotional leaflet	Planned M3 Achieved M10

Horizontal Work packages

Work package title : Evaluation of the project
Work package Number : 3
Work package Leader: Prof. Helen Dolk (Main Partner and Project Leader)
Number of associated partners involved : Main partner (UU)
Number of person/ days of this work package:

58

Total budget of this work package:

Total Cost	EU funded	Contribution
22,916.00	8,850.00	14,066.00

Starting Date: 01/01/2011 **Ending date :** 31/12/2013

Evaluation plan available: yes
External evaluation: yes

Description of the work package

Please see Deliverable 3 – Evaluation Report.

Five potential evaluation providers were identified as suitably equipped to evaluate large European projects. In accordance with the University of Ulster's procurement procedures, an invitation to tender was sent to each of the five. Only one response was obtained and was subsequently determined by the EUROCAT PMC to be unsuitable (on the basis of both cost (which was over the allocated budget) and scope). It was determined in agreement with the Commission (via our Scientific Project Coordinator Georgios Margetidis) that it would be possible for us to do a much more informative evaluation ourselves and to use subcontracted consultancy to specifically pursue one element of independent evaluation (see Independent Evaluation of the Value of EUROCAT within the Evaluation Report annexed in Section VII – Deliverable 3).

The Independent Evaluation provider selected was Fistral Training and Consultancy Ltd (a UK company). See Letter of Agreement Annexed in Section VII.

Objective 1		**Prevalence information**	
	Process indicators	**Output Indicators**	**Outcome indicators**
1	Successful annual data transmission to Central Registry from all Associate Partner Registries.	Prevalence tables for 95 anomaly subgroups on the EUROCAT website, updated each year.	Citations of EUROCAT prevalence information.
Objective 2		**Network expansion and data quality improvement**	
	Process indicators	**Output Indicators**	**Outcome indicators**
1	Integration of Latvia, Slovenia and Valencia as new Full Members		Improvement in Data Quality Indicators in two thirds of registries.

	of EUROCAT, with successful data transmission.		
2	Submission of revised ICD11 proposal to WHO.		
Objective 3		**Early warning**	
	Process indicators	**Output Indicators**	**Outcome indicators**
1	Improvement in number of registries meeting earliest data transmission deadline.	Annual Statistical Monitoring Reports.	Generation and preliminary investigation of clusters/trends in each registry.
2		Five in-depth investigations, including one by the Taskforce for the Evaluation of Clusters and one of swine flu impact.	
3		Environmental data linkage feasibility report.	
Objective 4		**Primary prevention policy**	
	Process indicators	**Output Indicators**	**Outcome indicators**
1		Report on public health actions relevant to prevention of birth defects at EU Member State level.	
2		Report on actions to prevent Neural Tube Defects by raising folic acid status at EU Member State level.	
3		Report on potential consensus approach toward inclusion of primary prevention actions in national plans on rare diseases.	
Objective 5		**Prenatal screening information**	
	Process indicators	**Output Indicators**	**Outcome indicators**
1	Integration of England and Wales National Down Syndrome Cytogenic Registry into central database.	Expansion of prenatal diagnosis tables on EUROCAT website.	Publication of 6 genetic syndrome papers.
Objective 6		**Postmarketing drug surveillance**	

	Process indicators	Output Indicators	Outcome indicators
1	3 workshops on quality of medication exposure data.	3 scientific papers.	Protocol for early warning of drug-malformation associations.
2	Joint meeting with ISPE and ENTIS.		

List of deliverable(s) linked to this work package

Deliverable

	Title
1	**D3 – Evaluation Report**

Milestones reached by this WP

	Milestone title	Month of achievement
1	Project Management Committee Meeting 2011	Planned M11 Year 1 met in M1, M6 and M11
2	Project Management Committee Meeting 2012	Planned M23 Year 2 met in M15, M18 and M24
3	Project Management Committee Meeting 2013	Planned M35 Year 3 met in M30 and M35

Specific Work packages

Work package title : Registration, Central Database and Surveillance
Work package Number : 4
Work package Leader : Ms Maria Loane (Main Partner, EUROCAT Central Database Manager)
Number of associated partners involved : Principally Main Partner, KDB, Hospital Lillebaelt, UMCG, QMUL and all 36 associate partners for transmitting data. WP liaises with all 9 Collaborating partners.
Number of person/ days of this work package: 6496.27
Total budget of this work package:
Total: 1,452,836 EU: 171,901 Contribution: 1,280,935
Starting Date : 01/01/2011 **Ending date :** 31/12/2013

Description of the work package

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 and imported into the EUROCAT central database (ECD). ECD categorises cases into EUROCAT subgroups of congenital anomalies based on the malformation codes. 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, congenital anomaly prevalence data are uploaded to the live EUROCAT website tables by registry, year of birth, and type of birth: http://www.eurocat-network.eu/accessprevalencedata/prevalencetables. The proportions of cases prenatally diagnosed for select anomalies are uploaded to the website by registry and most recent 5-year period (in collaboration with WP8): http://www.eurocat-network.eu/prenatalscreeninganddiagnosis/prenataldetection(pd)rates. Prevalence rates of perinatal mortality associated with congenital anomalies are available by country and most recent 5-year period: http://www.eurocat-network.eu/accessprevalencedata/keypublichealthindicators. In addition, a description of each registry is uploaded to the website detailing organisational and operational aspects of the registry to aid interpretation and evaluation of the registry prevalence data http://www.eurocat-network.eu/aboutus/memberregistries.

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

ECD and EDMP are updated and refined according to user needs, improvements in surveillance of multiple malformations, pharmacovigilance, data quality and statistical methodology. In the period of this Joint Action, key revisions included:

- In 2011, EUROCAT Data Quality Indicators (DQI) were automated in ECD, increasing efficiency as these were manually calculated in the past. An additional new development in ECD allows cases classified as potentially multiple malformed by the EUROCAT algorithm to be extracted and uploaded to a secure web-based system for review by a panel of geneticists. Following review, the confirmed or corrected classifications are downloaded from the website and re-imported into ECD. This development considerably reduces the amount of administrative time required for this activity. ECD and EDMP

were also amended to enable improved pharmacovigilance using EUROCAT data i.e. the software was revised to allow 7 digit Anatomical Therapeutic Chemical (ATC) medication codes to be entered for cases born before 2005, an unlimited number of ATC codes per case can now be recorded, and an extra variable for recording maternal illness before pregnancy was created.

- In 2012 the new subgroup changes approved by the Coding & Classification Committee were implemented in ECD, EDMP and the website tables (http://www.eurocat-network.eu/content/EUROCAT-Guide-1.3-Chapter-3.3-Jan2012.pdf), requiring major software revisions. In addition, perinatal mortality data for the most recent 5-year period by country were uploaded to the website for the first time.

- In 2013, the prenatal diagnosis (PD) section of the website was re-designed. The proportions of congenital anomaly cases prenatally diagnosed are now available by graphical as well as tabular view, and by birth outcome, gestational age, maternal age and indication i.e. screening, ultrasound, maternal age and other. These options are also available in ECD and EDMP to allow registries to confirm the website data and for local use. In addition, the perinatal mortality tables were automated in ECD and EDMP. Finally, the new DQI developed in 2012 were automated in ECD.

Collaboration / Coordination with other projects or activities

Following permission from the Steering Committee and individual registries, EUROCAT data were extracted from the central database for the following projects:

- Epidemiology of Hirschsprung's disease in Europe: a register-based study (JA study led by Prof Judith Rankin, UK, in collaboration with WP6)
- The changing epidemiology of Gastroschisis in Europe: a register-based study (JA study led by Prof Elisabeth Draper, UK, in collaboration with WP6)
- The impact of prenatal screening and subsequent terminations on the prevalence of CHD anomalies in live born babies with Down syndrome (JA study led by Prof Joan Morris, UK, in collaboration with WP8)
- Trends in hypospadias in Europe in the period 2001-2010 (JA study led by Dr Jorieke Bergman, Northern Netherlands, , in collaboration with WP6)
- The Prevalence of Tetralogy of Fallot and Ebstein's anomaly in Europe (JA study led by Dr Breidge Boyle, UK)
- Epidemiology of congenital diaphragmatic hernia in Europe: a register-based study (non-JA study led by Prof Judith Rankin, UK)
- The increasing reported incidence of echogenic lung lesions (non-JA study led by Dr David T Howe, UK)

In keeping with the ethos of the JA, an agreement was reached between EUROCAT and the British Isles Network of Congenital Anomaly Registries (BINOCAR) in 2012, whereby EUROCAT releases confirmed data from the 6 UK registries to BINOCAR for surveillance and research within BINOCAR. This avoids duplication of effort on the part of the registries and allows "cleaned" national data to be available for research within the UK. The 6 UK registries, East Midlands & South Yorkshire, Wessex, Thames Valley, N England, SW England and Wales, gave permission for EUROCAT to release their data. Work is currently progressing towards a French national database whereby EUROCAT, with the permission of the French registries in EUROCAT, will send a database consisting of all the French data to the French Institute for Public Health Surveillance.

Finally, the central database data security procedures were reviewed in 2012. All members of the Central Registry staff and PhD students signed the EUROCAT Central Registry Database: System Level Security Policy document in 2013. The revised document is available at: http://www.eurocat-

network.eu/aboutus/datacollection/datasecurityandconfidentiality

2. Statistical Monitoring

Statistical Monitoring systematically monitors the prevalence of congenital anomalies over time to detect if any changes in the prevalence are unlikely to have arisen due to chance and may indicate new or increasing teratogenic exposures requiring public health action. Statistical monitoring for both trends and clusters in time is run by Central Registry in April each year, using confirmed data from registries that fulfil the monitoring criteria. Identified trends are reviewed by the PMC and trends of public health significance are prioritised for registry investigation. Registries report on their preliminary trend and cluster investigations using standard reporting templates. Selected anomalies are also investigated by Central Registry. Anomalies thought to be of particular clinical interest are presented at the annual RLM and an annual Statistical Monitoring Report is produced (in collaboration with WP6).

3. Develop statistical monitoring methods

The statistical monitoring methodology continues to be refined. In 2011, we developed and tested statistical methods for trisomy 18 and trisomy 13 to allow for increases in maternal age and increasing prenatal detection of these trisomies. This was done by adjusting for fetal loss up to 20 weeks gestational age and maternal age specific risks for both trisomies. For all anomalies 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 or decrease in prevalence over the period then the significant trend is reported despite the presence of significant variation from linearity. For the first time, a forest plot summarising the pan-Europe trends (i.e. all registries combined) and the average annual change in prevalence was included in the output.

In 2012, the methodology of adjusting for increases in maternal age and increasing prenatal detection for trisomy 18 and trisomy 13 were implemented in ECD and EDMP. In addition, the pan-Europe analyses included an adjustment for the effect of registry, by fitting multi-level models. Forest plots showing average annual percentage change in prevalence were also available for each registry and for each anomaly subgroup included in the trend analyses. The effects of coding changes and of incomplete data transmission during the monitoring period on the trend analysis were investigated. The models used in the trend analysis were not sensitive to the coding changes.

In 2013, cluster monitoring at country level was implemented i.e. countries with more than one registry were monitored to detect clusters at a national as well as at a regional level. In the pan-Europe trend analysis, the EUROCAT average prevalence is now plotted on the congenital anomaly forest plots so that a registry can see if it is above or below the average prevalence for that anomaly. Full details of all changes are listed in the Statistical Monitoring Protocol available at: http://www.eurocat-network.eu/content/Stat-Mon-Protocol-(May-2013)-2011.pdf.

4. Perinatal Mortality

In 2011, work had not begun on validating and analysing EUROCAT perinatal mortality data. In March 2012, a meeting with EUROPERISTAT took place in London to discuss collaboration and conduct joint work on perinatal and infant mortality due to congenital anomalies. EUROPERISTAT have some extra prevalence data from national sources not contributing to EUROCAT such as data on selected anomalies or for livebirths only. EUROPERISTAT also have data on cause of death which is useful for collaborative studies on perinatal mortality, and data on socioeconomic status which is valuable as EUROCAT does not have socioeconomic denominator data.

In 2013, Hermien de Walle continued the collaboration with EUROPERISTAT and had meetings with Dr Karin van der Pal, project leader of PERISTAT Netherlands.

PERISTAT data were required to advance the project comparing rates of fetal death and neonatal death due to congenital anomalies available from EUROCAT registries with estimates from civil registration or birth registers as provided by EUROPERISTAT. These data were still being cleaned and corrected early 2014, and the analysis was expected to be re-run in mid-February 2014. This had led to a delay in writing up the scientific paper. These data issues did not impact on the additional EUROCAT study investigating infant mortality rates in EUROCAT registries compared to World Health Organisation (WHO) rates which was conducted by Central Registry (draft paper, entitled "Methodological Issues in Estimating Mortality due to Congenital Anomaly", Annexed in Section VII under WP4). The results found that WHO mortality data based on death certificates gives a better estimate of infant mortality than congenital anomaly registries in many European countries. Estimates of mortality tend to be about 20% higher in EUROCAT registries with good ascertainment of infant survival, possibly due to the difference between "death with congenital anomaly" as opposed to "death due to congenital anomaly". This paper is currently being circulated for registry approval.

5. Registry Advisory Service for new registries

The Registry Advisory Service (RAS) organised a EUROCAT methodology and coding workshop on June 15, 2011 in Antwerp, Belgium, which was attended by 12 participants from different EU countries including new/ applicant members Valencia Region, Slovakia and Latvia. A one-year follow-up and evaluation of data collection was conducted for new applicant members Valencia Region, Hungary, Moldova and Slovenia. Dr Garne visited Valencia Region 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 were granted Affiliate member status. Reports to Moldova and Campania were sent with suggestions for improvement. Central Registry (R. Greenlees) developed a flowchart outlining the New Applicant Registry process which included the criteria for achieving Full, Associate or Affiliate EUROCAT member registry 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 on-going. Assistance with coding queries was provided by Central Registry and RAS members. The West Midlands registry in UK expressed an interest in joining EUROCAT. The National Centre for Disease Control and Public Health in Georgia also expressed interest in collaborating with EUROCAT while setting up a birth defect registry in their country.

A second workshop was held on June 15, 2012 during the Budapest RLM, which was attended by 15 participants, mainly new staff from existing registries. Topics covered included Procedure for Obtaining EUROCAT Data (Ingeborg Barisic); Coding rules for the anomalies - where to find help. Core variables (Ester Garne); Definition and coding of Syndromes, Associations and Sequences (Ingeborg Barisic); and Questions and closing remarks. Central Registry (R. Greenlees) has worked with new datasets from Latvia and Slovenia, which were evaluated by a member of the RAS, and feedback provoided. The Slovenian Registry description and Application form (EUROCAT Registry description Questionnaire) have been reviewed and will be resubmitted to PMC in 2013 for approval. The RAS continues to assist registries in the process of applying for EUROCAT membership (Latvia, West Midlands (UK), Mantova (Italy), Iceland, Georgia). Contacts have been made with Bulgaria and Lithuania with the prospect of developing partnership in 2014.

During the RLM in June 2013 in Zagreb, a third workshop on "How to become EUROCAT member?" was organised for new and applicant members, as well as the new world affiliates. The meeting was attended by 18 participants, mostly from countries that have applied for membership, but also by new members from existing registries (Hungary, Valencia Region, Northern Netherlands, and Germany). Topics covered included the Application process and membership criteria (I. Barisic); How to complete the EUROCAT Membership Application form (European and non-European version) (I. Barisic); Local methodology problems (E. Garne); and ended

with a Questions and Answers session (E. Garne and I. Barisic). The RAS also reviewed application forms and registry descriptions from the new applicant registries Bulgaria and Latvia. The applications were presented at the Steering Committee meeting in November 2013 in Ispra, Milan, Italy. The Pleven Registry (Bulgaria) of Congenital Anomalies (PRCA) led by Prof. Katya Kovacheva, MD and the 'Register of Patients with Particular Diseases, Patients with Congenital Anomalies' from Latvia, led by Ieva Grīnfelde and Santa Pildava, were granted Affiliate member status. In addition, affiliate membership was granted to the Greenland Registry of Congenital Malformations, led by Dr Flemming Kleist Stenz. The Slovenian Congenital Anomaly registry led by Rudolf Gorazd fulfilled requirements to be admitted to full membership as well as the Brittany Registry of Congenital Malformations, France led by Dr Florence Rouget. The RAS also considered several requests for World Affiliate membership. Applications for World Affiliate membership were received and approved for the following registries: National Registry of Congenital Anomalies of Argentina, led by Dr Rosa Liascovich; Tabriz Registry of Congenital Anomalies, Iran, led by Prof Saeed Dastgiri; Registry of Congenital Anomalies of Centre for Public Health Research, Wellington, New Zealand led by Prof Barry Borman; and Medical Service Department Birth Defects Registry of Prince Sultan Military Medical City, Saudi Arabia, led by Dr Ahmed M Kurdi.

Northern Ireland has no registry. A report on current sources of data on prevalence of congenital anomalies in Northern Ireland to inform the development of a Northern Irish EUROCAT registry was drafted in 2013 and will be published in 2014.

Task 1: Core database related activities

Individual case records for 20,551 valid EUROCAT cases (i.e. excluding cases with minor anomalies only and/or spontaneous abortions <20 weeks gestational age) born in year 2011 were imported to the central database for the following 28 full member registries: Antwerp, Hainaut (Belgium); Odense (Denmark); French West Indies, Ile de la Reunion, Paris (France); Mainz, Saxony-Anhalt (Germany); Hungary; Cork & Kerry, Dublin, SE Ireland (Ireland); Emilia Romagna, Tuscany (Italy); Malta; N Netherlands; Norway, S Portugal; Basque Country, Valencia Region (Spain); Vaud (Switzerland); Ukraine; E Midlands & S Yorkshire, N England, SW England, Thames Valley, Wales and Wessex (UK). Aggregate year 2011 data were received from 3 Associate member registries (n=4,996 cases by anomaly and type of birth): Rhone-Alpes (France), Spain Hospital Network and Sweden. These data were transmitted to Central Registry in February and October 2013.

Data up to year 2010 (n=21,931 case records) were imported to the central database for the registries listed above and the following full member registries: Zagreb (Croatia) and Wielkopolska (Poland). Year 2010 aggregate data were received from the associate member registries listed above and Czech Republic, Finland and Poland (n=15,971 cases by anomaly and type of birth). These data were transmitted to Central Registry in February and October 2012, with further updates transmitted in 2013.

Data up to year 2009 were imported to the central database for the registries listed above and Styria (Austria). Individual records on 21,954 congenital anomaly cases and aggregate data on 16,958 cases born in 2009 were received. These data were transmitted to Central Registry in February and October 2011, with further updates transmitted in 2012 and 2013.

The central database now holds data on 618,049 congenital anomaly cases from 1980-2011 i.e. 394,923 individual case records, and aggregate data on 223,126 cases.

A table outlining the coverage of the 2011 European birth population is Annexed in Section VII under WP4.

Website Epidemiological Tables updated annually to birth year 2009

(Milestone number 1, and Deliverable 4 – Website Epidemiological Tables updated to 2011)

Prevalence data including cases born in year 2009 were uploaded to the website tables in April and December 2011. For the 5 year time period 2005-2009, the prevalence of all congenital anomalies was 255.1 per 10,000 births (95% CI 253.6 - 256.6) and the prevalence of all non-chromosomal anomalies was 218.7 per 10,000 births (95% CI 217.3 - 220.1). Excluding chromosomal anomalies CHD and NTD accounted for 32.9% and 4.3% of these anomalies; while chromosomal anomalies accounted for 14.3% of all anomalies (Prevalence rates (including and excluding chromosomal cases) for all EUROCAT anomaly subgroups, 2005-2009, all full member registries are Annexed in Section VII under Deliverable 4).

Data on prenatal diagnosis (PD) 2005-2009 were 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 varied 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.

Website Epidemiological Tables updated annually to birth year 2010 (Milestone number 3, and Deliverable 4 – Website Epidemiological Tables updated to 2011)

Prevalence data including cases born in year 2010 were uploaded to the website tables in April and December 2012. For the 5 year time period 2006-2010, the prevalence of all congenital anomalies was 255.1 per 10,000 births (95% CI 253.6 - 256.6) and the prevalence of all non-chromosomal anomalies was 218.7 per 10,000 births (95% CI 217.3 - 220.1). Excluding chromosomal anomalies, CHD and NTD once again accounted for 32.9% and 4.2% of these anomalies respectively; while chromosomal anomalies accounted for 14.3% of all anomalies (Prevalence rates (including and excluding chromosomal cases) for all EUROCAT anomaly subgroups, 2006-2010, all full member registries are Annexed in Section VII under Deliverable 4).

PD data 2006-2010 were available for the following 26 registries: Styria (Austria); Hainaut (Belgium); Zagreb (Croatia); Odense (Denmark); Ile de la Reunion, Paris (France); Mainz, Saxony Anhalt (Germany); Hungary; Cork & Kerry, SE Ireland; Emilia Romagna, Tuscany (Italy); Malta; N Netherlands; Norway; S Portugal; Basque Country, Valencia Region (Spain); Vaud (Switzerland); Ukraine; E Midlands & S Yorkshire, N England, Thames Valley, Wales and Wessex (UK). In summary:

- Overall, 30% of all non-chromosomal anomalies and 70% of chromosomal anomalies were prenatally diagnosed. For non-chromosomal anomalies, the proportion prenatally diagnosed ranged from 38% of cases with transposition of great vessels and club foot to over 90% of anencephalus and gastroschisis cases. For chromosomal anomalies, 90% of trisomy 18 and 13 cases were prenatally

diagnosed compared to 63% of trisomy 21 cases.

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

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

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

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

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

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

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

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

Website Epidemiological Tables updated annually to birth year 2011 (Deliverable 4 – Website Epidemiological Tables updated to 2011)

Prevalence data including cases born in year 2011 were uploaded to the website tables in April and December 2013. For the 5 year time period 2007-2011, the prevalence of all congenital anomalies was 257.5 per 10,000 births (95% CI 256.0 – 259.0) and the prevalence of all non-chromosomal anomalies was 219.7 per 10,000 births (95% CI 218.3 – 221.1). Excluding chromosomal anomalies, congenital heart defects (CHD) and neural tube defects (NTD) continued to account for 33.0% and 4.2% of these anomalies respectively; while chromosomal anomalies accounted for 14.7% of all anomalies (Prevalence rates (including and excluding chromosomal cases) for all EUROCAT anomaly subgroups, 2007-2011, all full member registries are annexed in Section VII under Deliverable 4).

Prenatal diagnosis (PD) data were available for registries with a minimum of 4 years of data in the last 5-year period and time of diagnosis (the "when discovered" variable) known for ≥ 80% of cases. PD data 2007-2011 were available for the following 25 registries: Hainaut (Belgium); Zagreb (Croatia); Odense (Denmark); Ile de la Reunion, Paris (France); Mainz, Saxony Anhalt (Germany); Hungary; Cork &

Kerry, SE Ireland; Emilia Romagna, Tuscany (Italy); Malta; N Netherlands; Norway; S Portugal; Basque Country, Valencia Region (Spain); Vaud (Switzerland); Ukraine; E Midlands & S Yorkshire, N England, Thames Valley, Wales and Wessex (UK). In summary:

- Overall, 31% of all non-chromosomal anomalies and 71% of chromosomal anomalies were prenatally diagnosed. For non-chromosomal anomalies, the proportion prenatally diagnosed once again ranged from approximately 40% of cases with transposition of great vessels and club foot to over 90% of anencephalus and gastroschisis cases. For chromosomal anomalies, 90% of trisomy 18 and 13 cases were prenatally diagnosed compared to 64% of trisomy 21 cases.

- The rates of prenatal diagnosis varied greatly between registries, ranging from 11% in Hungary to 63% in Wessex for all non-chromosomal anomalies and from 13% in Malta to 90% in Paris for chromosomal anomalies.

The website Perinatal Mortality tables were updated to include data for the years 2007-2011 for the following 27 registries: Antwerp, Hainaut (Belgium); Zagreb (Croatia); Odense (Denmark); Ile de la Reunion, Paris (France); Mainz, Saxony Anhalt (Germany); Hungary; Cork & Kerry, Dublin, SE Ireland; Emilia Romagna, Tuscany (Italy); Malta; N Netherlands; Norway; S Portugal; Basque Country, Valencia Region (Spain); Vaud (Switzerland); Ukraine; E Midlands & S Yorkshire, N England, Thames Valley, Wales and Wessex (UK). In summary:

- The overall rate of late fetal deaths/stillbirths with congenital anomaly was 0.45 per 1,000 births, and the rate of deaths in the first week 0.48 per 1,000 births, resulting in a total perinatal mortality rate of 0.93 per 1,000 births associated with congenital anomaly.

- The main congenital anomaly subgroups contributing to perinatal mortality were CHD (24% of perinatal deaths have CHD), chromosomal anomalies (23%), and nervous system anomalies (17%).

- Perinatal mortality associated with congenital anomaly varied from 0.26 per 1,000 births in Portugal to 3.29 per 1,000 births in Malta.

- Perinatal mortality/TOPFA rate associated with congenital anomaly varied from 1.17 per 1,000 births in Portugal to 10.24 per 1,000 births in France.

Data on monogenic syndromes were uploaded to the website tables for the following 19 registries combined, 2005-2011: Styria (Austria); Antwerp (Belgium); Odense (Denmark), French West Indies, Ile de Reunion (France), Mainz (Germany); Cork and Kerry, Dublin, SE Ireland (Ireland); Malta; N Netherlands; Vaud (Switzerland); Basque Country, Valencia Region (Spain); Ukraine; N England, SW England, Wales and Wessex (UK). Only syndromes with ≥5 cases were included in the table. Prevalence ranged from 0.02 per 10,000 births for Albers-Schonberg syndrome (osteopetrosis), Cockayne's syndrome, Dubowitz syndrome and Robinow-Silverman-Smith syndrome to 0.82 per 10,000 births for Di George syndrome.

Task 2:

Annual Statistical Monitoring Report 2009 (Deliverable 5, Milestone 2)

The EUROCAT Statistical Monitoring Report 2009 (http://www.eurocat-network.eu/content/Stat-Mon-Report-2009-Combined.pdf) described statistical monitoring of both clusters and trends in Europe for the ten year period 2000-2009 (Annexed in Section VII under Deliverable 5). 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 NTD decreased by 10% and spina bifida by 19%
    - Severe CHD decreased by 19%

Investigation of clusters in the 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.

Annual Statistical Monitoring Report 2010 (Deliverable 5, Milestone 4)

The EUROCAT Statistical Monitoring Report 2010 (http://www.eurocat-network.eu/content/Stat-Mon-Report-2010.pdf) described statistical monitoring of both clusters and trends in Europe for the ten year period 2001-2010 (Annexed in Section VII under Deliverable 5). Key findings were:

- Rates of NTD declined on average by 1.7% per year, with rates for spina bifida declining on average by 2.1% per year.
- Prevalence of CHD decreased over time. However increasing trends were detected in two of the more severe types of CHD: Tetralogy of Fallot increased on average by 2.3% per year and single ventricle increased on average by 5.9% per year.
- Increasing trends were found for Oesophageal atresia with or without trachea-oesophageal fistula, duodenal atresia and stenosis, and atresia and stenosis of other parts of the small intestine. In contrast, atresia of bile ducts decreased by an average of 9% per year.
- The prevalence of the abdominal wall defect gastroschisis increased on average by 1.6% per year. Four out of five registries with the highest prevalence rates were located in the UK.
- Prevalence of the 3 chromosomal autosomal trisomies increased on average by 1.0% to 2.4% per year (Down syndrome, 1%; Edwards syndrome, 2.3%; Patau syndrome, 2.4%). This increase in prevalence was explained by the increase in the proportion of older mothers giving birth.

Annual Statistical Monitoring Report 2011 (Deliverable 5)

EUROCAT annually performs statistical monitoring for both trends and clusters in time in order to detect signals of new or increasing teratogenic exposures and monitor progress in the prevention of congenital anomalies. The EUROCAT Statistical Monitoring Report 2011 (http://www.eurocat-network.eu/clustersandtrends/statisticalmonitoring/statisticalmonitoring-2011)

publishes details of the trends and clusters detected in individual registries and in all registries combined (pan-Europe) for the ten year period 2002-2011 (Annexed in Section VII under Deliverable 5). Key findings at the European level are:

- Rates of Neural tube defects (NTDs) declined on average by 1% per year, with rates for Anencephalus declining on average by 2% per year.
- Although, there was an overall decreasing trend in Congenital Heart Defects (CHD) over time, increasing trends were detected for some of the more severe types of CHD. Atrioventricular septal defect and Tetralogy of Fallot increased on average by 2-3% per year, Pulmonary valve atresia increased on average by 4% per year and Single ventricle increased on average by 6% per year.
- Prevalence rates for the following digestive anomalies increased on average by 2-4 % per year: Ano-rectal atresia and stenosis, Duodenal atresia and stenosis, Atresia and Stenosis of other parts of the small intestine. In contrast Atresia of bile ducts decreased by an average of 6% per year.
- The prevalence of Craniosynostosis increased on average by 3% per year.
- Increasing trends over time were found for the chromosomal autosomal trisomies (Down syndrome and Edward syndrome), which were explained by the increase in the proportion of older mothers giving birth in Europe. In contrast, prevalence rates of Klinefelter syndrome decreased on average by 4% per year.

Investigation of clusters in the last 2 years (2010-2011) identified no clusters of immediate public health concern. The report also includes the findings of cluster detection conducted at country level i.e. countries with more than one registry are monitored to detect clusters at a national as well as at a regional level. This is the first time this methodology has been applied. The Taskforce for the Evaluation of Clusters (TEC) continues to be available for consultation on clusters identified by statistical monitoring (See WP6 report).

Task 5: Registry Advisory Service for new members

Successful data transmission from new registries (Milestone number 5)

In the period of this Joint Action, data were uploaded to the website for the first time for the following new member registries: French West Indies (France), Valencia Region (Spain) and South West England. Hungary renewed data transmission after a lapse of several years.

If applicable, the reasons for deviations from Annex I and their impact on other tasks as well as on resource execution.

The main reason for not completing the joint EUROCAT/ EUROPERISTAT task was that the task leader faced internal registry difficulties in 2013. The newly appointed Registry Leader of the N Netherlands registry stepped down, thus the task leader was forced to step in and take on the role of Registry Leader. This had clear implications for the amount of time available for progressing this task. This deviation from the work plan did not impact on other tasks within the WP.

Specific objectives of this WP

	Title
1	Prevalence information
2	Network expansion and data quality improvement
3	Early warning

List of deliverable(s) linked to this work package

Deliverable

	Title
1	**D4 – Website Epidemiological Tables updated to 2011** Website tables updated annually to birth year 2011, for 95 congenital anomaly subgroups, by registry, year and pregnancy outcome, on prevalence, perinatal mortality and prenatal diagnosis, with data quality indicators (Months 4, 16 and 28)
2	**D5 – Statistical Monitoring Reports Part A** 3 Annual Statistical Monitoring Reports (Part A) on the detection of clusters and trends (Months 12, 24 and 36)

Milestones reached by this WP

	Milestone title	Month of achievement
1	Website Epidemiological Tables updated to 2009	Planned M4 Achieved M4
2	Annual Statistical Monitoring Report 2009	Planned M12 Achieved M13
3	Website Epidemiological Tables updated to 2010	Planned M16 Achieved M16
4	Annual Statistical Monitoring Report 2010	Planned M24 Achieved M25
5	Successful data transmission from new member registries	Planned M26 Achieved M26

Work package title : Coding and Classification, Data Quality
Work package Number : 5
Work package Leader : Dr. Ester Garne (Associate Partner No. 5 (Hospital Lillebaelt, Chair of EUROCAT Coding and Classification Committee)
Number of associated partners involved : Main partner plus 7 associates Hospital Lillebaelt, The Coding and Classification Committee (Hospital Lillebaelt, KDB, SUHT, IMER, CARIS, UDS), UU, UNEW
Number of person/ days of this work package: 382.93
Total budget of this work package:
Total: 116,674 EU: 65,881 Contribution: 50,793
Starting Date: 01/01/2011 **Ending date :** 31/12/2013

Description of the work package

Description of the activities
All use of the EUROCAT database depends on accuracy and standardisation of malformation coding, clinically and aetiologically relevant classification, and high quality data on all variables in the common dataset.

1. The EUROCAT Coding and Classification Committee have over many years developed tools to improve the malformation coding within EUROCAT. These tools have to be continuously updated and improved following changes and progress in diagnostics and treatment. Planned activity of the EUROCAT Coding and Classification Committee for WP5 included the update of EUROCAT congenital anomaly subgroups with special emphasis on congenital heart defects (CHD) subgroups, the update of classifications and definitions of congenital anomalies, the dissemination of coding guidelines and responding to coding queries.
2. By the time the EUROCAT Joint Action commenced the EUROCAT Coding and Classification Committee had submitted a major revision of the WHO ICD10 malformation chapter to the WHO ICD11 Rare Diseases TAG. WP5 intended to use the WHO website for ICD11 proposals to propose further improvements of coding within the malformation chapter, and to respond to the results of consultations.
3. By the time the EUROCAT Joint Action commenced a computer algorithm had been developed for use by EUROCAT to filter out multiply malformed cases that required review by medical geneticists. WP5 planned to implement this algorithm and a website review tool to enable separate surveillance of isolated and multiply malformed cases (to facilitate planned activity in WP4, WP6 and WP9).
4. WP5 also planned to revise the coding relevant components of EUROCAT's Guide 1.3: Instructions for the registration and surveillance of congenital anomalies to version Guide 1.4. This planned activity would involve evaluation of existing variables, addition of new variables, and the need to conduct pilot studies of revised and new variables. It was planned to place special emphasis on Body Mass Index and diabetes for surveillance of impact of diabetes and obesity on prevalence of congenital anomaly, and improvement of reporting of surgery and survival for analysis of severity and health service needs.
5. WP5 also planned to evaluate EUROCAT's existing data quality indicators (DQI) for assessment of data quality from local registries.

Members of Coding and Classification Committee
- Ester Garne (Chair) (Hospital Lillebaelt, DE)
- Ingeborg Barisic (KDB, HR)
- Elisa Calzolari (IMER, IT)
- David Tucker (CARIS, UK)
- Diana Wellesley (SUHT, UK)

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:
Meetings (re Milestone 1 of WP5):
June 2011 (M6) at the annual Registry Leaders' Meeting in Antwerp (½ day). Several coding tips were written, a document with clinical definitions of the revised EUROCAT subgroups was approved and a table with prevalence of syndromes in Europe was discussed and agreed (Minutes of meeting annexed in Section VII under WP5).
June 2012 (M18) at the annual Registry Leaders' Meeting in Budapest (½ day): Exclusions of cases with known aetiology for the statistical monitoring was agreed, coding tips were written and the epidemiology on multiple malformations was discussed (Minutes of meeting annexed in Section VII under WP5).
February 2013 (M26) in Berlin (1 day). Agreement of difficult cases from the web-review of potential multiple malformations. Methodology for surveillance of multiples. Coding tips and other coding issues. Subgroups for EUROmediCAT pharmacovigilance (Minutes of meeting annexed in Section VII under WP5).
June 2013 (M30) at the annual Registry Leaders' Meeting in Zagreb (½ day). Second step in developing the method for surveillance of multiples. Definition of aetiologic subgroups. More coding tips (Minutes of meeting annexed in Section VII under WP5).
November 2013 (M35) in London (1 day). Final agreement on multiple surveillance method and review of cases. New CHD subgroups and revision of minors (Minutes of meeting annexed in Section VII under WP5).

Milestone 1 of WP5 indicated five meetings of the EUROCAT Coding and Classification Committee would take place by M30. It was necessary to stretch this to M35 to meet the particular requirements of the activities taking place within WP5. The delay in meetings did not have a knock on effect on tasks or on allocation of resources.

Coding queries from local registries have been answered throughout the three years. The document with coding tips has been updated after each coding committee meeting and is provided to EUROCAT member registries on the member's only section of the EUROCAT website and via the EUROCAT Communication emailing system.

After submission of data to Central Registry in February 2011 (M2), Ester Garne reviewed data from all registries. All registries received an email with comments and proposals for improving their coding of the congenital anomalies. Registries not sending data at this deadline were reviewed after the two deadlines in 2012. The first dataset from Valencia received in autumn 2011 were reviewed and commented.

Case lists from annual clusters and trends have been reviewed to verify coding and classification. Feedback to local registries and to central registry as part of the statistical monitoring (See WP4 report).

A report on coding of CHD in the EUROCAT database was discussed and agreed after the coding meeting in London in November 2013 (M35) and a proposal for new CHD subgroups was defined. Data cleaning of complex cardiac defects was done during this process with feedback to local registries (The report was published on the EUROCAT website and is Annexed in Section VII under WP5).

In autumn 2011, a document with the European prevalence of monogenic syndromes was developed and placed at the open website. The document included data from 21 registries covering more than 2 million births in the years 2005-2009. In December 2013 (M36) the document was updated with more years included (Annexed in Section VII under WP4. See WP4 and WP8 report).

Activity 2 - ICD11
Meetings
September 2011 (M9) in Haarlem (1 day). Discussion of the first draft of ICD11.
March 2012 (M15) in Oxford. A short meeting after the PMC meeting to discuss the third ICD11 proposal from Orphanet.

In July 2011 (M7) the 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 2011 (M9) to discuss and write the response from EUROCAT. The final document was sent to Orphanet on October 28th 2011 (M10). Diana Wellesley and Ester Garne attended a meeting in Luxembourg on December 1st 2011 (M12) organised by EUCERD for discussion of the second draft of ICD11.
The third ICD11 proposal from Orphanet was released on February 17th 2012 (M14). The coding committee discussed this proposal at the meeting in Oxford in March 2012 (M15). A document with EUROCAT recommendations for improvements in the malformation chapter was sent to Orphanet April 1st 2012 (M16).

See Process Indicator 2 (Submission of revised ICD11 proposal to WHO) of Objective 2 of the Joint Action (Network expansion and data quality improvement) in WP3.

The beta version of ICD11 for public consultation was released in summer 2012. Due to technical problems, Segolene Ayme (Chair of WHO ICD11 Rare Diseases TAG) advised that EUROCAT did not work on the version before the website was stable regarding the content. At the EUCERD meeting in Luxembourg in November 2012 (M23), we were informed that the website now worked properly and EUROCAT could start sending comments. Coding committee members have submitted proposals through the ICD11 website during 2013 to follow-up on previous proposals send to Orphanet.

Activity 3 - Surveillance of cases with multiple congenital anomalies: a computer algorithm for classification of congenital anomalies followed by manual review of approximately 10% of the cases had been developed. The task in this joint action was 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 (in WP4). Use of the website tool was delayed until 2012, but since then three years of data (that otherwise would have been reviewed on an annual basis) have been evaluated (2009, 2020, and 2011) (re Milestone 2 of WP5). This activity was planned for completion in M27. This was not possible as the registries had not confirmed their 2011 data by then. Maria Loane (WP4 Leader) uploaded potential multiples to the website in M28, and the geneticists reviewed the cases in the weeks after. Remaining disagreements were resolved at the coding meeting in Zagreb (M30). The delay did not impact on other work.

The statistical methodology for surveillance of multiples has been developed by Joan Morris during 2013 and discussed and improved at the coding meetings in 2013. The final output of the statistical surveillance was reviewed at the coding committee meeting in London in November 2013 (M35). The geneticists discussed all positive associations. The final conclusion of the multiple surveillance was that only already known associations were found, examples are the anomalies included in the VATER association and anomalies involved in the laterality association. The surveillance of multiples will continue as part of the annual statistical monitoring and the methodology will be further developed.

A report entitled "Developing the surveillance of multiple congenital anomalies" was produced by the Coding Committee and published on the EUROCAT website at http://www.eurocat-network.eu/content/Pubs-2014-WP5-Surveillance-Multiple-CA-

EG.pdf (annexed in Section VII).

A scientific paper on epidemiology of multiple malformations has been accepted for publication (in February 2014) in Birth Defects Research part A (A confidential author's proof submitted version is annexed in Section VII under WP5, as the final print version is not yet available).

E Calzolari, I Barisic, M Loane, J Morris, D Wellesley, H Dolk, M-C Addor, L Arriola, F Bianchi, A Neville, JLS Budd, K Klungsoyr, B Khoshnood, B McDonnell, V Nelen, A Queisser-Luft, J Rankin, A Rissmann, C Rounding, D Tucker, C Verellen-Dumoulin, H de Walle, E Garne (2014). Epidemiology of multiple congenital anomalies in Europe: A EUROCAT population-based registry study. Accepted for publication in Birth Defects Research Part A: Clinical and Molecular Teratology.

This study described the prevalence, associated anomalies and demographic characteristics of cases of multiple congenital anomalies (MCA) in nineteen population-based European registries (EUROCAT) covering 959,446 births in 2004 and 2010. EUROCAT implemented a computer algorithm for classification of congenital anomaly cases followed by manual review of potential MCA cases by geneticists. MCA cases are defined as cases with two or more major anomalies of different organ systems, excluding sequences, chromosomal and monogenic syndromes. The combination of an epidemiological and clinical approach for classification of cases has improved the quality and accuracy of the MCA data. Total prevalence of MCA cases was 15.8 per 10,000 births. Fetal deaths and termination of pregnancy were significantly more frequent in MCA cases compared with isolated cases ($p < 0.001$) and MCA cases were more frequently prenatally diagnosed ($p < 0.001$). Live born infants with MCA were more often born preterm ($p < 0.01$) and with birth weight < 2500 grams ($p < 0.01$). Respiratory and ear, face and neck anomalies were the most likely to occur with other anomalies (34% and 32%) and congenital heart defects and limb anomalies were the least likely to occur with other anomalies (13%) ($p < 0.01$). However, due to their high prevalence congenital heart defects were present in half of all MCA cases. Among males with MCA, the frequency of genital anomalies was significantly greater than the frequency of genital anomalies among females with MCA ($p < 0.001$).

Although rare, MCA cases are an important public health issue, because of their severity. The EUROCAT database of MCA cases will allow future investigation on the epidemiology of these conditions and related clinical and diagnostic problems.

Activity 4 - Revision of the coding relevant components of Guide 1.3 to Guide 1.4: The first meeting in the Guide 1.4 committee was held in Haarlem in September 2011 (M9). 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 winter 2011-12 in six EUROCAT member registries during the period of data collection for 2010. Results of the pilot study from the six registries were received at Central Registry in February 2012 (M14). The results of the pilot study were discussed at the PMC meeting in Oxford in March 2012 (M15) and later at the RLM in Budapest (M18) to reach agreement of which new variables to implement and which old variables to move to local variables. The final decision was taken at a meeting between the PMC and the Guide 1.4 committee in Budapest. The new variables were BMI before pregnancy, maternal pregestational diabetes, prenatal diagnosis for each anomaly, a "yes, no, undetermined" question on maternal medication in the first trimester of pregnancy and genetic test information for syndromes.

During the autumn the final document was written with special focus on the text to avoid misunderstandings at local level. Despite the pilot study, the variable "First trimester medication" was very difficult and discussed in many emails and two phone meetings. Further, it was decided to backdate some of the most important variables to be available for births back to 2005.

The final Guide 1.4 document with the EUROCAT variables for use from 2013 births onwards (re Milestone 3 of WP5) was circulated by email to the registries in December 2012 (M24). During 2013 all other sections of the EUROCAT instructions have been revised and updated, so we now have a completely up-to date document on EUROCAT methodology. This is publically accessible on the EUROCAT website at http://www.eurocat-network.eu/aboutus/datacollection/guidelinesforregistration/guide1_4

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 was written by Ruth Greenlees (EUROCAT Central Registry) and Ester Garne in the Summer of 2011. This document was discussed at the PMC meeting in November 2011 (M11) and a revised set of DQI was agreed. The final DQI document was ready and published on the EUROCAT website in February 2012 (M14) (Annexed in Section VII under WP5). Using the new definitions of DQI, the first set of the DQIs was presented to registry leaders at the RLM in Budapest in June 2012 (M18) including the years 2005-2009. Small revisions were made to the new DQI before the next set of DQI (years 2006-2010) were published at the RLM in Zagreb in June 2013 (M30) and placed on the website in August 2013 (M32) (Annexed in Section VII under WP5). In autumn 2013 the DQI calculations were programmed and automated within the EUROCAT Central Database, which makes the annual process of publishing the DQI much faster. DQI documents are published on the EUROCAT website and are accessible at http://www.eurocat-network.eu/aboutus/datacollection/dataquality/dataqualityindicators

Regarding the Outcome Indicator 1 (Improvement in DQI in 2/3 of registries) relating to Objective 2 of the Joint Action (Network expansion and data quality improvement) as listed in WP3 - The set of DQIs were amended in the EUROCAT Joint Action period.

Improvements in DQIs were observed in 2011 when comparing DQIs from the time period 2006-2010 to the time period 2007-2011:

% live births with Atrial Septal Defect (a CHD), Ventricular Septal Defect (also a CHD), Hydronephrosis (an obstruction of the urinary flow from kidney to bladder), Hypospadia (a defect of the placement of the opening of the urethra in the penis) or Clubfoot with surgery data: 2/3 of the EUROCAT member registries collecting surgery data showed improvement in the recording of the surgery variable for these chosen conditions (conditions that typically require surgery). EUROCAT average increasing from 17.2% to 20.0%.

% Genetic syndromes and microdeletions with syndrome text completed: Overall improvement from 70.9% to 75.4%. 2/3 of all EUROCAT member registries showed improvement in the recording of the syndrome text variable (that gives us more detail to distinguish between related syndromes).

For further information on EUROCAT DQIs, access,

Loane M, Dolk H, Garne E, Greenlees R and a EUROCAT Working Group (2011), "EUROCAT Data Quality Indicators for Population-Based Registries for Congenital Anomalies", Birth Defects Research (Part A), Vol 91, pp S23-S30 at http://www.eurocat-network.eu/content/Pubs-2011-Loane-Report9(3)-DQI.pdf.

Methodology applied as planned
Yes, although the ICD11 has been more complicated to work with than expected

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 (UK) and Hospital Lillebaelt (DE).

Coordination with other projects or activities
The ICD11 work has been done in collaboration with Orphanet and EUCERD

Milestones achieved
Five meetings of the Coding and Classification Committee with minutes published on the EUROCAT website.
Annual review of multiple malformed cases from 2009, 2010 and 2011.
Implementation of Guide 1.4 for births from 2013.
A revised set of DQI has been published on the EUROCAT website and implemented for use.
A scientific paper on epidemiology of multiple malformations has been accepted for publication (in February 2014) in Birth Defects Research part A.

Deliverables
Two documents with comments and proposals for the development of ICD11 have been sent to Orphanet/WHO (October 2011 (M11) and April 2012 (M16)). See Process Indicator 2 (Submission of revised ICD11 proposal to WHO) of Objective 2 of the Joint Action (Network expansion and data quality improvement) as listed in WP3.

Specific objectives of this WP

	Title
1	Network expansion and data quality improvement

List of deliverable(s) linked to this work package

Deliverable

	Title
1	**D6 – ICD11 Coding Revision Submission** Revised submission to ICD11 for congenital anomaly coding revision (Month 18)

Milestones reached by this WP

	Milestone title	Month of achievement
1	5 meeting of the coding and classification committee with minutes	Planned M30 Actual M35
2	Annual review of multiply malformed cases Months 3, 15 and 27	Planned M27 Actual M30
3	Implementation of EUROCAT Guide 1.4	Planned M24 Actual M24
4	Publication of revised set of data quality indicators on website	Planned M12 Actual M14
5	Scientific paper on epidemiology of multiple malformations	Planned M15 Actual Feb 2014

Work package title : Investigation of Trends, Clusters and New Exposures
Work package Number : 6
Work package Leader : Dr. Martine Vrijheid (Associate Partner No. 28 (CREAL))
Number of associated partners involved : Main partner plus all 36 associates 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
Number of person/ days of this work package: 1634.51
Total budget of this work package:
Total: 353,225 Contribution: 206,001 EU: 147,224
Starting Date : 01/01/2011 **Ending date :** 31/12/2013

Description of the work package

Activity 1: Annual Statistical Monitoring

Trends and clusters signalled by statistical monitoring (detailed further in the WP4 report) are investigated by EUROCAT member registries and reported on at the annual EUROCAT Registry Leaders Meeting, and an annual Statistical Monitoring Report is produced (in collaboration with WP4). Full EUROCAT members that meet the inclusion criteria are included in EUROCAT Statistical Monitoring. This activity is led by EUROCAT Central Registry but involves most or all EUROCAT member registries. The Task Force for Evaluation of Clusters (TEC) provides advice on clusters identified in the annual monitoring (see activity 2).

Three EUROCAT Statistical Monitoring Reports (annexed in Section VII under Deliverable 5 (and listed but not annexed also in Deliverable 7), relating to Output Indicator 1 (Annual Statistical Monitoring Reports) of Objective 7 of the EUROCAT Joint Action (Early Warning)) were published on the EUROCAT website and included:

EUROCAT Statistical Monitoring Report 2009 available at http://www.eurocat-network.eu/content/Stat-Mon-Report-2009-Combined.pdf (made available on website in M13)

EUROCAT Statistical Monitoring Report 2010 available at http://www.eurocat-network.eu/content/Stat-Mon-Report-2010.pdf (made available on website M25)

EUROCAT Statistical Monitoring Report 2011 available at http://www.eurocat-network.eu/clustersandtrends/statisticalmonitoring/statisticalmonitoring-2011

The reports describe statistical monitoring of both clusters and trends in Europe using data up to birth year 2009, 2010 and 2011 respectively. Details of the clusters and trends identified at pan-Europe level (all registries combined), in individual registries and the results of subsequent local registry investigations are presented (relates to Outcome Indicator 1 (generation and preliminary investigation of clusters/trends in each registry) of Objective 7 of the EUROCAT Joint Action (Early Warning)).

During the period of the EUROCAT Joint Action, Maria Loane (leader of WP4), with colleagues from EUROCAT Central Registry, the EUROCAT PMC, and the TEC liaised with EUROCAT member registries (at the annual Registry Leaders Meetings) to improve the mechanism by which EUROCAT member registries conduct and feedback to EUROCAT Central Registry the outcome of their preliminary investigations, following the occurrence of a cluster identified through Statistical Monitoring. This involved the creation of an improved version of a form, referred to as the "Cluster

Template" for registries to complete. Changes included the addition of a list of aetiological factors that should be investigated, where possible, with a response format that allows the registries to clearly indicate if they did or did not investigate these factors (see Activity 2). Cluster templates returned by registries are made available to all EUROCAT members on the member's only section of the EUROCAT website.

Activity 2: Task Force for Evaluation of Clusters (TEC)

It was planned, during the period of the EUROCAT Joint Action, to establish a Task Force for the Evaluation of Clusters, to enable rapid response to clusters including self-reported clusters and exposures of concern. This was to involve the establishment of a core-group, the development of protocols and the administration and running of ad-hoc tasks, led by FHI (NO).

EUROCAT Members:
Lorentz M Irgens, chair (NO), *until June 2013*
Ingeborg Barisic (KDB, HR)
Helen Dolk (UU, UK)
Nichola McCullough secretary (UU, UK)
Vera Nelen (PIH, BE), *became chair in June 2013*

External Members:
Petter Kristensen (NO)
Rolv Terje Lie (NO)

Meetings
The TEC convened for its first meeting in Bergen (NO) 12th -13th May 2011 (M5).

Telephone conferences were organized on 29th August 2011 (M8) and 19th October 2011 (M11).

In M8 TEC agreed a mandate. TEC has the following functions:

- On request by the EUROCAT PMC to comment on the output of cluster investigations conducted by EUROCAT (see Activity 1).

- Serve as a consulting unit in cases of clusters, commissioned by EUROCAT or individual member registries.

- In the assessment of a cluster the TEC may:

    - Correspond and get written information and data from the EUROCAT member registries involved.

    - Pay site visits for meetings with the EUROCAT member registries involved and, if considered expedient, with other parties.

    - Propose and advise on ad hoc studies aiming at clarification of a cluster.

At the first EUROCAT annual Registry Leaders Meeting (M6), EUROCAT member registries were informed about the creation of and role of TEC. TEC were also present in panel format during the annual Registry Leaders Meetings (M18 and M30) when the results of Statistical Monitoring and subsequent EUROCAT member registry investigations were being presented to EUROCAT member registries. This provided member registries with an opportunity to receive advice on clusters detected in their registry and to discuss in general how the preliminary investigation of clusters by the registries could be improved. It was highlighted by members of TEC that as a dedicated committee they would have more time to investigate clusters compared to

registries, and that there was expertise available to provide advice on the medical genetic components of clusters.

A key concern raised by the registry leaders during these sessions was the difficulty in obtaining and interpreting the aetiological data needed to inform the preliminary investigation of clusters. In particular the paucity of population-based exposure data for comparison was highlighted. It was suggested that available data on exposures between registries could be compared to determine if there is something different about the detected cluster. Registries were reminded that the purpose of the preliminary investigation of clusters was not to prove cause, but to generate hypotheses that can be tested through further research. Also identified was the variability in the quality of reports sent to Central Registry, using the cluster template (subsequent improvements reported in Activity 1). The high number of explained excesses of cases" were discussed, and the importance of continuing with high quality surveillance in order to prevent another thalidomide type event was emphasised. Registries were reminded that EUROCAT"s statistical monitoring is the only surveillance of congenital anomalies that takes place in Europe at present.

The TEC continues to be available for consultation on clusters identified by registries.

Plans are ongoing for the TEC to be involved in investigating a cluster of holoprosencephaly (a structural abnormality of the brain) in the Ukraine. This cluster was identified through EUROCAT's Statistical Monitoring process.

A report of the TEC was expected in M20 (relates to Deliverable 7 and to output indicator 2 (Five in-depth investigations, including one by the TEC and one of swine flu) of objective 3 of the EUROCAT Joint Action (Early Warning)). This report was not created as planned, instead resources were allocated to the response to the swine flu epidemic (see Activity 3). Resources were redirected by agreed grant amendment with the EAHC.

Activity 3: Response to Swine Flu Epidemic

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

The survey of European policies was conducted in cooperation with the European Medicines Agency (EMA) and involved 23 EUROCAT registries. One of the objectives of conducting a policy survey of European pandemic influenza vaccination and antiviral policies was to gather population data of exposure of pregnant women to pandemic influenza vaccine and antivirals. Only few European Departments of Health were able to provide some type of exposure data.

i) The policy survey has been published in BMC Public Health in M10 (Annexed in Section VII under Deliverable 7).

Luteijn JM, Dolk H, Marnoch GJ (2011), Differences in pandemic influenza vaccination policies for pregnant women in Europe, BMC Public Health, 11: 819

ii) The seasonality study has been accepted for publication in Human Birth Defects Research A (Annexed in Section VII under Deliverable 7).

Luteijn JM; Dolk H, Addor M-C, Arriola L, Barisic I, Bianchi F, Calzolari E, Draper E, Garne E, Gatt M, Haeusler M, Khoshnood B, McDonnell R, Nelen V, O'Mahony M,

Mullaney C, Queisser-Luft A, Rankin J, Tucker D, Verellun-Dumoulin C, Walle H, Yevtushok L (2014), Seasonality of congenital anomalies in Europe Birth Defects Research Part A: Clinical and Molecular Teratology – in press.

We plan to follow up the study of the effect of the 2009-2010 pandemic influenza season on congenital anomaly prevalence with a more general influenza study which will involve additional influenza seasons and EUROCAT registries. The analysis for this study has been completed and this study is scheduled for submission late 2014.

iii) The systematic review plus meta-analysis has been published in Human Reproduction (Annexed in Section VII under Deliverable 7).

Luteijn JM, Brown MJ, Dolk H (2013), Influenza and congenital anomalies: a systematic review and meta-analysis. Human Reproduction -Epub ahead of print

Iv and v) The ecological time series analysis and case-malformed control analysis are currently in preparation for submission to a peer-reviewed journal early 2014. Recorded instances of 1st trimester pandemic influenza vaccine (n=5) and neuraminidase inhibitor (n=6) exposure in the study population of the pandemic influenza case-malformed control study turned out to be lower than expected. We intended to utilize pandemic influenza vaccination counts of pregnant women in our ecological time series analysis. Instead of using vaccination counts, we created a proxy variable for pandemic influenza vaccination policy based on results of the policy survey as exposure. The analyses for 1st trimester pandemic influenza vaccination and neuraminidase inhibitor exposure were dropped from the case-malformed control study and instead we opted to report the few exposures in the form of a case series.

Cluster surveillance – Situs inversus cluster in Belgium (relates to Activities 1-3)

For the first time in 2013, EUROCAT conducted statistical monitoring for detection of clusters (in the birth period 2006-2011), at a country level, rather than just a registry level (described further in WP4 report). EUROCAT cluster surveillance detected a cluster of situs inversus (inverse position of thoracic or abdominal organs or both) in Belgium. For Belgian pregnancies with estimated date of conception between September 19th, 2009 and June 7th, 2010, a total of 5 registrations of situs inversus were detected. A total of 1.18 cases were expected in this timeframe, and the associated p-value is 0.047. This cluster of situs inversus is especially interesting since the EUROCAT seasonality study, which was conducted as part of the EUROCAT pandemic influenza surveillance response, detected strong seasonality in the prevalence of situs inversus, with conception peaks in the winter. The Belgian situs inversus clusters' dates of conception coincide with the 2009 H1N1 pandemic influenza outbreak and for this reason, the Belgian situs inversus cluster is being investigated in the context of the EUROCAT pandemic influenza surveillance response (see Activity 3). Investigation is currently ongoing (February 6th, 2014) and will be reported to the TEC when available.

Further draft scientific papers describing the response to the swine flu epidemic will be submitted to the TEC for comment. Most of the resources allocated to the TEC were redirected to the response to swine flu epidemic as the in-depth investigation was carried out in relation to swine flu (relates to Deliverable 7 and to output indicator 2 (Five in-depth investigations, including one by the TEC and one of swine flu) of objective 3 of the EUROCAT Joint Action (Early Warning)).

Activity 4: Investigation of specific trends of:

4.1. Hypospadias

Hypospadias are a common congenital malformation (a defect of the placement of the opening of the urethra in the penis) with more than 10,000 newborn boys affected in Europe every year (Eurostat 2011: 5.2 million children were born in EU-

27). This activity planned to investigate the increasing trends (suspected to be due in part to endocrine disruptors) of hypospadias between 2001 and 2010 (identified through EUROCAT's Annual Statistical Monitoring activity) in Europe in relation to hypospadias type and registration policies of the different EUROCAT member registries. A study protocol was submitted and approved by the EUROCAT Steering Committee in 2012. Following permission from participating EUROCAT member registries, data was received from EUROCAT Central Database in March 2013 (M27).

The study included 23 EUROCAT full member registries. These were registries that registered hypospadias subtypes and had data over the complete period 2001 – 2010 and were able to provide detailed information about ascertainment of hypospadias cases via a questionnaire that was specifically designed for this study. All cases with hypospadias (isolated or associated with other anomalies) born between 1 January 2001 and 31 December 2010 were included. The study involved analysis of the prevalence and trends of total hypospadias, hypospadias per etiology and hypospadias subtypes in Europe in the period 2001 – 2010 with special attention to the registration practice in the 23 different EUROCAT registries that contributed data to this study. In addition, we investigated whether maternal age was associated with hypospadias prevalence. The study was the largest of its kind in Europe and supplied recent data.

A scientific paper entitled "Prevalence and trends of hypospadias in 23 EUROCAT registries in 2001 – 2010 with special attention to registration policy", has been drafted for submission (in 2014) to either the Journal of Urology or the European Journal of Urology. This paper has been circulated to lead authors and will be circulated to all remaining authors when the first author returns from maternity leave in May). The delay in submission did not impact on other activity within the WP or on the allocation of resources.

4.2. Multiple births with congenital anomalies (UU, UK)

This activity planned, (i) to assess the public health consequences of the rise in the rate of multiple births in Europe in terms of the associated risk of congenital anomalies, (ii) to describe the epidemiology of Down Syndrome in multiple births in Europe, and (iii) to explore the association of specific non-chromosomal congenital anomalies with multiple birth in the context of specific aetiologic pathways.

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

Results showed that within the European population studied, there was approximately a 50% rise in the multiple birth rate from 1984 to 2007. Of the 5.4 million births during the study period, 3.0% of babies were from multiple births. Of the total number of major congenital anomaly cases (148,359), 3.83% were from multiple births. The study found that the prevalence of congenital anomalies from multiple births increased from 5.9 (1984 – 1987) to 10.7 (2004 – 2007) per 10,000 births. Furthermore, the risk of congenital anomalies was 27% higher in multiple than singleton births, with this risk increasing over time. This increase may be related to Artificial Reproductive Technology rather than multiple birth status. Multiple births with congenital anomalies were more than twice as likely to be stillbirths compared to singleton births (4.6% compared to 1.8%) and more than twice as likely to be early neonatal deaths (5.45% compared to 2.51%). However, cases from multiple pregnancies were less likely to be terminations of pregnancy for fetal anomaly.

A scientific paper was submitted to the British Journal of Gynaecology: An International Journal of Obstetrics and Gynaecology (M18) and was accepted for

publication and published in M29 (Annexed in Section VII under Deliverable 7).

Boyle B, McConkey R, Garne E, Loane M, Addor M-C, Bakker M, Boyd P, Gatt M, Greenlees R, Haeusler M, Klungsoyr Melve K, Latos- Bielenska A, Lelong N, McDonnell R, Metneki J, Mullaney C, Nelen V, O'Mahony M, Pierini A, Rankin J, Rissmann A, Tucker D, Wellesley D and Dolk H (2013). Trends in the prevalence, risk and pregnancy outcome of multiple births with congenital anomaly: a registry-based study in 14 European countries 1984-2007, British Journal of Gynaecology, 120, 707-716 (see associated press releases in WP2 report).

During the analysis phase it was discovered that there were a number of duplications of cases from multiple births registered in the EUROCAT Central Database. Some differences in interpretation in the registration of a multiple birth as opposed to a multiple pregnancy were also noted. To resolve this, the principal investigator of this study, Dr. Briedge Boyle liaised with WP4 and 5 to carry out a validation exercise to identify and remove duplicates from the EUROCAT Central Database (in consultation with EUROCAT member registries who had contributed that data). The "nbrbaby" variable was reviewed and the coding instructions changed in Guide 1.4 (implemented for births from January 2013 on).

(ii) A second study, a population-based prevalence study (involving 10 EUROCAT member registries in 8 European countries) was conducted to determine risk of Down syndrome in multiple relative to singleton pregnancies, and to compare prenatal diagnosis rates and pregnancy outcome. The study population was 14.8 million births from 1990–2009, 2.89% of which were multiple births. Down Syndrome cases included live births, fetal deaths from 20 weeks, and terminations of pregnancy for fetal anomaly. Zygosity was inferred from like/unlike sex for birth denominators, and from concordance for Down Syndrome cases.

Poisson and logistic regression stratified for maternal age, country and time was used to analyse relative risk of Down Syndrome per fetus/baby from multiple versus singleton pregnancies and per pregnancy in monozygotic/dizygotic versus singleton pregnancies. Proportion of prenatally diagnosed and pregnancy outcome was also analysed.

Results showed that the adjusted relative risk of Down Syndrome for fetus/babies from multiple versus singleton pregnancies was 0.58 (95% CI 0.53–0.62), similar for all maternal ages except for mothers over 44, for whom it was considerably lower. In 8.7% of twin pairs affected by Down Syndrome, both co-twins were diagnosed with the condition. The adjusted relative risk of Down Syndrome for monozygotic versus singleton pregnancies was 0.34 (95% CI 0.25–0.44) and for dizygotic versus singleton pregnancies 1.34 (95% CI 1.23–1.46). Down Syndrome fetuses from multiple births were less likely to be prenatally diagnosed than singletons (adjOR 0.62 [95% CI 0.50–0.78]) and following diagnosis less likely to be terminated following prenatal diagnosis (adjOR 0.40 [95% CI 0.27–0.59]). The risk of Down Syndrome per fetus/baby is lower in multiple than singleton pregnancies. These estimates can be used for genetic counselling and prenatal screening.

A scientific paper was submitted to British Journal of Gynaecology: An International Journal of Obstetrics and Gynaecology (M28) and was accepted for publication in February 2014 (Annexed in Section VII under Deliverable 7).

Boyle B, Morris JK, McConkey R, Garne E, Loane M, Addor MC, Gatt M, Haeusler M, Latos-Bielenska A, Lelong N, McDonnell R, Mullaney C, O'Mahony M, Dolk H (2014), Prevalence and risk of Down Syndrome in monozygotic and dizygotic multiple pregnancies in Europe: implications for prenatal screening , British Journal of Gynaecology, DOI: 10.1111/1471-0528.12574

The exploration of specific anomalies is complete and a scientific paper is in preparation. Further analysis regarding the relationship between twinning, assisted reproductive therapies and congenital anomalies was initiated in 2013 and remains

ongoing.

4.3. Gastroschisis (ULEIC, UK)

Gastroschisis is a protrusion of abdominal contents through an abdominal wall defect lateral to an intact umbilical cord and not covered by a membrane. EUROCAT's Annual Statistical Monitoring has been identifying increasing trends in this particular congenital anomaly and as a result further epidemiological investigation was planned as part of the EUROCAT Joint Action. Data were received from 23 full member EUROCAT registries (M19) and analysed in 2013. A scientific paper is not yet available. No resources were allocated to this activity other than for the provision of data in WP4.

4.4. Hirschsprung (UNEW, UK)

Hirschsprung congenital anomaly is defined as an absence of the parasympatic ganglion nerve cells (aganglionosis) of the wall of the colon or rectum. This condition can lead to severe constipation or abdominal obstruction. This activity aimed to describe the epidemiology of Hirschsprung's disease in Europe, including associated congenital anomalies, total prevalence, trends and association with maternal age. Singleton cases of Hirschsprung's disease delivered during 1980-2009 notified to 31 EUROCAT member registries formed the population-based case-series. Prevalence rates and 95% confidence intervals (CIs) for each register were calculated as the number of cases per 10,000 births (live and stillbirths). Multilevel Poisson regression was performed to identify trends in prevalence, to examine geographical variation and to investigate the association with maternal age. There were 1322 cases of Hirschsprung's disease among 12,146,210 births. The total prevalence was 1.18 (95% CI: 1.12-1.24) per 10,000 births and there was a small but significant overall increasing trend in prevalence over time (relative risk (RR) =1.01 (per year), 95% Credible interval: 1.0-1.02; p=0.004). There was evidence of geographical heterogeneity in prevalence (p<0.001) but trends over time didn't vary significantly by register (p=0.203). Overall, 146 (11.0%) cases were associated with chromosomal anomalies or genetic syndromes, including 123 (93.9%) with Down syndrome. Excluding cases with chromosomal anomalies or genetic syndromes, there were 1176 cases (1.05 (95% CI: 0.99, 1.11) per 10,000 births), of which 137 (11.6%) had major structural anomalies. There was no evidence of a significant increased risk of Hirschsprung's disease in cases born to women aged ≥35 compared to those aged 25-29 (RR=1.17, 95% CrI: 1.01, 1.35; p=0.355). This large population-based study found evidence of a small increasing trend in Hirschsprung's disease and differences in prevalence by geographic location.

A scientific paper has been submitted (in February 2014) to the journal, Birth Defects Research, and is currently under peer review (A confidential submitted version has been annexed in Section VII under Deliverable 7).

Best KE, Nelan V, Arriola L, O'Mahony M, Sipek A, McDonnell B, Draper E, Calzolari E, Beres J, Queisser-Luft A, Gatt M, Bakker M, Klungsoyr K, Garne E, Khoshnood B, Randrianaivo H, Matias Dias C, Rissman A, Mullaney C, Thompson R, Doray B, Hauesler M, Rounding C, Bianchi F, Wertelecki W, Zurriaga O, Addor M-C, Tucker D, Wellesley D, Materna-Kiryluk A, Barisic I, Curran RM and Rankin J (2014). Hirschsprung's disease prevalence in Europe: a register based study.

Additional Activity added to WP6 (Activity 4) throughout the course of the EUROCAT Joint Action

Diaphragmatic hernia study

Diaphragmatic hernia is a defect in the diaphragm with protrusion of abdominal content into the thoracic cavity. Published prevalence rates of congenital diaphragmatic hernia (CDH) vary. This study aimed to describe the epidemiology of CDH using cases of CDH between 1980 and 2009 notified to 31 EUROCAT member registries. There were 3373 CDH cases reported among 12 155 491 registered births.

This large population-based study found an increase in total CDH prevalence over time. CDH prevalence also varied significantly according to geographical location. No significant association was found with maternal age.

A scientific paper has been submitted (in February 2014) to the journal, Archives of Disease in Childhood, and is currently under peer review (A confidential submitted version has been annexed in Section VII under Deliverable 7).

McGivern MR, Best, KE, Rankin J, Wellesley D, Greenlees, R, Addor M-C, Arriola L, de Walle H, Barisic I, Beres J, Bianchi F, Calzolari, E, Doray, B, Draper ES, Garne E, Gatt M, Haeusler M, Khoshnood B, Klungsoyr K, Latos-Bielenska A, O'Mahony M, Braz P, McDonnell B, Mullaney C, Nelen V, Queißer-Luft A, Randrianaivo H, Rissmann A, Rounding C, Sipek A, Thompson R, Tucker D, Wertelecki W, Martos C (2014), Epidemiology of congenital diaphragmatic hernia in Europe: a register-based study.

The addition of this activity did not impact on other activity within the WP. Some funds from within the WP, were diverted to this new activity that were no longer needed for Activity 6 (See Activity 6).

ACTIVITY 5: INVESTIGATION OF EPIDEMIOLOGY OF CONGENITAL HEART DISEASE (CHD)

5.1 Trends in prevalence of CHD (INSERM U953, FR)

This activity aimed to examine trends in the prevalence of CHDs in Europe and to compare these trends with the recent decrease in the prevalence of CHDs in Canada (Quebec) that was attributed to the policy of mandatory folic acid fortification. This study used data for the period 1990-2007 for 47 508 cases of CHD not associated with a chromosomal anomaly from 29 EUROCAT member registries in 16 countries covering 7.3 million births. The total prevalence of CHDs increased during the 1990s and the early 2000s until 2004 and decreased thereafter. The prevalence of CHDs decreased in recent years in Europe in the absence of a policy for mandatory folic acid fortification. One possible explanation for this decrease may be an as-yet-undocumented increase in folic acid intake of women in Europe following recommendations for folic acid supplementation and/or voluntary fortification. However, alternative hypotheses, including reductions in risk factors of CHDs (eg, maternal smoking) and improved management of maternal chronic health conditions (eg, diabetes), must also be considered for explaining the observed decrease in the prevalence of CHDs in Europe or elsewhere.

A scientific paper was published in its final version in January 2013 (M25) in the Journal of Pediatrics (Annexed in Section VII under Deliverable 7).

Khoshnood B, Loane M, Garne E, Addor M-C, Arriola L, Bakker M, Barisic I, Bianca S, Boyd P, Calzolari E, Doray B, Draper E, Gatt M, Haeusler M, Klungsoyr Melve K, Latos- Bielenska A, McDonnell R, Mullaney C, Nelen V, O'Mahony M, Pierini A, Queisser-Luft A, Randrianaivo-Ranjatoelina H, Rankin J, Rissmann A, Salvador J, Tucker D, Verellen-Dumoulin C, Wellesley D, Zymak-Zakutnya, N and Dolk H (2012), Recent decrease in the prevalence of congenital heart defects in Europe. Journal of Pediatrics. 162: (1). 108-113

5.2 Epidemiology of selected CHD (Hospital Lillebaelt, DE)

This activity aimed to describe the epidemiology of chromosomal and non-chromosomal cases of atrioventricular septal defects (AVSD) in Europe. Data from 13 EUROCAT member registries for the period 2000–2008 were included. There were a total of 993 cases of AVSD, with a total prevalence of 5.3 per 10,000 births (95% confidence interval 4.1 to 6.5). Of the total cases, 250 were isolated cardiac lesions, 583 were chromosomal cases, 79 had multiple anomalies, 58 had heterotaxia

sequence, and 23 had a monogenic syndrome. The total prevalence of chromosomal cases was 3.1 per 10,000 (95% confidence interval 1.9 to 4.3), with a large variation between registers. Of the 993 cases, 639 cases were live births, 45 were stillbirths, and 309 were terminations of pregnancy owing to foetal anomaly. Among the groups, additional associated cardiac anomalies were most frequent in heterotaxia cases (38%) and least frequent in chromosomal cases (8%). Coarctation of the aorta was the most common associated cardiac defect. The 1-week survival rate for live births was 94%. Of all cases, three-quarters were associated with other anomalies, both chromosomal and non-chromosomal. For infants with AVSD and no chromosomal anomalies, cardiac defects were often more complex compared with infants with AVSD and a chromosomal anomaly. Clinical outcomes for AVSD varied between regions. The proportion of termination of pregnancy for fetal anomaly was higher for cases with multiple anomalies, chromosomal anomalies, and heterotaxia sequence.

A scientific paper on the epidemiology of AVSD among infants in Europe was submitted for publication in 2011 and was published in November 2012 (M23) (Annexed in Section VII under Deliverable 7).

Christensen N, Andersen H, Garne E, Wellesley D, Addor M-C, Haeusler M, Khoshnood B, Mullaney C, Rankin J, Tucker D (2012), Atrioventricular septal defects among infants in Europe: A population based study of prevalence, associated anomalies and survival, Cardiology in the Young, 23, 560-567.

This work was done in collaboration with Hans Christian Andersen Children's Hospital in Odense.

Additional Activity added to WP6 (Activity 5) throughout the course of the EUROCAT Joint Action

Anthony Wemakor (PhD student), while working with Helen Dolk (Project Leader) at EUROCAT Central Registry on the association between Selective Serotonin Reuptake Inhibitors (SSRIs) and congenital heart disease (Activity 3.1 in WP9), had confirmed signals for specific associations between maternal use of SSRIs in the first trimester of pregnancy and two congenital anomalies – Tetralogy of Fallot (TOF) and Ebstein's Anomal;y (EA). As a result two additional follow-up studies were planned to be carried out by UU (UK) and Hospital Lillebaelt (DK). The first exploring the epidemiology of Tetralogy of Fallot and Ebstein's anomaly which was added as additional activity to activity 5.2 of WP6, and the second (which is ongoing) will be part of the FP-7 funded EUROmediCAT study with special emphasis on medication exposure.

A short EUROCAT report (Annexed in Section VII under WP6) reviewing the prevalence of TOF and EA in Europe was prepared in response to an observation that the prevalence of TOF had risen over the past decade (as identified through EUROCAT Annual Statistical Monitoring).

5.3 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. This protocol was submitted to a local charity for funding which began 1st December 2013. The study will recruit mothers of CHD cases and non-CHD controls to fill out a questionnaire concerning early pregnancy exposures, using a specially designed i-pad application.

The protocol including questionnaire and i-pad application, will also be made available to other EUROCAT partners during 2014. EUROCAT Wales is already trying

to organise funding to carry out a parallel study.

ACTIVITY 6: ACTIONS TOWARDS EUROPEAN ENVIRONMENTAL SURVEILLANCE

It was planned, during the period of the Joint Action to do the following:

- Feasibility of linkage with environmental pollution map
- Literature reviews on air pollution and congenital anomaly
- Inventory of European Pollutant maps, including from ESCAPE and E-PRTR
- Establish contacts with relevant exposure experts
- Feasibility of geographical linkage studies in EUROCAT registries
- Air pollution pilot study in seven centres
- Feasibility of epidemiological investigation in small polluted areas (hot spots)
- Preparation of common protocols for epidemiological investigations related to both smaller (hot spot) and larger-scale environmental surveillance.

The Final Report of this Task "Actions Towards European Environmental Surveillance: Feasibility of Environmental Linkage" is appended in Section VII under Deliverable 7.

A systematic review of air pollution and congenital anomalies was published by CREAL (Vrijheid et al 2011) which formed a basis for this activity, funded outside the Joint Action.

The air pollution pilot study was conducted in one centre only (Barcelona) and furthermore proceeded to a full study, establishing the utility of the approach if used by other EUROCAT registries. Pilot studies could not be implemented elsewhere due to delays in the availability of ESCAPE air pollution data, feasibility issues described in the Final Report, and lack of resources for overcoming these issues.

In addition to the work described in the Final Report of this Activity, efforts have been ongoing to collaborate with COPHES, the European biomonitoring network - a joint funding application was submitted to Framework 7 in 2012 that was not successful but is being reconsidered, and a meeting (including both COPHES and EUROCAT participants) was held under the auspices of the WHO Regional Office for Europe "Human biomonitoring survey as a tool for assessing early life exposures to priority chemical pollutants" Bonn, Germany 18-19 Sept 2013.

Specific objectives of this WP

	Title
1	Early warning

List of deliverable(s) linked to this work package

Deliverable

	Title
1	**D7 – Investigation Reports** 3 Annual Statistical Monitoring Reports Part B (Months 12, 24 and 36). Report of the Taskforce for the Evaluation of Clusters (Month 20). Report of Environmental Pollution Data Linkage (Month 36) and protocols. 5 Epidemiological papers (Months 24 and 36).

Milestones reached by this WP

	Milestone title	Month of achievement
1	Annual Statistical Monitoring Report 2009 (Part B)	Planned M12 Achieved M13
2	Annual Statistical Monitoring Report 2010 (Part B)	Planned M24 Achieved M25
3	Taskforce for the Evaluation of Clusters Protocol	Planned M18 Not created – related resources were diverted to other activity within the WP
4	Set of scientific papers on epidemiology of selected anomalies and risk factors (Months 12, 24 and 36)	Planned M36 Achieved M36
5	Report of feasibility of environmental data linkage and pilot study results	Planned M36 Achieved March 2014

Work package title : Primary Prevention of Congenital Anomalies
Work package Number : 7
Work package Leader : Dr. Domenica Taruscio (Associate Partner No. 15 (ISS))
Number of associated partners involved : Main partner plus 13 associates
UU, KDB, UDS, NCHAI, IMER, ISS, IFC-CNR, MCAR DHIR, UMCG, UMCL, ASEREMAC, AO "G Rummo", PUMS, INSERM U953
Number of person/ days of this work package: 529.19
Total budget of this work package:
Total: 107,055 EU: 38,541 Contribution: 68,514
Starting Date : 01/01/2011 **Ending date :** 31/12/2013

Description of the work package

Introduction

WP7 had two major activities (A and B). The main objective was to build a consensus approach among Joint Action partners on a range of policies relevant to primary prevention of congenital anomalies (CA). The final aim of WP7 was to establish a shared primary prevention strategy for CA by developing recommendations to be incorporated into EU MS National Plans with the support of EUROPLAN, European Project for Rare Diseases National Plans Development.

Activity A - Description

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

A1 Activity - pre- and peri-conceptional care, namely: folic acid (FA) supplementation; maternal lifestyles (smoking, alcohol, recreational drugs); counselling and management of chronic maternal conditions (epilepsy, diabetes, obesity, etc.) and use of drugs and health-promoting products (including dietetic or herbal products, etc.), in collaboration with WP9; genetic counselling, in collaboration with WP8

A2 Activity - 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 improve research on CA as well as socio-economic and ethnic determinants. WP7 will evaluate a potential consensus approach toward inclusion of the above actions into national plans on RD.

Activity A - Outcomes and deliverables achieved

To achieve the A1 Activity, WP7 set up specific Working Groups (WG) on seven specific defined issues:

- WG 1 - Folic acid and related nutritional aspects
- WG 2 - Maternal lifestyles
- WG 3 - Chronic and infectious maternal conditions
- WG 4 - Environment, home and workplace
- WG 5 - Drugs
- WG 6 - Food safety
- WG 7 - Genetic factors and genetic counselling

WG participants were identified among EUROCAT partners on the basis of specific

expertise and a declaration of interest (April 2011).

Each WG covered collection and analysis of the relevant literature (peer-reviewed papers, reports from authorities from EU, EU Member States and outside the EU) to define:

- the main evidences on risk factors for CAs, and
- the achievable and applicable public health actions on primary prevention of CAs.

To achieve the A2 Activity, WP7 performed a survey to collect the existing health policies regarding primary prevention with relevance to CA in European countries. Two questionnaires were designed and administered in collaboration with the EUROPLAN project:

- the first questionnaire (Title: Policies for primary prevention of NTDs with Folic acid and folate) aimed at collecting national policies and actions on FA and Folates (M11) (Annexed in Section VII under WP7);
- the second questionnaire (Title: Public Health Actions on Primary Prevention of CA) aimed at collecting policies and actions related to other CA risk factors connected with maternal lifestyles, infectious diseases, chronic diseases, medications, environmental, home and working conditions (M12) (Annexed in Section VII under WP7).

Each WG prepared specific questions for their inclusion in the Questionnaire regarding 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

The questionnaires were submitted using the Surveymonkey web platform:

- The 1st questionnaire was launched on 8 November 2011 and the deadline was December 15, 2011 **(Milestone 2 - Achieved collection of actions to prevent NTD by raising folic acid status)**

- The 2nd questionnaire was launched on 20 October 2012 and the deadline was December 12, 2012 **(Milestone 1 - Achieved collection of public health actions relevant to prevention of CA)**

The 1st questionnaire was widely disseminated, including 68 EUROCAT Member Registries and 108 EUCERD members. This strategy was adopted to ensure that at least one complete questionnaire per European country was collected. For the 2nd questionnaire, it was decided to collect data from a selected panel of European countries' national experts. In this case, a single expert belonging to one of the 27 European invited Countries, was required to fill out the questionnaire regarding his/her own Country.

EUROCAT WGs reached a consensus on the main fields for CA primary prevention

among the JA EUROCAT experts and a shared document on CA primary prevention recommendations was delivered.

A draft was prepared on April 2012 relative to the seven specific issues covered by the Questionnaire on CA primary prevention. This first draft was discussed in several joint sessions for its validation according to scientific evidence and to its wide applicability to European local settings.

An advanced draft was presented during a specific session at the EUROCAT Registry Leaders' Meeting (Budapest, June 13-15, 2012). Thereafter, in June 2012, this draft was revised taking into account the input of the EUROCAT Registry Leaders and the comments of the EUROCAT Project Management Committee. After approval by the EUROCAT Steering Committee (December 2012), the document was sent (in 2013) to the policy officer at the Directorate of Public Health at the European Commission in Luxembourg, in order to obtain a final approval of the European Union Committee of Experts on Rare Diseases (EUCERD).

Methodology, results and consensus process details will be described in the "Report on Primary Prevention of Congenital Anomalies in the European countries". The field work and data analysis has been completed (Annexed in Section VII under WP7) and the final report (**Deliverable D8 - Report on Primary Prevention of Congenital Anomalies**), is structured into three sub-reports:

Part 1. Description of the survey conducted to determine the existing policies for the prevention of NTD in the European Countries through folic acid.

Part 2. Description of the survey conducted to determine existing policies for the prevention of CA in the European Countries.

Part 3. Description of the consensus process and the results for the inclusion of primary prevention actions in the national plans on rare diseases in the European Countries.

The amended recommendations were published on the EUROCAT and EUCERD website (Annexed in Section VII under WP7):
- http://www.eurocat-network.eu/content/EUROCAT-EUROPLAN-Primary-Preventions-Reccomendations.pdf
- http://www.eucerd.eu/wp-content/uploads/2013/03/Eurocat_Reco_PrimaryPrevention.pdf

The recommendations in their original format and how the recommendations were formulated (consensus process) are reported in a paper recently accepted for publication in "Public Health Genomics" (a peer-reviewed international journal): *DOI number 10.1159/000360602.* The title of the article is*: "European recommendations for primary prevention of congenital anomalies: a joined effort of EUROCAT and EUROPLAN projects to facilitate inclusion of this topic in the National Rare Disease Plans".*

A1 Activity has been useful: i) to collect and review scientific evidence on CA risk factors and prevention; ii) to prepare a first draft of recommendations on primary prevention of CAs for joint discussion among WP7 partners.

A2 Activity has been useful: i) to reinforce the construction of a network across EU Countries; ii) to exchange experiences; iii) to facilitate a potential consensus approach toward the inclusion of CA primary prevention into national plans on RD.

A1 and A2 activities have also contributed to support the construction of a network in EU Countries to exchange experiences regarding the activities, initiatives and best

practices for the primary prevention of CA.

In order to facilitate the networking process WP7 has:

- established in EUROCAT a "Folic acid committee" to plan future actions on folic acid, to respond to EUROCAT requests and to consider dissemination strategies in the field of CA primary prevention;

- involved JA EUROCAT partners and external experts to define recommendations for primary prevention on CA;

- established a collaboration with EUROPLAN Project to support and facilitate the inclusion of primary prevention of CA into the national plan/strategy for rare diseases.

Furthermore, Dr. Antoni Montserrat, the policy officer at the Directorate of Public Health at the European Commission in Luxembourg, was contacted soliciting his support for the inclusion of the CA primary prevention recommendation in the Member States national plans for rare diseases.

Activity A - Problems encountered

The following are some critical areas faced by this WP during its implementation:

- The elaboration and finalisation of the two questionnaires was very laborious and quite complex.

- Operational problems were encountered in the filling in of the two questionnaires, namely:

    1. the questionnaires were considered too complex to be filled in by one respondent per country alone.
    2. the thorough review of the collected information has revealed itself more cumbersome than planned, requiring additional time and personnel for its process. This is true, in particular, for the first questionnaire, where more than one respondent per Country was included. In fact, while this allowed the collection of data from various sources, it also required a greater effort in the comparison, the control and the validation of the information collected. In some cases, for example, contradictory information was provided by different respondents from the same Country and this had to be checked and validated.

- Data validation, which is the critical step to ensure that only valid and clean data is reported in the final report, is time consuming given the amount of data to be processed.

- Furthermore, the WP leader associate partner, the Istituto Superiore di Sanità – ISS, requested a sensible cut of the total budget, thus implying a corresponding reduction of personnel involved in the project. Clearly this was an unplanned situation with critical consequences, the main one being a minor delay in the finalization of deliverable D8: "Report on Primary Prevention of Congenital Anomalies".

Activity A – Solutions to the above problems

The following are some of the solutions that have been adopted in order to minimise the effects of the problems encountered.

- To ensure that only valid and clean data is reported in the WP7 final report,

collected data was validated by comparing the questionnaires' replies with the corresponding scientific literature and with the grey literature, official European special reports and documents published by European agencies, such as EFSA, from the EUROCAT Network, and from Institutes and Research Centres. This documentation, cited as a reference by questionnaires respondents, though available online, was sometimes in national languages. In the latter case, further research from other sources were consulted to validate the correct information. This has also contributed to the unplanned delay.

- The reduction in personnel, due to the budget cuts, as described above, has been partly minimised through a more effective collaboration with professionals of other departments of our institution interested in this field, at no additional costs to the project.

Activity B - Description

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:

B1 Activity - updated survey of policies in MS
B2 Activity - track prevalence rates of NTD through the registries
B3 Activity - approaches to assess knowledge and attitude toward FA of women in childbearing age
B.4 Activity - appraisal of strategies to monitor population folate status

Activity B - Outcomes and deliverables achieved

The following is the detailed description of Activity B outcomes and the achieved deliverable.

- To achieve B1- Activity, WP7 used the 1st questionnaire described in A2-Activity. The questionnaire collected all the necessary information to describe progress in developing and implementing public health policies on primary prevention of CA by raising folic acid intake and folate status in European countries **(Milestone 2 - Achieved collection of actions to prevent NTD by raising folic acid status)**.

- To achieve B2 - Activity, trends in the prevalence of NTD in Europe were analysed using data from EUROCAT registries (1991-2009). This activity was performed in collaboration with WP4 "Registration, central Database and Surveillance" and WP6 "Investigation of Trends, Clusters and New Exposures". NTD trends in time reported into Statistical Monitoring Reports (Part A and B) (Milestone reached by WP4)

We analysed trends in the prevalence of NTD in Europe using data from EUROCAT registries (1991-2009). The results of the analyses were presented at the annual meeting in Budapest in June 2012. A draft scientific paper was created. Thereafter it was decided to update the analysis with one more year's data. This update has been slightly delayed due to technical software issues (resulting from an update of the STATA software) experienced by the principal investigator of this activity (INSERM U953). The analysis and preparation of scientific paper for submission are expected to be completed within 2014.

- To achieve B3 – Activity, WP7 worked on the basis of a validated questionnaire used by the Tuscany Registry of Congenital Anomalies (RTDC) to measure knowledge and awareness toward folic acid supplementation and food folate intake in Tuscany. The questionnaire, specifically developed to interview women during pregnancy or soon after delivery, permitted to define a baseline of items for a national survey: i) items on source of information on folic acid; ii) folic acid in medical counselling iii) time/type/dosage of folic acid consumption; iv) reasons

for folic acid consumption, v) knowledge on folic acid benefits for pregnancy vi) knowledge on the appropriate time for taking folic acid, vii) knowledge on foods rich of folic acid, vii) knowledge on folic acid and congenital anomalies, knowledge on other risk factor for congenital anomalies, viii) information on present and previous pregnancies, ix) personal data. Despite the reduction of personnel, it was possible to develop a new model of the questionnaire to be adaptable to local needs and cultural characteristics. The questionnaire, entitled "questionnaire on the attitude, knowledge and behaviour of women who have recently given birth towards folic acid and folate consumption" is ready to be tested, adjusted and validated taking into consideration also its adaptability to the various European contexts (Annexed in Section VII under WP7).

- The B4 – Activity, whose responsibility was given to the Northern Netherlands EUROCAT Registry (UMCG), who collaborated with an independent research organisation, MediClara. This activity, carried out by Dr. Denhard de Smit of MediClara, aimed at exploring the relevance and feasibility of strategies to monitor population folate status with respect to the prevention of CA. Furthermore, it can support health policy as well as scientific investigations concerning folate intake and birth defects by providing new scientific evidences. The methodology and results are described in a Specific report entitled "Appraisal of strategies to monitor (population) folate status with respect to the prevention and scientific study of congenital anomalies" (Annexed in Section VII under WP7). The study comprises the development of a framework for the collection and the study of relevant sources of information, and for the appraisal of a variety of folate status monitoring scenario's using the framework and the information collected. The report results are based on the review of the applicable scientific and policy literature and of consultations with an expert advisory team.

Activity B - Problems encountered

During project implementation, the WP7 associate partner ISS had decided to cut its contribution to the project, with a consequential reduction of the personnel working on B3-Activities.

Activity B - How were problems resolved

The reduction of the WP7 contribution and the consequent reduction of personnel have had only a minor negative impact on the realisation of the B3-Activities. In fact, through active internal collaboration, and with no additional costs to the project, we were able to develop a Questionnaire to assess the state of knowledge, attitude and behaviour on folic acid (FA) and folate. The questionnaire is now ready to be tested and validated.

Other relevant Activity

Liaison
For liaison activity in relation to primary prevention of Congenital Anomalies see WP2 report.

Fetal Alcohol Spectrum Disorders
The first international conference on the Prevention of Fetal Alcohol Spectrum Disorder (FASD) was held in Edmonton, Alberta, Canada in September 2013. Permission was granted by the EAHC to enable representation of EUROCAT at the conference. Ireland's EUROCAT Registry Leader for the Cork and Kerry Congenital Anomaly Register (Dr Mary O'Mahony) attended and reported back to EUROCAT Central Registry (See Report on the First International Conference on the Prevention of Fetal Alcohol Spectrum Disorder (FASD), annexed in Section VII under WP7).

Specific objectives of this WP

	Title
1	Primary Prevention Policy

List of deliverable(s) linked to this work package

Deliverable

	Title
1	**D8 – Report on Primary Prevention of Congenital Anomalies** A 3-part report : I. Public Health Actions (Month 24). II. Prevention of Neural Tube Defects with Folic Acid (Month 24). III. National Plans (Month 36)

Milestones reached by this WP

	Milestone title	Month of achievement
1	Achieved collection of public health actions relevant to prevention of birth defects	Planned M12 Achieved M24
2	Achieved collection of actions to prevent Neural Tube Defects by raising folic acid status	Planned M12 Achieved M12

Work package title : Prenatal Screening, Down Syndrome and Genetic Syndromes
Work package Number : 8
Work package Leader : Prof. Joan Morris (Associate Partner No. 33 (QMUL))
Number of associated partners involved : Main partner plus all 36 associates 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
Number of person/ days of this work package: 427.17
Total budget of this work package:
Total: 132,360 EU: 46,855 Contribution: 85,505
Starting Date: 01/01/2011 **Ending date :** 31/12/2013

Description of the work package

WP8 was divided into 4 main activities.

Activity 1 - Down syndrome and cardiac anomalies

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

In accordance with EUROCAT data request procedures, a protocol for this study was written and approved by the EUROCAT SC during the first reporting period (M1 -12). During the second reporting period (M13-24) data was requested from the EUROCAT member registries. Data was received from those EUROCAT member registries that had given permission (28 EUROCAT registries in19 countries covering over 7 million births from 2000-2010), then cleaned and analysed in accordance with the protocol. During the final reporting period (M25-36) a scientific paper "Major Congenital Anomalies in babies born with Down syndrome: a EUROCAT population-based registry study" was drafted. It was circulated to several registries for comments and after redrafting was circulated to all the registries who had contributed data in Jan 2014 (A CONFIDENTIAL draft is annexed in Section VII under Deliverable 9 and relates to Outcome Indicator 1 (Publication of 6 genetic syndrome papers) of Objective 5 of the Joint Action (Prenatal Screening Information) as listed in WP3). Once the registries have submitted their comments and have confirmed they are happy with the paper to be submitted it will be submitted to The American Journal of Medical Genetics. The study sample consisted of 7115 live and still births with Down syndrome. Overall, 43.4% (95% CI: 42.3% - 44.6%) of births with Down syndrome had a cardiac anomaly and 14.9% (14.1% - 15.8%) had a non-cardiac anomaly. The prevalence of cardiac and non-cardiac congenital anomalies in babies with Down syndrome remained constant from 2000 to 2010 suggesting that population screening for Down syndrome has not influenced the prevalence of these congenital anomalies in babies born with Down syndrome.

Submission of this scientific paper was due in M21 (Milestone 1 of WP8), but was delayed to early 2014, due to time delays in acquiring permissions to use data from participant registries. The delay in submission of the paper to a scientific journal did not impact on other tasks or on the allocation of resources. Once the paper is published a press release about the results will be conducted by the press office at Queen Mary University of London.

Activity 2 - Prevalence of Down syndrome

The increases in Down syndrome diagnoses in Europe due to delaying childbearing and the introduction of earlier prenatal screening have been quantified up to 2007. Activity 2 set out to calculate estimates up to 2011. As part of Activity 2 in

collaboration with WP4, expansion of the EUROCAT Central Database to include the England and Wales National Down Syndrome Cytogenetic Register (NDSCR) data was planned in addition to incorporation of NDSCR data in EUROCAT website epidemiological tables (relates to Process Indicator – Integration of England and Wales NDSCR into Central Database).

Regarding update of estimates to 2011…..

A EUROCAT scientific paper, "Twenty-year trends in the prevalence of Down syndrome and other trisomies in Europe: impact of maternal age and prenatal screening" was submitted to (M11) and then published in the European Journal of Human Genetics (Milestone 2 of WP8, Annexed in Section VII under Deliverable 9 and relates to Outcome Indicator 1 (Publication of 6 genetic syndrome papers) of Objective 5 of the Joint Action (Prenatal Screening Information) as listed in WP3). This paper describes trends and geographical differences in total and live birth prevalence of trisomies 21 (Down syndrome), 18 (Edward syndrome) and 13 (Patau syndrome) with regard to increasing maternal age and prenatal diagnosis in Europe, using data from 21 EUROCAT registries in 12 countries covering over 6 million births. In every 10,000 births, 22 resulted in a Down syndrome pregnancy, 5 resulted in an Edward syndrome pregnancy and 2 resulted in a Patau syndrome pregnancy. Between 1990 and 2009, the proportion of births to mothers aged 35 years and older in Europe increased from 13% in 1990 to 19% in 2009. This rise in the proportion of births to older mothers has led to an increase in the number of trisomy-affected pregnancies in Europe. For trisomy 21, there was a three-fold variation in live birth prevalence between countries with the lowest live birth rates occurring in Spain and Switzerland and the highest rates occurring in Ireland and Malta where termination of pregnancy is illegal. Live birth prevalence has remained stable in most countries despite increasing maternal age over time due to increasing prenatal diagnosis and subsequent terminations (See related press release in WP2).

In addition to the above scientific paper (that updates estimates to 2009), website prevalence rates have been updated to 2011 (See further detail in WP4).

Regarding incorporation of NDSCR data in EUROCAT website epidemiological tables…..

NDSCR data was incorporated into the EUROCAT website as part of the prenatal diagnosis epidemiological tables (this relates to Process Indicator 1 (Integration of England and Wales Down Syndrome Cytogenic Register data into Central Database) of Objective 5 of the EUROCAT Joint Action (Prenatal Screening Information) as listed in WP3).

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

incorporated into the EUROCAT website prenatal diagnosis tables as part of Activity 4 (see below).

Activity 3 - Prevalence of genetic syndromes

Studies on the epidemiological characteristics of rare genetic syndromes, mostly single gene syndromes, are limited, because they require the analyses of large populations and a well-organised diagnostic network. This is made available through the EUROCAT network. Activity 3 aimed to extract cases from the EUROCAT Central Database for 8 specific syndromes and to have those cases reviewed by medical geneticists. This activity demonstrates the unique value of EUROCAT data to determine population prevalence of rare genetic syndromes.

A scientific paper, "Fraser Syndrome: Epidemiological Study in a European Population", using data from 34 EUROCAT registries in 16 European countries, covering 12,886,464 births (1990 to 2008), was submitted to the American Journal of Medical Genetics. Following the journals peer-review process, a revised submission was made and the paper was accepted for publication and published in M27 (Annexed in Section VII under Deliverable 9 and relates to Outcome Indicator 1 (Publication of 6 genetic syndrome papers) of Objective 5 of the Joint Action (Prenatal Screening Informations) as listed in WP3). 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 the European population, a high proportion (82%) of pregnancies is terminated, thus reducing the live birth prevalence to a third of the total prevalence rate.

A scientific paper, "Prevalence, prenatal diagnosis and clinical features of oculo-auriculo-vertebral spectrum (OAVS): a registry-based study in Europe", using data from 34 EUROCAT registries in 16 European countries (1990 to 2009), was submitted to the European Journal of Human Genetics in 2013. Following the journals peer-review process, a revised submission was made and the paper accepted for publication and published in January of 2014 (Annexed in Section VII under Deliverable 9 and relates to Outcome Indicator 1 (Publication of 6 genetic syndrome papers) of Objective 5 of the Joint Action (Prenatal Screening Informations) as listed in WP3). 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. Of 355 infants diagnosed with OAVS, 95.8% (340/355) were live births, 0.8% (3/355) fetal deaths, 3.4% of which were terminations of pregnancy for fetal anomaly and 1.4 % were neonatal deaths. In 18.9% there was prenatal detection of anomaly/anomalies, 69.7 % were diagnosed at birth, 3.9% in the first week of life, and 6.1% within 1 year of life. Twin pregnancies, assisted reproductive techniques and maternal pre-pregnancy diabetes were confirmed as risk factors for OAVS.

A scientific paper, "Meckel-Gruber syndrome: a population-based study on prevalence, prenatal diagnosis, clinical features and survival in Europe", using data from 34 EUROCAT registries in 16 European countries (1990 to 2011), was submitted to the European Journal of Human Genetics in February 2014 (A CONFIDENTIAL submitted copy is annexed in Section VII under Deliverable 9 and relates to Outcome Indicator 1 (Publication of 6 genetic syndrome papers) of Objective 5 of the Joint Action (Prenatal Screening Informations) as listed in WP3). A decision is pending. Meckel-Gruber syndrome is a rare autosomal recessive lethal ciliopathy characterized by the triad of cystic renal dysplasia, occipital encephalocele and postaxial polydactyly. The mean prevalence was 2.6 *per* 100 000 births in a subset of registries with good ascertainment. The prevalence was stable over time, but regional differences were observed. There were 145 (75.9%) terminations of pregnancy after prenatal diagnosis, 13 (6.8%) fetal deaths, 33 (17.3%) live births. Most cases (90.2%) are diagnosed prenatally at 14.3±2.6 (range 11-36) gestational weeks and pregnancies are mainly terminated, reducing the number of live births to

one fifth of the total prevalence rate. Early diagnosis is important for timely counseling of affected couples regarding the option of pregnancy termination and prenatal genetic testing in future pregnancies.

Work is ongoing on Holt Oram syndrome. The data have been analysed (see CONFIDENTIAL draft of tables, combined into one pdf and annexed in Section VII under Deliverable 9 and relates to Outcome Indicator 1 (Publication of 6 genetic syndrome papers) of Objective 5 of the Joint Action (Prenatal Screening Informations) as listed in WP3). The Tables are as follows:

Table 1: Prevalence of Holt Oram syndrome (HOS) in 16 selected EUROCAT registries according to the http://www.eurocat-network.eu/content/DQI-2013.pdf, 1990-2011

Table 2: The number of cases and prevalence of Holt Oram syndrome (HOS) patients in 16 selected EUROCAT registries with high dana quality according to the http://www.eurocat-network.eu/content/DQI-2013.pdf, in 1990-2011

Table 3: Descriptive epidemiological data on patients with Holt Oram syndrome (HOS) in the EUROCAT registries, 1990-2011

Table 4: Outcome of pregnancies and prenatal detection rate in Holt Oram syndrome (HOS) in the EUROCAT registries, 1990-2011

Table 5: Frequency and type of major congenital anomalies in Holt Oram syndrome (HOS) patients in present study and in previously published series of patients

Drafting and approval by all authors of the paper is expected in March 2014 (at no further budgetary cost).

The first two syndrome submissions were expected by M18, and the next two by M36. The Fraser paper was first submitted in 2011 but was delayed because the American Journal of Medical Genetics asked that we exclude clinical data, as they thought that clinical data on these cases had already been published in a previous paper dealing with genetic testing of Fraser Syndrome. We made contact again with participating registries to ensure that in most/all of the cases no genetic testing was performed, and that the data on our patients had not been published in a previous paper. We informed the Journal of this and sent the revised submission which was then accepted for publication in 2013. This did not impact on other activity within the WP or on the allocation of resources.

We did a preliminary analysis of Treacher Collins and Beckwith Wiedemann syndromes, but as checking and updating the large number of data is taking longer than expected, we decided to analyse and submit papers on Meckel Gruber and Holt Oram syndrome earlier than previously planned, for which we already had complete data. This increased activity, resulted in a general delay in submittance of genetic syndrome papers. This did not impact on other activity within the WP or on the allocation of resources.

Additional related activity included:

i) the creation and maintenance of a new "Prevalence of selected Monogenic Syndromes in Europe" table, publically available on the EUROCAT website http://www.eurocat-network.eu/accessprevalencedata/prevalencetables (described further in WP4 report, and appended in Section VII under WP4).

ii) creation of a special report for the attention of Orphanet, that included information on prevalence of rare genetic syndromes - EUROCAT: A potential source of prevalence data for Orphanet (Annexed in Section VII under WP8 and described further in WP2 report under liaison with Orphanet). Also available at http://www.eurocat-network.eu/content/EUROCAT-Report-Potential-Source-of-Data-

for-Orphanet.pdf

iii) creation and publication on the EUROCAT website of - EUROCAT (2012). EUROCAT Special Report: Congenital Anomalies are a Major Group of Mainly Rare Diseases. This report included information on prevalence of rare genetic syndromes (Annexed in Section VII under WP8 and described further in the WP2 report under general dissemination to and liaison with the wider Rare Diseases community). Also available at http://www.eurocat-network.eu/content/Special-Report-Major-Group-of-Mainly-Rare-Diseases.pdf

Activity 4 - Review of prenatal diagnosis tables

Prenatal screening and diagnosis technology and policy are constantly changing and unequally implemented across health systems and countries in Europe. EUROCAT population-based data on prenatal diagnosis are of great value in evaluating these changes.

The purpose of activity 4 was to agree and implement in coordination with WP4, modifications to increase the amount of prenatal diagnosis information available on the EUROCAT website tables (i.e. number of conditions, information on timing or diagnostic techniques). This relates to Output Indicator 1 (Expansion of prenatal diagnosis tables on the EUROCAT website) of Objective 5 of the Joint Action (Prenatal Screening Information) as listed in WP3. In support of this activity, a proposal was planned in collaboration with WP5 to revise EUROCAT variable codes to ensure that new advances in prenatal screening and diagnosis could be coded.

Regarding revision of EUROCAT variable codes……

A new prenatal diagnosis variable (described further in the WP5 report) was trialled during 2011-2012 by UK based EUROCAT registries and was then incorporated in to WP4 (in the new Guide 1.4. for births registered from 2013 onwards). Accurate population-based prenatal diagnosis data are increasingly in demand and congenital anomaly registries are a very useful resource for these. However, it is not sufficient to say that a 'case' was prenatally diagnosed, data are needed per anomaly. EUROCAT have therefore introduced a new variable whereby each anomaly can be individually coded as to whether, or not, it was prenatally detected. This will allow much more accurate data for epidemiological, clinical and audit purposes.

Draft versions of new website prenatal diagnosis tables containing English and Welsh data from the NDSCR were presented to the EUROCAT PMC in March and in December of 2012. The draft tables were also presented to the wider EUROCAT membership during the RLM in Budapest (June 2012, M18). Following feedback from the EUROCAT PMC and the general EUROCAT membership, website prenatal diagnosis tables containing data from the NDSCR were developed, to go live on the EUROCAT test website in January 2013 (EUROCAT member's only access)

Regarding increasing the amount of information available on prenatal diagnosis in website tables……

The original prenatal tables presented the proportion of cases that were diagnosed prenatally for all the registers combined for a specified set of conditions. The new prenatal diagnosis tables provide much more information according to individual registries. The user may choose from a list of specified anomalies and they are then presented with either a table or a figure (they can choose which) that presents the proportion prenatally diagnosed according to the different registers. Further details can then also be requested, such as the outcome of those cases diagnosed prenatally and also the gestational age at diagnosis. For Down, Edwards and Patau syndrome additional information on maternal age and the indication for the diagnosis is available. This enables researchers to get a picture of the state of prenatal diagnosis across Europe and to investigate if issues such as differences in maternal age distributions across Europe may explain the variations. Differences between different anomalies can also be examined. The new tables are now publically accessible on the

EUROCAT website at http://www.eurocat-network.eu/prenatalscreeninganddiagnosis/prenataldetection(pd)rates (April 2013).

Additional activity regarding prenatal diagnosis….

A scientific editorial was published in January 2014 (Annexed in Section VII under WP8).

Dolk H and Wellesley D (2014). Antenatal screening for Down Syndrome and other chromosomal abnormalities: increasingly complex issues. Arch Dis Child Fetal Neonatal Ed, 99, F2-F3.

Deliverable list – set of 6 scientific papers on Down Syndrome and other Genetic Syndromes (Annexed in Section VII under Deliverable 9) Morris JK, Garne E, Wellesley D, Addor M-C, Arriola L, Barisic I, Beres J, Bianchi F, Budd J, Calzolari E, Matias Dias C, Doray B, Gatt M, Haeusler M, Klungsoyr K, Khoshnood B, Latos-Bielenska A, Mullaney C, Nelen V, O'Mahony M, Queisser-Luft A, Randrianaivo H, Rankin J, Rissman A, Rounding C, Sipek A, Stoianova S, Tucker D, Visser J, Yevtushok L, Loane M, Dolk H (2014). Major Congenital Anomalies in babies born with Down syndrome: a EUROCAT population-based registry study. *To be submitted in April 2014.*

Loane M, Morris J, Addor M-C, Arriola L, Budd J, Doray B, Garne E, Gatt M, Haeusler M, Khoshnood B, Klungsoyr Melve K, Latos- Bielenska A, McDonnell R, Mullaney C, O'Mahony M, Queisser-Wahrendorf A, Rankin J, Rissmann A, Rounding C, Salvador J, Tucker D, Wellesley D, Yevtushok L and Dolk H (2013). Twenty-year trends in the prevalence of Down syndrome and other trisomies in Europe: impact of maternal age and prenatal screening. European Journal of Human Genetics. 21: 27-33.

Barisic I, Odak L, Loane M, Garne E, Wellesley D, Calzolari E, Dolk H, Addor MC, Arriola L, Bergman J, Bianca S, Boyd PA, Draper ES, Gatt M, Haeusler M, Khoshnood B, Latos-Bielenska A, McDonnell B, Pierini A, Rankin J, Rissmann A, Queisser-Luft A, Verellun-Dumoulin C, Stone D, Tenconi R (2013), Fraser Syndrome: Epidemiological Study in a European Population, *American Journal of Medical Genetics*, 161A (5), 1012-1018.

Barisic I, Odak L, Loane M, Garne E, Wellesley D, Calzolari E, Dolk H, Addor MC, Larriola L, Bergman J, Bianca S, Doray B, Khoshnood B, Klungsoyr K, McDonnell B, Pierini A, Rankin J, Rissmann A, Rounding C, Queisser-Luft A, Scarano G, Tucker D (2014), Prevalence, prenatal diagnosis and clinical features of oculo-auriculo-vertebral spectrum: a registry-based study in Europe, *European Journal of Human Genetics*, In press.

Barisic I, Boban L, Loane M, Garne E, Wellesley D, Calzolari E, Dolk H, Addor M-C, Bergman JEH, Braz P, Draper ES, Haeusler M, Khoshnood B, Klungsoyr K, Pierini A, Queisser-Luft A, Rankin J, Rissmann A, Verellen-Dumoulin C (2014), Meckel-Gruber syndrome: a population-based study on prevalence, prenatal diagnosis, clinical features and survival in Europe, *submitted to the European Journal of Human Genetics.*

See above for progress of the one remaining scientific paper, and additional deliverables in collaboration with WP2, WP4 and WP5.

Specific objectives of this WP

	Title
1	Prevalence information
2	Prenatal screening information

List of deliverable(s) linked to this work package

Deliverable

	Title
1	**D9 – Set of 6 Scientific Down Syndrome and Other Genetic Syndrome Papers** 2 scientific papers on Down Syndrome (Months 18 and 36). 4 papers on other genetic syndromes (Months 9, 18, 27 and 36).

Milestones reached by this WP

	Milestone title	Month of achievement
1	Submission of scientific paper on prevalence of cardiac anomalies in Down Syndrome	Planned M21 Expected Early 2014
2	Submission of scientific paper on changes in the prevalence of Down Syndrome	Planned M31 Achieved M11
3	Submission of 2 scientific papers on descriptive epidemiology of selected genetic syndromes	Planned M18 1 paper submitted in 2011 and published M27 1 paper submitted in 2013 and published January 2014
4	Submission of 2 scientific papers on descriptive epidemiology of selected genetic syndromes	Planned M36 1 paper submitted February 2014 and 1 paper ready to be submitted

Work package title : Medication During Pregnancy
Work package Number : 9
Work package Leader : Dr. Marian Bakker (Associate Partner No. 20 (UMCG))
Number of associated partners involved : 18
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).
Number of person/ days of this work package: 925.26
Total budget of this work package:
Total: 209,264 EU: 34,843 Contribution: 174,421
Starting Date : 01/01/2011 **Ending date :** 31/12/2013

Description of the work package

EUROCAT's pharmacovigilance activities relating to medication safety in pregnancy have been given the label "euromedicat" to distinguish this branch of activity. Subsequent to being granted EUROCAT Joint Action funding for the period Jan 2011-Dec 2013, were successful in obtaining EU Framework 7 funding for the period March 2011-Feb 2015 (www.euromedicat.eu). In order to avoid confusion between the euromedicat project and the euromedicat branch of EUROCAT activities, we have reserved the label EUROmediCAT for the FP7 funded project. Nevertheless, pharmacovigilance related activities continued to be carried out within the EUROCAT Joint Action distinct from the activities included in EUROmediCAT. The Joint Action activities are reviewed below.

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

At the Antwerp RLM (M6) a workshop on ATC coding was organised (Milestone 1 of WP9), in which the ATC system was explained, as was how to find the appropriate ATC code for drugs. The ATC coding workshop was planned to take place annually at each RLM. At the second RLM in Budapest (June 2012, M18) it was decided that most EUROCAT member registries knew how to find ATC codes and use them for coding medications, and so WP9 time within the RLM was used to discuss the new variable to be implemented in Guide 1.4 (see below) and also to distribute a questionnaire/table to registries for information on data sources used for collecting information on medication use in pregnancy. The information collated was added to the information obtained from a questionnaire referred to in Activity 3.1 (below) for a report and paper on the usefulness of congenital anomaly register data on studies of medication use in pregnancy. The report, "Sources of Information on Medication Use in Pregnancy", has been written up and is currently being distributed among participating EUROCAT member registries for feedback. (The report (Milestone 2 of WP9) was expected in M12, but was delayed because it was preferable to combine the description of the sources of medication data with the new DQI used on the new dataset (see below). The delay did not impact on other activities within WP9 or on the allocation of resources). The final version of the report (Annexed in Section VII under Deliverable 10) will be published on the EUROCAT website and converted into a scientific paper for publication in a peer-reviewed scientific journal (re Deliverable 10 and Output Indicator 1 (3 scientific papers) of Objective 6 (Postmarketing Drug Surveillance) of the Joint Action as listed in WP3). At the third RLM in Zagreb (June 2013, M30), instead of an ATC coding workshop, WP9 time was used to provide an overview of EUROmediCAT to attendees and to update on the lamotrigine, clubfoot and data collection methods studies.

Also at the RLM in Antwerp (June 2011, M6) UMCG (NL) presented the evaluation of data quality on medication use. Data from 21 EUROCAT member registries were included.

The evaluation showed that 'blanks' were used by EUROCAT member registries when coding to cases of congenital anomaly to indicate unknown and no medication use and that the difference between 'unknown' and 'no' medication use was not always clear. The recorded use of medication in first trimester varied between 2% (Dublin (IE) EUROCAT registry) to 40% (Emilia Romagna (IT) and North Netherlands (NL) EUROCAT registries). These differences were thought not to reflect 'real' differences in medication use between different registries, and were more likely attributed to the availability of information sources on medication use. As a result of this evaluation, to improve data quality a new variable to clarify better whether the mother used medication in the first trimester was piloted in the EUROCAT Data Management Program (by 6 EUROCAT member registries including OVGU (DE), UNEW (UK), HSE (IE), Hospital Lillebaelt (DK), UMCG (NL), SUHT (UK)) for Guide 1.4 (in collaboration with WP5). The new variable was "First trimester medication use: yes / no / unknown". The results of the first pilot indicated that an extra category should be added: "yes/no/undetermined/unknown", in which undetermined means that sources were consulted, but the information on medication use was not clear and unknown refers to the situation in which the sources could not be consulted. This new addition to the variable was further piloted (by 5 EUROCAT member registries including Hospital Lillebaelt (DK), IFC-CNR (IT), UMCH (NL), PIH (BE), IMER (IT)) and then included in the new Guide 1.4 in M24 (for cases born from 2013 onwards, or back dated cases to 2005 where possible).

Evaluation of data quality on antidepressant use was also performed by UU (UK) as part of the SSRI use and congenital malformations study (see activity 3.1). For antiasthmatics (Hospital Lillebaelt, DK) and antidiabetics (RUG, NL), this becames part of the FP7 funded EUROmediCAT project (see explanation at the beginning of WP9 report).

In the version of EDMP (issued M14), the possibility to add more than 5 medications was added for cases where medication use in the first trimester of pregnancy was known. The previous version had only allowed coding of 3 medications, which was sometimes not enough.

A proposal for new DQI (in collaboration with WP5 and in line with developing work on drug surveillance) was discussed at the PMC meeting (M11). It was decided that 2 new DQI would be implemented on medication use:

(i) Medication exposure recorded using 7-digit ATC-codes (yes/no)

(ii) % of ATC codes with 7 digits and in correct format

EUROCAT reports on the DQIs on an annual basis, see http://www.eurocat-network.eu/aboutus/datacollection/dataquality/dataqualityindicators. For further information on EUROCAT DQIs, see WP5 report or access,

Loane M, Dolk H, Garne E, Greenlees R and a EUROCAT Working Group (2011), "EUROCAT Data Quality Indicators for Population-Based Registries for Congenital Anomalies", Birth Defects Research (Part A), Vol 91, pp S23-S30 at http://www.eurocat-network.eu/content/Pubs-2011-Loane-Report9(3)-DQI.pdf.

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

Most of this activity was moved to the FP7-funded EUROmediCAT project, where more resources were available. The role of the EUROCAT Joint Action activity is to integrate the pilot carried out in EUROmediCAT into future EUROCAT surveillance. Under the EUROmediCAT project (FP7) a protocol for prescription data linkage and a software module have been developed. Those EUROCAT member registries that are also part of the EUROmediCAT project are currently piloting this software module. As soon as this has finished and the results are known, 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. The registry in EUROCAT registry in Valencia has already expressed an interest in the protocol and software module that have been developed for the EUROmediCAT project. UMCG will contact them when the software module has been used in the EUROmediCAT project and the first results are known. The new software will also be showcased at the EUROCAT Registry Leaders' Meeting in 2014.

Activity 3 - Signal detection and evaluation - Specify and pilot signal detection methods (UMCG, NL)

A pilot study was completed (by UMCG and RUG, NL) to test a methodology to identify signals by comparing prevalence of maternal medication use in malformed cases (using data from the North Netherlands EUROCAT member registry) to the prescription rates in the general pregnant population using data from a population-based prescription database (IADB.nl) - the case-population surveillance approach. A scientific paper (Annexed in Section VII under Deliverable 10, and relates to Output Indicator 1 (3 scientific papers) of Objective 6 (Postmarketing Drug Surveillance) of the Joint Action as listed in WP3) detailing the study was submitted, accepted and published.

de Jonge L, Zetstra-van der Woude PA, Jens Bos H, de Jong-van den Berg LTW, Bakker MK (2013), Identifying Associations between Maternal Medication Use and Birth Defects Using a Case-Population Approach: An Exploratory Study on Signal Detection, *Drug Safety*, 36(11), 1069-78.

Further signal detection methodology is being developed as part of the FP7-funded EUROmediCAT project.

3.1 Selective Serotonin Reuptake Inhibitors (SSRI) study – Analyse EUROCAT database in relation to antidepressants (UU, UK)

The prevalence of major depression in women in Europe in a 12- month period has been estimated at 3.0-11.2%. Untreated depression in pregnancy is associated with significant morbidity and unhealthy lifestyle behaviours and increases the risk of poor birth outcomes. Pharmacotherapy with SSRIs is a common treatment approach, including in pregnancy, but there are concerns about effects on the fetus, including an increased risk of congenital heart defects (CHDs).

A study protocol was presented to EUROCAT members at the 2010 RLM in Dublin. Approval from the EUROCAT SC was given in late 2010. The study was conducted entirely during the EUROCAT Joint Action. The aim of the study was to investigate the teratogenic risks of antidepressant use by pregnant women in order to inform clinical practice and public health interventions. Drug exposure data spanning 1990-2007 held at the EUROCAT Central Registry (within the EUROCAT Central Database) were evaluated and 12 EUROCAT member registries (from 12 different countries) meeting specified criteria for specific birth years were invited to participate in the case-malformed control study. Consent was received from these 12 registries. In order to ascertain the sources of information for drug exposure among the women to the EUROCAT member registries, and to understand the coding of drug exposure data by the EUROCAT member registries, a questionnaire was designed and sent to registry leaders (also relates to Activity 1 above). All EUROCAT member registries responded to the SSRI drug exposure information sources/data coding questionnaire and that was useful in guiding the analysis and interpretation of the data. Preliminary results of data analysis were presented at the 2011 RLM in Antwerp (M6). Further results of data analysis were presented at the 2012 RLM in Budapest (M18). The results showed that infants/fetuses with congenital heart defects (CHDs) were significantly more likely to have been exposed in the first trimester to SSRIs compared to infants/fetuses with congenital anomalies other than CHD (Odds Ratio 1.38, 95% Confidence Interval 1.05-1.82). The association was stronger for severe CHD (OR 1.54, 95% CI 1.04-2.28) and, therefore, cannot be explained as a product of neonatal or infant examination bias. Specific associations were demonstrated for Ebstein's anomaly, and Tetralogy of Fallot. Five signals in the literature for anorectal atresia and stenosis, gastroschisis, renal dysplasia, clubfoot, and

hypospadias were supported, and a new association detected for microcephaly. In all the observed associations, there was little evidence of specificity as to SSRI type.

A scientific paper (Abstract and relevant Tables are annexed in Section VII under Deliverable 10, relating also to Output Indicator 1 (3 scientific papers) of Objective 6 (Postmarketing Drug Surveillance) of the Joint Action as listed in WP3) has been prepared for submission to the Obstetrics & Gynecology journal (in Spring 2014), entitled Selective Serotonin Reuptake Inhibitor Antidepressant Use in First Trimester Pregnancy and Risk of Congenital Anomalies: A European Register-based Study in 12 European Countries (re Deliverable 10). Submission of this paper was delayed due to the PhD student involved starting a new job.

Anthony Wemakor (the PhD student responsible for Activity 3.1 in WP9), while working with Helen Dolk (Project Leader) at EUROCAT Central Registry on the association between Selective Serotonin Reuptake Inhibitors (SSRIs) and congenital heart disease, had confirmed signals for specific associations between maternal use of SSRIs in the first trimester of pregnancy and two congenital anomalies – Tetralogy of Fallot (TOF) and Ebstein's Anomal;y (EA). As a result two additional follow-up studies were planned to be carried out by UU (UK) and Hospital Lillebaelt (DK). The first exploring the epidemiology of Tetralogy of Fallot and Ebstein's anomaly which was added as additional activity to activity 5.2 of WP6 (see WP5 report), and the second (which is ongoing) will be part of the FP-7 funded EUROmediCAT study with special emphasis on medication exposure.

3.2 Newer Antiepileptics including Lamotrigine (RUG, NL)

In 2007 a signal was found for maternal first trimester lamotrigine exposure and the risk for isolated orofacial clefts (24-times increased risk), especially for isolated cleft palate. This signal was based on data from the North American antiepileptic drug Pregnancy Registry and was followed by a Food and Drug Administration alert. The signal was examined in the European Surveillance of Congenital Anomalies (EUROCAT) antiepileptic-study database. No significantly increased risk of orofacial clefts was found, either for isolated orofacial clefts or for isolated cleft palate relative to other non-chromosomal registrations. However, the confidence intervals were wide due to the small number of cases exposed to lamotrigine monotherapy. In order to estimate the risk of orofacial clefts relative to other malformations more precisely, and in order to explore further whether lamotrigine exposure may be associated with other malformations, a follow-up study was commissioned by GlaxoSmithKline to update the data (annually, each year of the EUROCAT Joint Action) up to birth year 2011, with yearly updated reporting (the most recent update available has been annexed to Section VII under WP9).

RUG (NL) and UU (UK) are currently working on the final update of the lamotrigine report. This update to the study now includes a 10.1 million birth population, from 22 EUROCAT member registries. A total of 1,364 congenital anomaly registrations with maternal first trimester antiepileptic drug exposure are now in the dataset, of which 157 include lamotrigine monotherapy exposure. The Swedish EUROCAT registry was added to the study in 2011, and Finnish EUROCAT registry was included in 2013. The case-malformed control analysis results show that there remains no evidence of an association between orofacial clefts and lamotrigine monotherapy relative to other malformations (OR 1.26 (95% CI: 0.71 - 2.23) for all orofacial clefts; OR 1.40 (95% CI: 0.77 - 2.53) for isolated orofacial clefts), and the confidence intervals now exclude a risk above 2-2.5-fold. There was no new evidence in this fifth update to support the signal of an association with clubfoot. The independent evidence relating to clubfoot since the original study is no longer statistically significant, but the overall excess (including the original data) remains statistically significant. No new signals of note were generated.

RUG (NL) performed a background descriptive epidemiological study of clubfoot which served as a context for the lamotrigine study. A total of 20 registrations with clubfoot in the period of 2005 relating to the 2011 update of the lamotrigine study were randomly selected from each registry. A questionnaire on laterality, treatment and family history

which was needed to be answered by checking the paediatric records were sent out to 16 EUROCAT registries, comprising 308 cases. Replies were received from all 16 EUROCAT registries, comprising 301 registrations. Of 301 registrations with clubfoot, clubfoot diagnoses were confirmed for 286 registrations (95.0%), of which176 registrations (61.5%) were based on medical information. The results showed that registrations with the coding "clubfoot Q660" in the EUROCAT database are likely to be "real clubfoot – talipes equinovarus", not postural clubfoot.

Two abstracts ((i) lamotrigine use and risk of club foot (poster), (ii) lamotrigine use during pregnancy and risk of oral clefts (oral presentation)) using data from the 2011 update were submitted to the International Conference on PharmacoEpidemiology (ICPE, 23-26 August 2012 in Barcelona). Both abstracts were accepted and presented by Hao Wang (RUG, NL). A poster on the signal of lamotrigine and clubfoot was presented by Jan Mejnartowicz (PUMS, PL) at the 20th World Congress of Neurology (Morocco, 12 - 17 November 2011). EUROCAT's posters relating to Medication Use During Pregnancy are made accessible at http://www.eurocat-network.eu/preventionandriskfactors/medicationduringpregnancy/medicationposters.

Both studies will be written as scientific papers for submission to peer-reviewed scientific journals for publication (re Deliverable 10).

The EUROCAT Project Manager (Dr. Rhonda Curran) was also responsible for developing an impact case study, entitled "Antiepileptic Drug Safety in Pregnancy - epidemiological surveillance of congenital anomalies (birth defects)", for submission to the Research Excellence Framework (REF) the new system for assessing the quality of research in UK higher education institutions (HEIs) such as the University of Ulster (Co-ordinating Centre of the EUROCAT Joint Action and home of EUROCAT Central Registry). The case study is described further under impact tracking in WP3 report.

3.3 Drugs of new concern/Drug signal queries (UMCG, NL)

Several pharmaceutical companies have contacted the EUROCAT Central registry with respect to the use of drugs (A log of medication queries is Annexed in Section VII under WP9). Since we expect more queries from researchers and pharmaceutical companies a EUROCAT Medication Enquiry form, and a EUROCAT response form was developed for use in this type of query (Annexed in Section VII under WP9).

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

UMCG (NL) submitted a symposium abstract (that was accepted) to the International Conference on Pharmacoepidemiology (ICPE, 23-26 August 2012 in Barcelona), together with the European Network Teratology Information Service (ENTIS), for a symposium on Bias and Confounding in Studies on Medication Use in Pregnancy (M20, Milestone 3 of WP9, See also Process Indicator 2 (Joint Meeting with ISPE and ENTIS) of Objective 6 of the Joint Action (Postmarketing Drug Surveillance) as listed in WP3). Speakers were Hao Wang (EUROCAT and RUG, NL), Corinne de Vries (University of Bath, UK), Rachel Charlton (University of Bath, UK), Heli Malm (ENTIS and Helsinki University Central Hospital, Finland) and Kristin Palmsten (Harvard School of Public Health, USA).

Prof Dolk (UU, UK) and Prof de Jong-van den Berg (RUG, NL) are members of ENCePP. Prof de Jong-van den Berg presented at the plenary ENCePP meeting in October 2012 the different approaches on signal detection and signal evaluation of adverse effects of medication use in pregnancy. The EUROCAT database and Antiepileptic Drug (AED) studies were included in this presentation. Prof Dolk has been working within the EncePP Working Group on Scientific Independence and Transparency, the EncePP Working Group on Data Integration and the EncePP Special Interest Group in Pregnancy.

Other

A section of the EUROCAT website has been created for matters relating to medication use in pregnancy. To access Medication During Pregnancy information on the EUROCAT website visit http://www.eurocat-network.eu/preventionandriskfactors/medicationduringpregnancy/medicationintroduction and Medication During Pregnancy specific EUROCAT publications visit http://www.eurocat-network.eu/preventionandriskfactors/medicationduringpregnancy/medicationpublications

Specific objectives of this WP

	Title
1	Postmarketing drug surveillance

List of deliverable(s) linked to this work package

Deliverable

	Title
1	**D10 – EUROmediCAT Papers** 3 scientific papers on risks of specific medications and pharmacovigilance methodology (Month 36)

Milestones reached by this WP

	Milestone title	Month of achievement
1	First annual workshop on ATC coding	Expected M6 Achieved M6
2	Updated report on sources of data on maternal medication use used by registries contributing data to EUROCAT	Expected M12 Achieved early 2014
3	Joint symposium with ISPE and ENTIS (Florence)	Expected M24 Achieved M20
4	Linkage performed between birth defects registry and prescription database in selected registries	Expected M30 Not part of FP7-funded EUROmediCAT project

SECTION VII

ANNEXES

Documents types	Tab	Code doc	Code status	Access
Final report (publishable summary)	Reports & deliverables	SFR	PS	Internal and External
Full final report	Reports & deliverables	FFR	PS	Internal and External
Evaluation report	Reports & deliverables	E	IS	Internal and External
EAHC SANCO internal assessment	Reports & deliverables	IAR	IS	Internal
Deliverable 1 – Final Report 20102204 D01-01 FFR UK PS.PDF	Reports & deliverables	FFR	PS	Internal and External
Deliverable 1 – Final Report 20102204 D01-02 IR UK PS.PDF 1st interim report	Reports & deliverables	IR	PS	Internal and External
Deliverable 1 – Final Report 20102204 D01-03 IR UK PS.PDF 2nd interim report	Reports & deliverables	IR	PS	Internal and External
Deliverable 2 – Two European Symposia 20102204 D02-01 OTH UK PS. PDF Abstract Book including Programme of 1st EUROCAT European Symposium	Reports & deliverables + Other Information	OTH	PS	Internal and External
Deliverable 2 –Two European Symposia 20102204 D02-02 OTH UK PS. PDF Abstract Book including Programme of 2nd EUROCAT European Symposium	Reports & deliverables + Other Information	OTH	PS	Internal and External
Deliverable 3 – Evaluation Report	Reports & deliverables	EVR	PS	Internal and External

20102204 D03 EVR UK PS.PDF				
Deliverable 4 - Website Epidemiological Tables updated to 2011 20102204 D04-01 OTH UK PS.PDF Table: Prevalence rates (including and excluding chromosomal cases) for all EUROCAT anomaly subgroups, 2005-2009, all full member registries	Reports & deliverables + Other Information	OTH	PS	Internal and External
Deliverable 4 - Website Epidemiological Tables updated to 2011 20102204 D04-02 OTH UK PS.PDF Table: Prevalence rates (including and excluding chromosomal cases) for all EUROCAT anomaly subgroups, 2006-2010, all full member registries	Reports & deliverables + Other Information	OTH	PS	Internal and External
Deliverable 4 - Website Epidemiological Tables updated to 2011 20102204 D04-03 OTH UK PS.PDF Table: Prevalence rates (including and excluding chromosomal cases) for all EUROCAT anomaly subgroups, 2007-2011, all full member registries	Reports & deliverables + Other Information	OTH	PS	Internal and External
Deliverable 5 – Statistical Monitoring Reports Part A 20102204 D05-01 OTH UK PS.PDF EUROCAT Statistical Monitoring Report 2009 available at http://www.eurocat-network.eu/content/Stat-Mon-Report-2009-Combined.pdf (made available on website in M13)	Reports & deliverables + Other Information	OTH	PS	Internal and External

Deliverable 5 – Statistical Monitoring Reports Part A 20102204 D05-02 OTH UK PS.PDF EUROCAT Statistical Monitoring Report 2010 available at http://www.eurocat-network.eu/content/Stat-Mon-Report-2010.pdf (made available on website M25)	Reports & deliverables + Other Information	OTH	PS	Internal and External
Deliverable 5 – Statistical Monitoring Reports Part A 20102204 D05-03 OTH UK PS.PDF EUROCAT Statistical Monitoring Report 2011 available at http://www.eurocat-network.eu/clustersandtrends/statisticalmonitoring/statisticalmonitoring-2011 (made available on website April 2014)	Reports & deliverables + Other Information	OTH	PS	Internal and External
Deliverable 6 – ICD11 Coding Revision Submission Submissions were made (See WP5 report). These were confidential submissions made on the WHO ICD11 website, tailored for this purpose. Therefore we have no document to annex in relation to Deliverable 6.	Reports & deliverables + Other Information	OTH	IS	External
Deliverable 7 – Investigation Report 20102204 D07-01 OTH UK PS.PDF EUROCAT Statistical Monitoring Report 2009 available at http://www.eurocat-network.eu/content/Stat-Mon-Report-2009-Combined.pdf (made available on website in M13)	Reports & deliverables + Other Information	OTH	PS	Internal and External
Deliverable 7 – Investigation Report 20102204 D07-02 OTH UK PS.PDF EUROCAT Statistical	Reports & deliverables + Other Information	OTH	PS	Internal and External

Monitoring Report 2010 available at http://www.eurocat-network.eu/content/Stat-Mon-Report-2010.pdf (made available on website M25)				
Deliverable 7 – Investigation Report 20102204 D07-03 OTH UK PS.PDF EUROCAT Statistical Monitoring Report 2011 available at http://www.eurocat-network.eu/clustersandtrends/statisticalmonitoring/statisticalmonitoring-2011	Reports & deliverables + Other Information	OTH	PS	Internal and External
Deliverable 7 – Investigation Report 20102204 D07-04 OTH UK PS.PDF Report : Actions Towards European Environmental Surveillance: Feasibility of Environmental Linkage. http://www.eurocat-network.eu/content/Vrijheid-2013-Environmental-Linkage.pdf	Reports & deliverables + Other Information	OTH	PS	Internal and External
Deliverable 7 – Investigation Report 20102204 D07-05 OTH UK PS.PDF Luteijn JM, Dolk H, Marnoch GJ (2011), Differences in pandemic influenza vaccination policies for pregnant women in Europe, BMC Public Health, 11: 819	Reports & deliverables + Other Information	OTH	PS	Internal and External
Deliverable 7 – Investigation Report 20102204 D07-06 OTH UK PS.PDF Luteijn JM; Dolk H, Addor M-C, Arriola L, Barisic I, Bianchi F, Calzolari E, Draper E, Garne E, Gatt M, Haeusler M, Khoshnood B, McDonnell R, Nelen V, O'Mahony M,	Reports & deliverables + Other Information	OTH	PS	Internal and External

Mullaney C, Queisser-Luft A, Rankin J, Tucker D, Verellun-Dumoulin C, Walle H, Yevtushok L (2014), Seasonality of congenital anomalies in Europe Birth Defects Research Part A: Clinical and Molecular Teratology, 100, 260-269				
Deliverable 7 – Investigation Report 20102204 D07-07 OTH UK PS.PDF Luteijn JM, Brown MJ, Dolk H (2013), Influenza and congenital anomalies: a systematic review and meta-analysis. Human Reproduction, 29, 809-23	Reports & deliverables + Other Information	OTH	PS	Internal and External
Deliverable 7 – Investigation Report 20102204 D07-08 OTH UK PS.PDF Boyle B, McConkey R, Garne E, Loane M, Addor M-C, Bakker M, Boyd P, Gatt M, Greenlees R, Haeusler M, Klungsoyr Melve K, Latos-Bielenska A, Lelong N, McDonnell R, Metneki J, Mullaney C, Nelen V, O'Mahony M, Pierini A, Rankin J, Rissmann A, Tucker D, Wellesley D and Dolk H (2013). Trends in the prevalence, risk and pregnancy outcome of multiple births with congenital anomaly: a registry-based study in 14 European countries 1984-2007, British Journal of Gynaecology, 120, 707-716	Reports & deliverables + Other Information	OTH	PS	Internal and External
Deliverable 7 – Investigation Report 20102204 D07-09 OTH UK PS.PDF Boyle B, Morris JK, McConkey R, Garne E, Loane M, Addor MC, Gatt M, Haeusler M, Latos-Bielenska A, Lelong N, McDonnell R, Mullaney C, O'Mahony M, Dolk H (2014), Prevalence and risk of Down Syndrome in monozygotic and	Reports & deliverables + Other Information	OTH	PS	Internal and External

dizygotic multiple pregnancies in Europe: implications for prenatal screening, British Journal of Gynaecology, epub ahead of print DOI: 10.1111/1471-0528.12574				
Deliverable 7 – Investigation Report 20102204 D07-10 OTH UK PS.PDF Best KE, Nelan V, Arriola L, O'Mahony M, Sipek A, McDonnell B, Draper E, Calzolari E, Beres J, Queisser-Luft A, Gatt M, Bakker M, Klungsoyr K, Garne E, Khoshnood B, Randrianaivo H, Matias Dias C, Rissman A, Mullaney C, Thompson R, Doray B, Hauesler M, Rounding C, Bianchi F, Wertelecki W, Zurriaga O, Addor M-C, Tucker D, Wellesley D, Materna-Kiryluk A, Barisic I, Curran RM and Rankin J (2014). Hirschsprung's disease prevalence in Europe: a register based study. Birth Defects Research, In press	Reports & deliverables + Other Information	OTH	IS	Internal
Deliverable 7 – Investigation Report 20102204 D07-11 OTH UK PS.PDF McGivern M, Best, K, Rankin J, Wellesley D, Greenlees, R, Addor M-C, Arriola L, de Walle H, Barisic I, Beres J, Bianchi F, Calzolari, E, Doray, B, Draper E, Garne E, Gatt M, Haeusler M, Khoshnood B, Klungsoyr K, Latos-Bielenska A, O'Mahony M, Mullaney C, Braz P, McDonnell B, Nelen V, Queißer-Luft A, Randrianaivo H, Rissmann A, Rounding C, Thompson R, Tucker D, Wertelecki W, Martos C (2014), Epidemiology of congenital diaphragmatic hernia in Europe: a register-based study. Submitted to Archives of Disease in Childhood	Reports & deliverables + Other Information	OTH	IS	Internal
Deliverable 7 – Investigation	Reports & deliverables	OTH	PS	Internal and External

Report 20102204 D07-12 OTH UK PS.PDF Khoshnood B, Loane M, Garne E, Addor M-C, Arriola L, Bakker M, Barisic I, Bianca S, Boyd P, Calzolari E, Doray B, Draper E, Gatt M, Haeusler M, Klungsoyr Melve K, Latos-Bielenska A, McDonnell R, Mullaney C, Nelen V, O'Mahony M, Pierini A, Queisser-Luft A, Randrianaivo-Ranjatoelina H, Rankin J, Rissmann A, Salvador J, Tucker D, Verellen-Dumoulin C, Wellesley D, Zymak-Zakutnya, N and Dolk H (2012), Recent decrease in the prevalence of congenital heart defects in Europe, Journal of Pediatrics, 162 (1) 108-113.	+ Other Information			
Deliverable 7 – Investigation Report 20102204 D07-13 OTH UK PS.PDF Christensen N, Andersen H, Garne E, Wellesley D, Addor M-C, Haeusler M, Khoshnood B, Mullaney C, Rankin J, Tucker D (2012), Atrioventricular septal defects among infants in Europe: A population based study of prevalence, associated anomalies and survival, Cardiology in the Young, 23, 560-567.	Reports & deliverables + Other Information	OTH	PS	Internal and External
Deliverable 7 – Investigation Report 20102204 D07-14 OTH UK PS.PDF Short EUROCAT Report: The Prevalence of Tetralogy of Fallot and Ebstein's anomaly in Europe http://www.eurocat-network.eu/content/Press-2014-TOP-and-EB-BB.pdf	Reports & deliverables + Other Information	OTH	PS	Internal and External
Deliverables	Reports & deliverables	OTH	PS	Internal and External

D08 20102204 D08-01 OTH UK PS.PDF Executive Report on Primary Prevention of Congenital Anomalies in European countries	+ Other Information			
Deliverables 20102204 D09-01 OTH UK PS.PDF Morris JK, Garne E, Wellesley D, Addor M-C, Arriola L, Barisic I, Beres J, Bianchi F, Budd J, Calzolari E, Matias Dias C, Doray B, Gatt M, Haeusler M, Klungsoyr K, Khoshnood B, Latos-Bielenska A, Mullaney C, Nelen V, O'Mahony M, Queisser-Luft A, Randrianaivo H, Rankin J, Rissman A, Rounding C, Sipek A, Stoianova S, Tucker D, Visser J, Yevtushok L, Loane M, Dolk H (2014). Major Congenital Anomalies in babies born with Down syndrome : a EUROCAT population-based registry study. CONFIDENTIAL VERSION to be submitted in April 2014.	Reports & deliverables + Other Information	OTH	IS	Internal
Deliverables 20102204 D09-02 OTH UK PS.PDF Loane M, Morris J, Addor M-C, Arriola L, Budd J, Doray B, Garne E, Gatt M, Haeusler M, Khoshnood B, Klungsoyr Melve K, Latos- Bielenska A, McDonnell R, Mullaney C, O'Mahony M, Queisser-Wahrendorf A, Rankin J, Rissmann A, Rounding C, Salvador J, Tucker D, Wellesley D, Yevtushok L and Dolk H (2013). Twenty-year trends in the prevalence of Down syndrome and other trisomies in Europe: impact of maternal age and prenatal screening. European Journal of Human Genetics. 21: 27-33.	Reports & deliverables + Other Information	OTH	PS	Internal and External

Deliverables 20102204 D09-03 OTH UK PS.PDF Barisic I, Odak L, Loane M, Garne E, Wellesley D, Calzolari E, Dolk H, Addor MC, Arriola L, Bergman J, Bianca S, Boyd PA, Draper ES, Gatt M, Haeusler M, Khoshnood B, Latos-Bielenska A, McDonnell B, Pierini A, Rankin J, Rissmann A, Queisser-Luft A, Verellun-Dumoulin C, Stone D, Tenconi R (2013), Fraser Syndrome: Epidemiological Study in a European Population, American Journal of Medical Genetics, 161A (5), 1012-1018.	Reports & deliverables + Other Information	OTH	PS	Internal and External
Deliverables 20102204 D09-04 OTH UK PS.PDF Barisic I, Odak L, Loane M, Garne E, Wellesley D, Calzolari E, Dolk H, Addor MC, Larriola L, Bergman J, Bianca S, Doray B, Khoshnood B, Klungsoyr K, McDonnell B, Pierini A, Rankin J, Rissmann A, Rounding C, Queisser-Luft A, Scarano G, Tucker D (2014), Prevalence, prenatal diagnosis and clinical features of oculo-auriculo-vertebral spectrum: a registry-based study in Europe, European Journal of Human Genetics, In press.	Reports & deliverables + Other Information	OTH	PS	Internal and External
Deliverables 20102204 D09-05 OTH UK PS.PDF Barisic I, Boban L, Loane M, Garne E, Wellesley D, Calzolari E, Dolk H, Addor M-C, Bergman JEH, Braz P, Draper ES, Haeusler M, Khoshnood B, Klungsoyr K, Pierini A, Queisser-Luft A, Rankin J, Rissmann A, Verellen-Dumoulin C (2014), Meckel-Gruber syndrome: a population-based study on prevalence, prenatal diagnosis, clinical features and survival in Europe, CONFIDENTIAL VERSION	Reports & deliverables + Other Information	OTH	IS	Internal

submitted to the European Journal of Human Genetics.				
Deliverables 20102204 D09-06 OTH UK PS.PDF Paper on Holt Oram syndrome to be submitted early 2014. Annexed are the CONFIDENTIAL DRAFT Tables to be included within this submission (combined into one pdf).	Reports & deliverables + Other Information	OTH	IS	Internal
Deliverables 20102204 D10-01 OTH UK PS.PDF Scientific Report : Sources of Information on Medication Use in Pregnancy http://www.eurocat-network.eu/content/Pubs-2014-WP9-Sources-Medication-MB.pdf	Reports & deliverables + Other Information	OTH	PS	Internal and External
Deliverables 20102204 D10-02 OTH UK PS.PDF de Jonge L, Zetstra-van der Woude PA, Jens Bos H, de Jong-van den Berg LTW, Bakker MK (2013), Identifying Associations between Maternal Medication Use and Birth Defects Using a Case-Population Approach: An Exploratory Study on Signal Detection, Drug Safety, 36(11), 1069-78.	Reports & deliverables + Other Information	OTH	PS	Internal and External
Deliverables 20102204 D10-03 OTH UK PS.PDF Wemakor A, Casson K, Garne E, Bakker M, Tucker D, Khoshnood B, Nelen V, O'Mahoney M, Pierini A, Klungsoyr K, Gatt M, Addor CM, Rissmann A, Arriola L, de Jong-van den Berg L, Dolk H (2014), Selective Serotonin	Reports & deliverables + Other Information	OTH	IS	Internal

Reuptake Inhibitor Antidepressant Use in First Trimester Pregnancy and Risk of Congenital Anomalies: A European Register-based Study in 12 European Countries. Draft in preparation for submission in 2014 (CONFIDENTIAL Draft of Abstract and Tables Annexed).				
Communication documents **NOT linked** to a deliverable EUROCAT PMC minutes (January, June, November 2011; March, December 2012; April, June 2013)	Other Information	OTH-01 to 07	IS	Internal
Communication documents **NOT linked** to a deliverable EUROCAT SC minutes (January 2011; March, June 2012; June, November 2013)	Other Information	OTH-08 to 12	IS	Internal
Communication documents **NOT linked** to a deliverable EUROCAT Dissemination Plan	Other Information	OTH-13	PS	Internal and External
Communication documents **NOT linked** to a deliverable EUROCAT's JA Promotional Leaflet	Other Information	LFT-01	PS	Internal and External
Communication documents **NOT linked** to a deliverable EUROCAT JA Newsletters	Other Information	NWL-01 to 03	PS	Internal and External
Communication documents **NOT linked** to a deliverable An Overview of EUROCAT's Liaison with other Networks, Organisations and Committees	Other Information	OTH-14	PS	Internal and External
Communication documents **NOT linked** to a deliverable EUROCAT's presentations at scientific meetings/conferences	Other Information	OTH-15	IS	Internal
Communication documents **NOT linked** to a deliverable	Other Information	OTH-16	PS	Internal and External

EUROCAT's publications list				
Communication documents **NOT linked** to a deliverable EUROCAT's Press Releases combined	Other Information	PRR-01	PS	Internal and External
Communication documents **NOT linked** to a deliverable EUROCAT's Joint Action Poster for DG Sanco	Other Information	POS-01	PS	Internal and External
Communication documents **NOT linked** to a deliverable Methodological Issues in Estimating Mortality due to Congenital Anomaly (CONFIDENTIAL draft paper to be submitted)	Other Information	OTH-17	IS	Internal
Communication documents **NOT linked** to a deliverable Coverage of the European Population, Birth Year 2011, by EUROCAT Full or Associate Member Registries (August 2013)	Other Information	OTH-18	PS	Internal and External
Communication documents **NOT linked** to a deliverable EUROCAT Coding and Classification Committee Minutes (June 2011; June 2012; February, June, November 2013)	Other Information	OTH-19 to 23	IS	Internal
Communication documents **NOT linked** to a deliverable EUROCAT Special Report: Coding of Congenital Heart Defects in the EUROCAT Database	Other Information	OTH-24	PS	Internal and External
Communication documents **NOT linked** to a deliverable European Prevalence of Monogenic Syndromes – Website Table	Other Information	OTH-25	PS	Internal and External

Communication documents **NOT linked** to a deliverable E Calzolari, I Barisic, M Loane, J Morris, D Wellesley, H Dolk, M-C Addor, L Arriola, F Bianchi, A Neville, JLS Budd, K Klungsoyr, B Khoshnood, B McDonnell, V Nelen, A Queisser-Luft, J Rankin, A Rissmann, C Rounding, D Tucker, C Verellen-Dumoulin, H de Walle, E Garne (2014). Epidemiology of multiple congenital anomalies in Europe: A EUROCAT population-based registry study. Birth Defects Research Part A: Clinical and Molecular Teratology, 100, 270-6	Other Information	OTH-26	PS	Internal and External
Communication documents **NOT linked** to a deliverable Data Quality Indicators (Birth years 2005-2009)	Other Information	OTH-27	PS	Internal and External
Communication documents **NOT linked** to a deliverable Data Quality Indicators (Birth years 2006-2010)	Other Information	OTH-28	PS	Internal and External
Communication documents **NOT linked** to a deliverable EUROCAT Special Report: Developing the surveillance of multiple congenital anomalies http://www.eurocat-network.eu/content/Pubs-2014-WP5-Surveillance-Multiple-CA-EG.pdf	Other Information	OTH-29	PS	Internal and External
Communication documents **NOT linked** to a deliverable 1st Questionnaire – Policies for Primary Prevention of Neural Tube Defects with Folic Acid and Folate	Other Information	OTH-30	IS	Internal
Communication documents **NOT linked** to a deliverable 2nd Questionnaire – Public Health Actions on Primary Prevention of Congenital	Other Information	OTH-31	IS	Internal

Anomalies				
Communication documents **NOT linked** to a deliverable Field Work/Data Collection Summary for Questionnaire 1	Other Information	OTH-32	IS	Internal
Communication documents **NOT linked** to a deliverable Field Work/Data Collection Summary for Questionnaire 2	Other Information	OTH-33	IS	Internal
Communication documents **NOT linked** to a deliverable PRIMARY PREVENTION OF CONGENITAL ANOMALIES: EUROCAT (European Surveillance of Congenital Anomalies) and EUROPLAN (European Project for Rare Diseases National Plans Development) Recommendations on policies to be considered for the primary prevention of congenital anomalies in National Plans and Strategies on Rare Diseases http://www.eurocat-network.eu/content/EUROCAT-EUROPLAN-Primary-Preventions-Reccomendations.pdf	Other Information	OTH-34	PS	Internal and External
Communication documents **NOT linked** to a deliverable Questionnaire on the attitude, knowledge and behaviour of women who have recently given birth towards folic acid and folate consumption	Other Information	OTH-35	IS	Internal
Communication documents **NOT linked** to a deliverable MediClara Report: Appraisal of strategies to monitor (population) folate status with respect to the prevention and scientific study of congenital anomalies http://www.eurocat-network.eu/content/de-Smit-2013-Folate-Status.pdf	Other Information	OTH-36	PS	Internal and External

Communication documents **NOT linked** to a deliverable Report on the First International Conference on the Prevention of Fetal Alcohol Spectrum Disorder (FASD)	Other Information	OTH-37	PS	Internal and External
Communication documents **NOT linked** to a deliverable EUROCAT Special Report (2013): EUROCAT, A potential source of prevalence data for Orphanet	Other Information	OTH-38	PS	Internal and External
Communication documents **NOT linked** to a deliverable EUROCAT Special Report (2012): Congenital Anomalies are a Major Group of Mainly Rare Diseases.	Other Information	OTH-39	PS	Internal and External
Communication documents **NOT linked** to a deliverable Dolk H and Wellesley D (2014). Antenatal screening for Down Syndrome and other chromosomal abnormalities: increasingly complex issues. Arch Dis Child Fetal Neonatal Ed, 99, F2-F3.	Other Information	OTH-40	PS	Internal and External
Communication documents **NOT linked** to a deliverable GSK report 4th update (CONFIDENTIAL)	Other Information	OTH-41	IS	Internal
Communication documents **NOT linked** to a deliverable Log of Medication Queries (26th Nov 2013)	Other Information	OTH-42	IS	Internal
Communication documents **NOT linked** to a deliverable EUROCAT Medication Enquiry Form	Other Information	OTH-43	PS	Internal and External
Communication documents **NOT linked** to a deliverable EUROCAT Response to Medication Enquiry	Other Information	OTH-44	IS	Internal

Communication documents **NOT linked** to a deliverable Letter of Agreement with Independent Evaluator (subcontracted in WP3)	Other Information	OTH-45	IS	Internal