Final Report

CHAFEA Operating Grant Nr:
2013 3307

Acronym:
UU_FY2014

Title:
EUROCAT: European Surveillance of Congenital Anomalies

Authors:
Dr Rhonda Curran (EUROCAT Project Manager),
Prof Helen Dolk (EUROCAT Project Leader),
Dr Maria Loane (Research Fellow)
Ms Ruth Greenlees (Research Assistant)

Date:
14 April 2015
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Declaration by the operating grant coordinator

I, as coordinator of this operating grant and in line with the obligations stated in the Grant Agreement, declare that:

- The report represents an accurate description of the work carried out under this operating grant for this reporting period;

- 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.

Name of the coordinator:

Prof Helen Dolk

Signature:


Date:

24 April 2015
## Specification of the action

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<td>Duration of the grant agreement (in months):</td>
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<td>EC co-funding:</td>
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<td>Priority area:</td>
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<td>WP2013 4.2.4.2 WP2013 4.3.1.1 WP2013 4.2.4.4 WP2103 4.1.2 WP2013 4.2.1.1 WP2013 4.2.3 WP2013 4.2.2.5 WP2013 4.1.5.2</td>
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<td>Action:</td>
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<td>Main partner information and contact person:</td>
<td>Prof Helen Dolk Professor of Epidemiology and Health Services Research Room 12L09, EUROCAT Central Registry University of Ulster Shore Road, Newtownabbey Co Antrim, Northern Ireland UK, BT37 0QB Telephone: +44(0)2890366639 Fax: +44(0)2890368341 Email: <a href="mailto:h.dolk@ulster.ac.uk">h.dolk@ulster.ac.uk</a></td>
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Keywords (using MESH terms):
1. Congenital Abnormalities
2. Rare Diseases
3. Population Surveillance
4. Primary Prevention
5. Registries
Acknowledgements

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The content of this final report represents the views of the authors and it is their sole responsibility; it can in no way be taken to reflect the views of the European Commission and/or the Executive Agency for Health and Consumers or any other body of the European Union. The European Commission and/or the Executive Agency do(es) not accept responsibility for any use that may be made of the information it contains.
Executive Summary

PROJECT SCOPE AND OBJECTIVES

EUROCAT is a European network of population-based registries for epidemiologic surveillance of congenital anomalies (CA). Established in 1979, EUROCAT currently surveys over 1.7 million births per year in Europe (30% of the EU birth population), via 37 registries in 21 countries.

Approximately 130,000 babies in the EU each year are affected by major CA, which are a major cause of perinatal mortality, childhood morbidity and disability. Most individual types of CA are Rare Diseases (RD) and persons with any CA form a large proportion of total persons with RD. EUROCAT’s mission is to support the primary prevention of CA (since it is possible to reduce the risk by modification of environmental factors) and the provision of appropriate services to pregnant and pre-pregnant women, affected children and their families by the collection, analysis, interpretation and dissemination of population-based epidemiologic data. Epidemiological surveillance informs policies and interventions to reduce the size of, and inequalities in, the public health burden of CA.

A DESCRIPTION OF THE COMPLETED WORK-PROGRAMME 2014

Co-ordination of EUROCAT Network by EUROCAT Central Registry, including financial management, organisation of Steering Committee meetings, internal communications and scientific co-ordination.

Assure Sustainability of EUROCAT Surveillance. EUROCAT Central Registry has been at Ulster University for 15 years, but will move to Joint Research Centre (JRC) Ispra in January 2015 under new EU funding arrangements for RD activities. The EUROCAT Steering Committee produced a document outlining “Future Strategy for EUROCAT”. EUROCAT Central Registry provided training and documentation to JRC, and transferred data for 25 of 38 current member registries to JRC on behalf of those registries. Negotiation for Software transfer took place. Future funding gaps for the continuation of current activities were identified which still need resolution. EUROCAT participated in the preparation of two Horizon2020 applications.

Update and management of EUROCAT Central Database (ECD). Birth year 2012 data and updated data from previous years were added to the Central Database and validated. Data Quality Indicators were produced and monitored. Data was transmitted to the British and French networks, and supplied for research.

Dissemination of EUROCAT Surveillance results. Two EUROCAT newsletters were mailed to 2,575 recipients worldwide. The EUROCAT website (www.eurocat-network.eu), including interactive prevalence data tables, was regularly updated. Four reports and 18 peer-reviewed journal papers were published. External liaison with WHO, EUROPLAN, EUROmedICAT, SCPE. EUROCAT joined a consortium of 10 organisations planning the first ever World Birth Defects Day to be held 3 March 2015.

Improvement of the Coding and Classification of congenital anomalies. Coding & Classification Committee activities included revision of EUROCAT Guide 1.4 in relation to definition of standard CA subgroups and minor anomalies for exclusion, and feedback to new and old registries to improved quality of CA coding.
Provision of accessible documentation of EUROCAT Procedures. An extensive EUROCAT Network Procedural Manual Part I and II was made available on the website and, with associated training, to JRC Ispra.

Provision of Essential Epidemiologic Information on congenital anomalies in Europe; assessment of the impact of changes in prenatal screening. Website interactive tables showing prevalence for 89 CA subgroups, as well as prenatal diagnosis and perinatal mortality tables, were updated to 2012. A set of Public Health Indicators was produced for 2008-2012, by registry and by country, covering perinatal mortality, prenatal diagnosis rates, rates of termination of pregnancy for fetal anomaly, Down Syndrome prevalence, NTD prevalence and paediatric surgery rates;

Facilitation of early warning of new teratogenic exposures; Evaluate Effectiveness of Primary Prevention; Act as an information and resource centre for the population, health professionals and policy makers. Statistical monitoring of pan-European trends covering 6 million births in 25 registries, 2003-2012, was carried out as well as cluster detection at registry and country level. Registries undertook investigations as appropriate. An analysis of trends since 1980 was conducted. EUROCAT collaborated with European Centre for Disease Prevention and Control (ECDC) by validating and supplying data on congenital rubella syndrome for 2000-2012 and circulating a survey to registries.

To conduct pharmacovigilance based on EUROCAT database. Three pharmacovigilance studies were carried out. A review of sources of medication data available on the website was updated to include Ukraine. Joint working with FP7 funded EURomediCAT: Safety of Medication Use in Pregnancy in relation to risk of CA.

Annual EUROCAT Registry Leaders’ Meeting
The 29th EUROCAT Registry Leaders’ Meeting (RLM) was hosted in Belfast, Northern Ireland (UK) on the 26th-27th June 2014 with 62 attendees.

Expansion of EUROCAT network and operation of Registry Advisory Service
At the RLM in June 2014, Registry Advisory Service (RAS) organised a workshop on coding and a roundtable for new applicant and affiliate registries. The registries of Auvergne, Brittany (France) and Pleven (Bulgaria) were granted affiliate membership and one-year follow-up and feedback on their data. A 2-day training course was held in Zagreb for the Pleven registry staff. Contacts with European and non-European registries interested in collaborating or joining EUROCAT network continued.

EVALUATION
• The EUROCAT website had 1,200+ visitors per month, from 152 countries, mainly professionals.
• EUROCAT guidelines and prevalence data continue to be highly valued and cited.
• External guidance was given on creating a public-facing website for the future
• A web-based Evaluation Survey was completed by members of the EC Expert Group on Rare Diseases. A need to increase communication between the Expert Group and EUROCAT at European and MS level was identified.

OUTPUTS AND OUTCOMES, AND THEIR POTENTIAL IMPACT AND USE
• Updated, accessible epidemiological information on CA in Europe on EUROCAT website for 1980-2012 births, for policymakers, health professionals, public.
• Central database of 420,000 individual anonymised CA records from full member registries 1980-2012, and 230,000 cases from associate member registries, for use in further research and surveillance.
• Revised EUROCAT Guide 1.4: Instructions for the registration of congenital anomalies, used worldwide as a resource for standardisation of CA recording.
• EUROCAT Special Report on Geographic Inequalities in Public Health Indicators related to Congenital Anomalies, based on the 2008-2012 data on prevalence of key CA, perinatal mortality, prenatal diagnosis, termination of pregnancy and paediatric surgery, showing large geographic differences which need attention by MS.
• Statistical Monitoring Report to inform action by Member State public health authorities, detailing increasing trends (2003-2012) in some CA including severe congenital heart defects, and lack of decreasing trend in neural tube defects due to failure of policies to promote periconceptional folic acid supplementation. Three scientific papers prepared detailing prevalence trends and cluster detection and investigation methodology and results.
• Report by ECDC in relation to the target for elimination of congenital rubella from the European Region by 2015, documenting 19 cases in 34 EUROCAT registries since 2000 and their implications and recommending links between EUROCAT registries and national authorities responsible for CRS surveillance.
• Further publications of the EUROCAT/EUROPLAN Recommendations for the Primary Prevention of Congenital Anomalies
• Pharmacovigilance results relating to lamotrigine, methadone and mental health-related medication to inform clinicians and regulators
• Population-based data on selected monogenic syndromes published on website and in scientific journals, for clinicians and patient organisations.
• Transfer of EUROCAT data, procedures and vision to JRC Ispra

STRATEGIC RELEVANCE & CONTRIBUTION TO THE EU HEALTH PROGRAMME
EU Public Health priorities to which EUROCAT activities are relevant:
• Generating and Disseminating Health Information
• Surveillance of non-communicable diseases (NCD) by improving timeliness, comparability, analysis and reporting of health data by efficient, well-established mechanisms, to produce scientific evidence and provide stakeholders with information to take decisions on issues affecting individual and collective health and planning to respond to potential risks.
• Effective prevention of NCD by taking action on common risk factors.
• Highlighting geographical inequalities in Europe
• EU added value where national action is not feasible or effective, specifically for RD including registries and databases co-ordinated at European level.
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.
• Public health emergency preparedness in case of emerging health threats – infections, environmental accidents, and biological threats.

CONCLUSIONS AND RECOMMENDATIONS
EUROCAT provides a well-established collaborative network and infrastructure for surveillance and research related to causes and prevention of CA and treatment and care of affected children, with a highly valued system of standardised data collection, analysis and dissemination. At a cost of 300,000 euros in 2014, the collaborative activity of EUROCAT cost and average 10,000 euros per MS, or 6 euros per birth. Post 2014, EUROCAT Central Registry will move to the EU Joint Research Centre at Ispra, thus achieving a long term sustainable future. Some EU Member States are under-represented in EUROCAT which needs attention. An intensification of response by public health authorities to EUROCAT results is needed.
Initial scope of the operating grant

Mission and vision of the operating grant

EUROCAT’s mission is to support the primary prevention of congenital anomalies (CA) 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 CA.

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 objectives of the organisation and its main activities

The aim of EUROCAT is the epidemiologic surveillance of CA. 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

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 livebirths, stillbirths, terminations of pregnancy), prenatal diagnosis and perinatal mortality; including geographic inequalities and trends.
- Detection, investigation and reporting of clusters/trends in CA 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 e.g. 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 e.g. 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 livebirth 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 EUROMEDI CAT (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 ICD10 to ICD11.
- Expansion of 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.
Summary of the organisation's work programme for 2014

The OBJECTIVES (see General Objectives above) of EUROCAT are met in the annual workplan by the following activities:

Activities
1. Coordination (financial and scientific)
2. Future sustainability of EUROCAT (in consultation with EC Expert Group on Rare Diseases)
3. Dissemination (see Dissemination section)
4. Evaluation
5. EUROCAT Central Database (transmission of data from network of registries to Central Registry, updating of central database to include birth year 2012, provision of data extracts for analysis to network members and external researchers, creation of documented archive, provide training for members on EUROCAT Data Management Programme)
6. Coding & Classification (Committee review coding and classification issues and classify cases for surveillance, contribute to ICD11 revision)
7. EUROCAT Network Procedures (compile EUROCAT Network Procedures Manual)
9. Surveillance – Detection and investigation of clusters and trends and investigation of new exposures of concern; analyse data in relation to issues arising e.g. congenital rubella with ECDC.
10. New Registries/Network Expansion/Registry Advisory Service (advice and training to new members)
11. Pharmacovigilance – expanding database, signal evaluation, coordination with EUROmediCAT, liaison with EncePP and other bodies.
12. Annual Registry Leaders Meeting (June)

Methods
Data collection by member registries according to standard variable and coding scheme. Registered cases of Congenital Anomaly include livebirths, stillbirths and terminations of pregnancy following prenatal diagnosis. Transmission to Central Database of anonymised individual data using common software (EUROCAT Data Management Program) in February and October. Classification of cases to 89 standard EUROCAT subgroups on the basis of ICD10 codes. Generation (in April) of standard epidemiological tables in website in interactive format (user chooses registries/countries, years, congenital anomaly subgroups of interest) - prevalence per 10,000 births by pregnancy outcome, perinatal mortality, proportion of cases prenatally diagnosed. Additional fixed tables for prevalence of monogenic syndromes. Statistical Monitoring Program (in April) detects trends and recent clusters for 89 CA subgroups, sent to registries for investigation with additional central registry investigation of trends and exposures - results compiled in Annual Surveillance Report. Pharmacovigilance database involves 19 of the EUROCAT registries which record medication exposure in the first trimester, now covering over 6 million births since 1995. Signal evaluation by case-malformed control methodology. Committees include Coding and Classification Committee, Registry Advisory Service (working with new registries, providing guidelines, software, and meetings), Dissemination Committee, Statistical Monitoring Committee and TEC (Task force for the evaluation of clusters).

Expected Outcomes
• Updated epidemiologic information on CA, including geographical inequalities, easily accessible on EUROCAT website.
- Detection, investigation and reporting of clusters and trends in CA prevalence and response to newly arising exposures.
- Facilitation of new CA registries.
- Expansion of pharmacovigilance activity.
- Increased awareness of EUROCAT - purpose, organisation, content - by stakeholders.

**Target Groups**
See Dissemination section.

**Ethical Aspects**
EUROCAT Central Registry has approval from the applicant institution’s (University of Ulster’s) Research Ethics Committee for holding and analysing the anonymised ECD. Data are held on behalf of the individual member registries, and continue to be owned by the member registries, subject to their own ethics approval requirements.

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<th>Months</th>
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<td>1. coordination</td>
<td>Prof. Helen Dolk (University of Ulster)</td>
<td>M 1</td>
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<tr>
<td>2. Future sustainability of EUROCAT</td>
<td>Prof. Ingeborg Saricic (Croatia)</td>
<td>M 2</td>
</tr>
<tr>
<td>3. Dissemination</td>
<td>Prof. Ingeborg Saricic (Croatia)</td>
<td>M 3</td>
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<tr>
<td>4. Evaluation</td>
<td>Dr. Rhonda Curran (University of Ulster)</td>
<td>M 4</td>
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<td>5. EUROCAT Central Database</td>
<td>Ms Maria Loane (University of Ulster)</td>
<td>M 5</td>
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<tr>
<td>6. Coding &amp; Classification</td>
<td>Dr. Peter Garne (Denmark)</td>
<td>M 6</td>
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<td>7. EUROCAT Network Procedures</td>
<td>Dr. Rhonda Curran (University of Ulster)</td>
<td>M 7</td>
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<tr>
<td>8. Surveillance - publication of epidemiological tables on EUROCAT website</td>
<td>Ms Maria Loane (University of Ulster)</td>
<td>M 8</td>
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<tr>
<td>9. Surveillance - detection and investigation of cluster and trends and exposure</td>
<td>Ms Maria Loane (University of Ulster)</td>
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<tr>
<td>10. New Registries/Network Expansion/Registry Advisory Service</td>
<td>Prof. Ingeborg Saricic (Croatia)</td>
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<td>11. Pharmacovigilance</td>
<td>Prof. Helen Dolk (University of Ulster)</td>
<td>M 11</td>
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<td>12. Annual Registry Leaders Meeting</td>
<td>Dr. Rhonda Curran (University of Ulster)</td>
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January - December 2014
Synergies of the organisation's activities with the priorities of the WP 2014

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 three priority objectives of the health programme’s WP2013: Improve Citizens Health Security; Promote Health and Generate and Disseminate Health Information. EUROCAT’s WP for 2014 will contribute 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) (e.g. improving coding and classification and 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, recognises the need for registries and databases to be 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 non-communicable diseases (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 will build on the EUROCAT Joint Action 2011-2013 and EUROCAT’s daughter project, FP7 funded EUROMedicAT (2011-15), 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.

**Dissemination strategy (external dissemination)**

EUROCAT has a well-established external dissemination strategy and Dissemination Committee.

**Purpose**

1. To disseminate the results of EUROCAT surveillance and its relevance to policy and service planning.
2. To raise awareness on the importance and use of congenital anomaly (CA) registries and the added value of their coordination at European level.
3. To raise awareness of the potential for primary prevention of CA and the importance of the periconceptional period.
4. To raise awareness of the need for pharmacovigilance in relation to pregnancy and EUROCAT's role.
5. To share methodological expertise on coding and classification of rare diseases, registries and databases, epidemiological analysis of CA-related data and perinatal mortality definitions.
6. To inform public and policy debates with the evidence base, as the need arises.

**External Stakeholders Include**

- Health professionals e.g. paediatricians, obstetricians, paediatric pathologists, medical geneticists and genetic counsellors and midwives actively involved in the care of children with CA and/or pregnant women. Public health professionals and those involved in health service planning at regional, national, EU and WHO level.
- 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 etc. and international research networks including Global Burden of Disease study which makes extensive use of EUROCAT data and International Clearinghouse).
- Politicians/policy makers.

**Dissemination Methods Include**

- EUROCAT website (www.eurocat-network.eu) - comprehensive access to information, publications, interactive epidemiological tables - over 2,000 visits per month.
- Promotional leaflet, biannual newsletters (sent to an extensive email database), press releases, contribution to Orphanews.
- Conference and meeting presentation/participation.
- Peer-reviewed publications.
- Biennial European Symposia (for the scientific/clinical community) - not 2014.
- Reports and contributions to Reports of other networks (e.g. EUROPERISTAT).

EUROCAT Dissemination Committee promotes setting up National Committees, with representatives of Registries, Ministries of Health, Patient Groups and Professional Associations to strengthen connections with local stakeholders, present EUROCAT outputs and encourage contact with media and wider audiences addressing issues of common interest. These committees will embed registries of CA in the local
community, connecting them with patients, government institutions and professional clinical/scientific communities with a view to securing future sustainability. This has been established so far in a minority of countries.

**Evaluation strategy**

**Approach**
The evaluation will be a systematic appraisal of project success and quality using formative and summative evaluation mechanisms. Internal and external evaluation will be integral to the project and will assess the ‘success’ of stated project and work package objectives against actual deliverables; validating the value of the project to the EUROCAT community. ‘Success’ will be measured in terms of delivering to the project plan and achieving quality, i.e. meeting stakeholder/end-user requirements.

**Process**
Evaluation will be given equality with overall project planning and implementation. Evaluation scheduling will be aligned with the overall project plan. Evaluation will be scoped, designed, modelled and mapped during the project planning stage and an Evaluation Plan will be developed. Recommendations made in previous EUROCAT projects will be incorporated where appropriate. Project targets and performance indicators will be identified to measure success and be combined with more qualitative methods. Evaluation will assess the success of delivery and quality in 3 key areas:

1. process (governance, project processes, planning, risk management, communication);
2. performance (milestones and deliverables, timeliness, cost/benefit) and
3. effects (impacts anticipated and not, value/added-value, stakeholder satisfaction and engagement).

**Data**
The main mechanisms for data collection will be: project management processes; online surveys; desk-review and stakeholder engagement. All data received will be handled sensitively. Data will be checked, prepared for analysis, analysed and reviewed, synthesised and interpreted to generate robust reports.

**Formative Evaluation**
Formative evaluation will be incorporated, for the main, into project management progress. Monitoring and responding to overall performance indicators aligned to project success will be ongoing. In addition to this quantitative approach, more qualitative methods will allow the Steering Committee and stakeholders to give their opinions on current project success, influence project direction and offer suggestions for improvement.

**Final Report**
An independent, summative evaluation of the EUROCAT project will be performed by an external company with experience of pan-European projects and extensive project management expertise. It will appraise whole-project success based on verifying deliverables and quality in the three key areas outlined in ‘Process’ above. The EUROCAT project team will liaise with the independent evaluators and provide information/assistance in a supporting role; having no influence over, or input into, evaluation findings. No findings will be shared with the project board/team until the report or presentation deadline to ensure integrity of the process. The independent evaluation will comprise a written report that will meet project/funding requirements, to be included in the EUROCAT end-project report.
Coordination with other organisations in the field

EUROCAT was formerly represented on EUCERD by the Chair of the EUROCAT Coding and Classification Committee (Dr Ester Garne) and a member of the EUROCAT Steering Committee (Dr Vera Nelen) as well as the EUROCAT President who represents Croatia (Dr Ingeborg Barisic). The new EU Expert Group on Rare Diseases has no EUROCAT representative, but Dr Barisic continues to represent Croatia.

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 CA 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 is involved (in collaboration with Orphanet) in the development of the malformation chapter for ICD11.
- As a WHO Collaborating Centre for the Surveillance of CA - EUROCAT Central Registry re-designated May 2011 for 4 years. In this capacity EUROCAT will assist 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 will also assist the WHO in implementing its strategy for the prevention and 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.
## Deliverables of the operating grant

### Deliverable 01:

<table>
<thead>
<tr>
<th>Title of deliverable</th>
<th>Website Tables</th>
</tr>
</thead>
<tbody>
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<td>1</td>
</tr>
<tr>
<td>Nature (eg. report, book, website etc.)</td>
<td>Website tables</td>
</tr>
<tr>
<td>Delivery date to CHAFEA</td>
<td>New 2012 data and updates to all years 24/03/2014. Updates to all years 20/11/2014. Data for six new anomaly subgroups 23/12/2014</td>
</tr>
<tr>
<td>Specific remarks on this deliverable</td>
<td>Epidemiological information on prevalence, prenatal diagnosis and perinatal mortality is routinely produced after data transmission and updated twice a year on the website. In 2014 there were six new congenital anomaly subgroups added at the end of the year. A selection of tables can be found within section 4 of the Annual Surveillance Report (Annex 10)</td>
</tr>
<tr>
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<td>The EUROCAT website tables could be accessed from CHAFEA’s project database by publishing the following link <a href="http://www.eurocat-network.eu/accessprevalencedata/prevalencetables">http://www.eurocat-network.eu/accessprevalencedata/prevalencetables</a> <a href="http://www.eurocat-network.eu/PrenatalScreeningAndDiagnosis/PrenatalDetectionRates">http://www.eurocat-network.eu/PrenatalScreeningAndDiagnosis/PrenatalDetectionRates</a> <a href="http://www.eurocat-network.eu/accessprevalencedata/keypublichealthindicators">http://www.eurocat-network.eu/accessprevalencedata/keypublichealthindicators</a></td>
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<td>Delivery date to CHAFEA</td>
<td>Posted September 2014, emailed October 2014</td>
</tr>
<tr>
<td>Specific remarks on this deliverable</td>
<td></td>
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<td>Can the deliverable be published at CHAFEA’s project database?</td>
<td>The EUROCAT promotional leaflet has been annexed to this report (Annex 4). It can also be accessed from the following link <a href="http://www.eurocat-network.eu/content/EUROCAT-Operating-Grant-Promotional-Leaflet.pdf">http://www.eurocat-network.eu/content/EUROCAT-Operating-Grant-Promotional-Leaflet.pdf</a></td>
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<tr>
<td>Nature (eg. report, book, website etc.)</td>
<td>E Newsletter</td>
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</table>
| Delivery date to CHAFEA | Newsletter 1 – issued September 2014  
Newsletter 2 – issued December 2014 |
| Specific remarks on this deliverable |  |
| Can the deliverable be published at CHAFEA's project database? | Pdfs of the newsletter have been annexed to the report (Annex 5). They can also be accessed from the following links [http://www.eurocat-network.eu/content/EUROCAT-Newsletter-September-2014.pdf](http://www.eurocat-network.eu/content/EUROCAT-Newsletter-September-2014.pdf) and [http://www.eurocat-network.eu/content/EUROCAT-Newsletter-December-2014.pdf](http://www.eurocat-network.eu/content/EUROCAT-Newsletter-December-2014.pdf) |

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<td>Took place on 26-27 June 2014 in Belfast.</td>
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<td>Specific remarks on this deliverable</td>
<td>Pdfs of the Agenda and Minutes have been annexed to the report (Annex 12). Available to EUROCAT members only <a href="http://www.eurocat-network.eu/aboutus/administrativeissues/rlmminutes">http://www.eurocat-network.eu/aboutus/administrativeissues/rlmminutes</a></td>
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<td>Delivery date to CHAFEA</td>
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<tr>
<td>Specific remarks on this deliverable</td>
<td>This report can be found in section 7 of the Annual Surveillance Report (Annex 10)</td>
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</tr>
<tr>
<td>Can the deliverable be published at CHAFEA's project database?</td>
<td>Yes. Pdfs of the Annual Surveillance Report have been annexed to the report (Annex 10). The report can also be found under the publications section of the website: <a href="http://www.eurocat-network.eu/content/EUROCAT-Annual-Surveillance-Report.pdf">http://www.eurocat-network.eu/content/EUROCAT-Annual-Surveillance-Report.pdf</a></td>
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</tr>
<tr>
<td>Delivery date to CHAFEA</td>
<td>Part I delivered to JRC in October 2014. Part II delivered by way of training week to JRC staff in October 2014 and final paper copy January 2015</td>
</tr>
<tr>
<td>Specific remarks on this deliverable</td>
<td>Pdfs of the Network Procedural Manual have been annexed to the report (Annex 9). Available to EUROCAT members only <a href="http://www.eurocat-network.eu/aboutus/administrativeissues/networkproceduralmanual">http://www.eurocat-network.eu/aboutus/administrativeissues/networkproceduralmanual</a></td>
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Can the deliverable be published at CHAFEA’s project database? No

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<td>Nature (eg. report, book, website etc.)</td>
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<tr>
<td>Delivery date to CHAFEA</td>
<td>Metadata manual uploaded to the website January 2014. Updated January 2015 Data Quality Indicators report uploaded to website June 2014 Update to Guide 1.4 anomaly subgroups November 2014 Registry Descriptions added and amended throughout the year</td>
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<td>The Metadata manual is available to members only on the website <a href="http://www.eurocat-network.eu/aboutus/datacollection/datamanagement/eurocatdatamanual">http://www.eurocat-network.eu/aboutus/datacollection/datamanagement/eurocatdatamanual</a></td>
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Can the deliverable be published at CHAFEA’s project database? Yes

The DQI report could be accessed from CHAFEA’s project database by publishing the following link [http://www.eurocat-network.eu/aboutus/datacollection/dataquality/dataqualityindicators](http://www.eurocat-network.eu/aboutus/datacollection/dataquality/dataqualityindicators) Guide 1.4 could be accessed from CHAFEA’s project database by publishing the following link [http://www.eurocat-](http://www.eurocat-)


network.eu/aboutus/datacollection/guidelinesforregistration/guide1_4
Member registry descriptions could be accessed from CHAFEA’s project database by publishing the following link http://www.eurocat-network.eu/aboutus/memberregistries

### Deliverable 09:

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<td>Delivery date to CHAFEA</td>
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<td>Specific remarks on this deliverable</td>
<td>Pdfs of the Network Procedural Manual have been annexed to the report (Annex 2). It can also be accessed from the following link <a href="http://www.eurocat-network.eu/content/EUROCAT-Future-Plan-for-EUROCAT.pdf">http://www.eurocat-network.eu/content/EUROCAT-Future-Plan-for-EUROCAT.pdf</a></td>
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Operating Grant implementation

Organisation and planning

1. Co-ordination of EUROCAT Surveillance Network

This included management of Central Registry, financial management, organisation of Steering Committee meetings, project management, administrative support, internal communications, maintaining mailing database for newsletter, archiving and compiling of the Final Report (deliverable 10).

The EUROCAT website (www.eurocat-network.eu) is open to public view but also has sections visible only to those who log in as members, for internal communications and management purposes. This was extensively used.

14 email Communications to all Registry Leaders were sent out and also made available on the internal website.

Barbara Norton, EUROCAT Administrator, was nominated for and received the Distinguished Employee Award for Ulster University 2014, on the basis of her outstanding work for EUROCAT.

April 2014 EUROCAT Steering Committee Meeting
This meeting took place in London (hosted by Professor Joan Morris (named subcontractor on Operating Grant) at Queen Mary University of London) on the 28 and 29 April. The event was organised jointly between Professor Morris at QMUL and EUROCAT Central Registry staff (University of Ulster: Operating Grant holder). Minutes of the meeting have been made available to EUROCAT members on the EUROCAT website (agenda and minutes have been provided in Annex 1).

June 2014 EUROCAT Steering Committee Meeting
This meeting took place during the Annual EUROCAT Registry Leaders’ Meeting in Belfast on 26 June. Minutes of the meeting have been made available to EUROCAT members on the EUROCAT website (agenda and minutes have been provided in Annex 1).

October 2014 EUROCAT Steering Committee Meeting
This meeting took place in London (hosted by Professor Joan Morris (named subcontractor on Operating Grant) at Queen Mary University of London) on the 1 October. The event was organised jointly between Professor Morris at QMUL and EUROCAT Central Registry staff (University of Ulster: Operating Grant holder). Minutes of the meeting have been made available to EUROCAT members on the EUROCAT website (agenda and minutes have been provided in Annex 1).

December 2014 EUROCAT Steering Committee Meeting
This meeting took place in Milan (hosted by JRC, Ispra) on 4 December. The event was organised jointly between Simona Martin at JRC and EUROCAT Central Registry staff (University of Ulster: Operating Grant holder). Minutes of the meeting have been made available to EUROCAT members on the EUROCAT website (agenda and minutes have been provided in Annex 1).
2. Assure Sustainability of EUROCAT Surveillance

In 2013, DGSanco signed a contract with the EU Joint Research Centre in Ispra to provide the Rare Diseases Platform, including co-ordinating both EUROCAT and SCPE (cerebral palsy). The main tasks completed were for:

- The Steering Committee to envisage a future plan for EUROCAT (Deliverable 9 – Annex 2). JRC were invited to all Steering Committee meetings to discuss the plan, which was first presented in draft form at the meeting of the SC in April 2014 and in its final form at the meeting of EUROCAT Association in Belfast in June 2014. The document defines main objectives of EUROCAT network, describes types of membership, the present role of the Central registry, Steering Committee (SC), and EUROCAT Programme Management Committee (EPMC). In addition, the document proposes a plan for the future organisation and activities of EUROCAT network. The document recommends actions that are necessary for timely and successful transition to the JRC, including the drafting of the document on transfer of the EUROCAT database and coordinating activities to the JRC and preparation of the Memorandum of Understanding and a contract template for obtaining registries’ permission for data transmission. The new organisation of the EUROCAT network at the JRC was addressed by proposing the new governance of the network by EUROCAT Management Committee (EMC). The composition and the activity of the EMC were outlined. The list of the activities of the scientific leader and JRC Central Registry was provided. Strategic objectives and future activities of the EUROCAT network were defined as follows: positioning within the Rare Disease Platform; improving the quality and the range of collected data; network expansion; connecting with other types of registries and other partners for policy and advocacy in relation to CA prevention; clinical practice; pharmacovigilance; envirovigilance and genetic research; development of project proposals and preparation of scientific/technical and strategic design reports/recommendations.

- The Central Registry (Ulster) to ensure training and documentation to be passed to the JRC. The Project Manager visited JRC in October 2014, and Dr Javier de la Cruz of JRC visited Ulster in October 2014 (see 7 below for Deliverable 7).

Despite efforts by both Central Registry and the Steering Committee to plan for a smooth transition allowing the usual surveillance timetable to continue uninterrupted, the JRC finally asked registries for permission to transfer data in mid-December 2014 and requested a formal offer for the software in January 2015. A particular point of difficulty was the JRC’s recognition that all registries own their own data, that Ulster could not transfer data without the permission of registries and that the permission of registries depended on a level of documentation of JRC intended processes and data security procedures in 2015. 25 current member registries gave permission for their data to be transferred to JRC in December 2014. 13 registries withheld their permission awaiting more documentation from the JRC (Annex 3).

In the workplan, it had been envisaged that the strategic development of EUROCAT would be developed in liaison with DGSanco and the EC Expert Group on Rare Diseases. It was clear, however, that from DGSanco’s point of view, the issue had been settled by the JRC contract and no further liaison was deemed necessary. No EUROCAT representatives were appointed to the new EC Expert Group on Rare
Diseases and EUROCAT was not called to a EC Expert Group on Rare Diseases meeting to discuss the developments.

EUROCAT expressed concern at Steering Committee meetings that the resources available at JRC would not in future allow the level of activity of the past to be maintained. The Steering Committee therefore proposed that complementary activities should be included in the RD application to Horizon2020 “Innorare” (Innovation and Research Acceleration for Rare Diseases) and the new Rare Diseases Joint Action, subject to agreement by Member States, as part of an “Epidemiology and Prevention of RD” workpackage. This latter proposal was not supported by DGSanco, although it did gain the support of several MS (e.g. Italy, Germany, Spain, Poland, and Croatia) who nominated EUROCAT institutions to be part of the Joint Action.

EUROCAT was represented by EUROCAT Poland at a meeting in September 2014 to finalise the RD Joint Action at which support for the work was expressed, but not followed up by inclusion. The workpackage was not included in the RD Joint Action proposal (led by INSERM Paris) and no budget has been designated for EUROCAT work in this context. The Horizon 2020 “Innorare” proposal included a work item led by EUROCAT Slovenia on linking registries to biobanks, but the entire funding proposal (led by Newcastle University) submitted September 2014 was later rejected for funding. The question of how to complement JRC activities with other funded EUROCAT activities remains unresolved. The exact scope of what JRC will be able to provide in the short and long term also remains uncertain and was apparently not specified in their service contract.

EUROCAT also expressed concern that there was no mechanism whereby JRC/DGSanco could fund activities involving personnel outside the Central Registry institution, as had been very important in the past. This was particularly potentially detrimental to the Coding and Classification Committee, central to the work of EUROCAT. The JRC is still exploring options to resolve this problem.

EUROCAT expressed concern that a transitional period of co-working between Ulster and JRC would be needed in order for JRC to learn the surveillance processes. JRC explored the option of some type of contract with Ulster for all or part of 2015, but in August 2014 declared that this would not be possible. In December 2014, this question was reopened and has yet to be resolved.

3. Dissemination of EUROCAT Surveillance results in relation to all EUROCAT objectives.

Promotional Leaflet (Deliverable 02)
The Promotional Leaflet was produced September 2014 and made available on the EUROCAT website (Annex 4). Responsible partner: Professor Ingeborg Barisic, in collaboration with Ulster (Project Manager and Administrator).

EUROCAT Newsletter (Deliverable 03)
Two newsletters were produced in September 2014 and December 2014, available in Annex 5 Responsible partner: Professor Ingeborg Barisic, in collaboration with Ulster (Project Leader, Project Manager and Administrator) and with contributions from across the EUROCAT network. The newsletter was sent to a mailing database of 2,575 persons/institutions worldwide. This mailing database, subject to opt-outs by recipients, is being transferred to JRC Ispra for future use.

EUROCAT Website
The EUROCAT website, publicly accessible, was kept up to date with new developments, in particular:
The Cluster Advisory Service section of the website was removed and the content found within this section of the website was combined into a EUROCAT Special Report entitled “An archive of the Cluster Advisory Service content of the EUROCAT website (August 2014)” and can be found using the following link http://www.eurocat-network.eu/content/Special-Report-CAS-with-Protocols.pdf

Guide 1.4 replaced Guide 1.3 in early 2014 and can be found using the following link http://www.eurocat-network.eu/content/EUROCAT-Guide-1.4-Full-Guide.pdf

Six new Congenital Anomaly subgroups – prevalence data for these subgroups was uploaded to the website in December 2014. Registries that did not approve their data have been excluded from these subgroups.

The Monogenic Syndrome Table has now been updated to include year 2012 data.

The Coverage of European Population Table was also updated and can be found using the following link http://www.eurocat-network.eu/content/EUROCAT-Population-Table-I-Year2012.pdf

Other updated documents include the final version of New Subgroups; Flowchart Algorithm and List of Minors for Exclusion; Statistical Monitoring Report 2012; Projects and Papers Table; DQI Table.

The website in general underwent a period of cleaning and revision in preparation for EUROCAT’s transition to the JRC, post 2014.

Announcements of new publications and events were also highlighted on the homepage and a link to the archive of these announcements can be found on http://www.eurocat-network.eu/content/EUROCAT-Website-Archive.pdf

The McDonnell R, Delany V, O’Mahony MT, Mullaney C, Lee B and Turner MJ (2014) publication resulted in the following media coverage:


**Publications List**

The publications list was kept up to date and the search engine for publications was improved to differentiate papers and reports http://www.eurocat-network.eu/aboutus/publications/publications. All EUROCAT publications are listed under the Dissemination on page 36. They include 18 papers in peer reviewed journals and four EUROCAT Reports – the peer reviewed papers that have been published in open-access can be seen in Annex 6. Due to the delay between paper submission and publication, 2014 journal publications may relate to work done under the EUROCAT Joint Action.
Conference Presentations
A copy of conference presentations can be found in Annex 7 and a list can be found under Dissemination on page 36.

Development of National EUROCAT Committees
EUROCAT continues to promote the development of national EUROCAT committees, but due to the impending changes with move to JRC, this activity was postponed to 2015, and the situation remains as reported in 2013.

Liaison with EUROPLAN to follow-up EUROCAT Primary Prevention Recommendations
Two papers have been published in a highly regarded journal regarding these Recommendations:


EUROCAT and EUROPLAN also proposed a collaborative input to the new RD Joint Action to follow up the Primary Prevention Recommendations, but this was not included in the JA (see section 2 above). The issue should be of high priority for further follow-up by the JRC and is included in the Future Strategy document. It is planned to have links with other partners for policy and advocacy particularly in relation to CA prevention.

Liaise with WHO and WHO Centres
The Centre for Maternal, Fetal and Infant Research at Ulster University where Central Registry was based is a WHO Collaborating Centre for Surveillance of Congenital Anomalies. As such, contacts have been maintained with WHO Geneva in relation to the Non-Communicable Disease Strategy, in relation to Birth Defects Surveillance in Africa and in relation to planning for the first World Birth Defects Day on 3 March 2015. In addition, a former EUROCAT PhD student (Ulster) has been invited by the WHO Initiative for Vaccine Research to join the “WHO TASKFORCE TO EVALUATE INFLUENZA DATA TO INFORM VACCINE IMPACT AND ECONOMIC MODELLING” to inform IVIR-AC and other vaccine advisory bodies. This is in relation to EUROCAT research carried out during the EUROCAT Joint Action on H1N1 and H1N1 vaccination.

Liaise with other organisations and Stakeholders
EUROCAT was represented at the International Clearinghouse for Birth Defects Surveillance and Research meeting in Helsinki, September 2014. A sub-meeting of stakeholders worldwide (including also the US national surveillance system and March of Dimes Foundation) was held to agree and plan the first World Birth Defects Day, to be held on 3rd March every year, to promote awareness of the prevention of birth defects and need for high quality care.
EUROCAT papers are reviewed in OrphaNews. After our 2013 report “EUROCAT: a potential source of prevalence data for Orphanet” no response has been received from DGSanco or Orphanet on how to progress the issues identifies.

EUROCAT and SCPE (Surveillance of Cerebral Palsy in Europe) maintained contact in relation to the transition to JRC co-ordination and future collaborative research.

EUROCAT and EUROCleftNET have continued to exchange information especially as they have complementarities and synergies in their research objectives with a strong common interest in congenital anomaly prevention.

EUROCAT and EUROPERISTAT maintain contact.

EUROCAT was invited to present at the International Conferences for Rare Diseases and Orphan Drugs (ICORD) on 8 October 2014. This was attended by Dr Amanda Neville.

EUROCAT is represented at the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) where it also liaises with ENTIS.

**National/local dissemination**

The above activities do not capture dissemination that goes on at national and subnational level since it is difficult to maintain a complete record of this. Most registries organise at least an annual information day, participate in scientific conferences according to their research interests, liaise with local patient organisations and maintain links with policymakers appropriate to their institutional situation. We believe that the further encouragement of national committees and national dissemination plans is a high priority for the future.

4. **Evaluation of EUROCAT network.**

See Evaluation Section below.

5. **Update and management of EUROCAT Central Database (ECD)**

On 15 February 2014 and/or 15 October 2014, member registries transmitted anonymised, uniformly coded data on congenital anomaly cases registered in their local population using the EUROCAT Data Management Program (EDMP). Of the 32 full member registries, 30 have transmitted data on cases born in 2012, one registry has sent data up to birth year 2011 and one registry has sent data up to birth year 2010. Of the six Associate member registries, two have transmitted aggregate data up to birth year 2012, two have sent data up to 2011 and two have sent data up to 2010. For the first time, the Pleven registry in Bulgaria sent data for the years 2008-2012. These data were imported into EUROCAT central database (ECD). A metadata manual describing these data is available on the members-only website http://www.eurocat-network.eu/content/EUROCAT-Data-Manual.pdf.

Data from the six UK registries were uploaded to the British Isles Network of Congenital Anomaly Registries (BINOCAR) Gateway in April and November 2014 for surveillance and research within BINOCAR. For the first time, data from six French registries (Auvergne, French West Indies, Ile de la Reunion, Paris, Rhone-Alpes and Strasbourg) were transmitted to a French national database at the French Institute for
Public Health Surveillance to enable national surveillance of congenital anomalies in France.

The annual Data Quality Indicators (DQI) were produced and uploaded to the website http://www.eurocat-network.eu/content/DQI-2014-v2.pdf. Across 31 registries, the mean prevalence of all anomalies was 260.3 per 10,000 births (95% CI 258.8-262.0) over the period 2008-2012. Only three registries had an overall prevalence below 1.8%. The EUROCAT registry descriptions describing how data was collected, definitions used and Registry Leader contact details have also been updated on the EUROCAT website http://www.eurocat-network.eu/aboutus/memberregistries. The registry descriptions, DQI and metadata are valuable resources for aiding understanding and interpretation of data between and within registries.

The new EUROCAT Guide 1.4 documenting the EUROCAT database system (i.e. EDMP, database dictionary, definitions, coding and classification, prevalence, data quality and data security to facilitate a standardised approach to surveillance within EUROCAT) was published on the website http://www.eurocat-network.eu/aboutus/datacollection/guidelinesforregistration/guide1_4. It is used for registering cases of congenital anomaly born from 1 January 2013, and consists of six sections, each with a separate link for ease of access as well as a link to the complete guide.

Following permission from the Steering Committee and individual registries, data were extracted from the central database in 2014 for the following projects:

**EUROCAT Internal Projects**
- Congenital Rubella Syndrome in EU (led by Tarik Derrough, ECDC)
- Epidemiology of rare syndromes: Beckwith Wiedemann, Ellis van Creveld, Fryns, Treacher Collins, (led by Professor Ingeborg Barisic, Croatia)
- Perinatal mortality burden associated with congenital anomalies (led by Dr Henk Groen, N Netherlands)

**EUROCAT External Projects**
- Association between maternal use of antibiotics in the first trimester and risk of congenital anomaly (led by Professor Helen Dolk, UK)
- Congenital anomalies associated with Edwards (trisomy 18) and Patau (trisomy 13) syndrome (led by Professor Joan Morris, UK)
- Hierarchical models in the analysis of congenital anomaly data (led by Professor Joan Morris, UK)
- Neuraminidase Inhibitors and congenital anomalies (led by Dr Michiel Luteijn, UK)
- Pierre Robin Sequence and Methadone Exposure in Pregnancy (led by Dr Brian Cleary, Ireland)

We also had 40 external email enquiries (see Annex 8) relating to congenital anomalies from individuals and/or organisations worldwide. The Chair of the United States National Birth Defects Prevention Network (NBDPN) Work Group on Monitoring Over Time, visited EUROCAT Central Registry in Belfast in March 2014 in order to learn about EUROCAT statistical monitoring.

Two EDMP training workshops were held at the annual Registry Leaders Meeting (RLM) in Belfast to answer queries and solve EDMP-related problems. In addition, a researcher from Central Registry visited N Netherlands registry in May 2014 and the Mainz registry in December 2014 to sort out issues with using EDMP.
6. Improvement of the Coding and Classification of congenital anomalies within EUROCAT and worldwide

Data cleaning activities
Based on the update of the monogenic syndrome prevalence table at the website and the report on coding of cardiac defects, both from December 2013, data cleaning in the central database was done in the beginning of 2014 with feedback to local registries. Coding of some of the severe CHD subgroups were improved. Further, some registries have received feedback on the coding of multiple malformed cases.

Coding committee meeting in May in London
Documents for the meeting were prepared months in advance to have documentation from the central database about actual coding and the problems. Revision of subgroups and list of minors were discussed and agreed at the meeting. Important to have changes were implemented before the transfer to JRC. Three new CHD subgroups were added; three aetiologic subgroups for pharmacovigilance were discussed and agreed. Renal dysplasia subgroup was changed to multicystic renal dysplasia subgroup, as the surveillance of this subgroup had shown too much heterogeneity in the cases included. Query cases from the surveillance of multiples were agreed at the meeting.

Revision of subgroups and list of minors
During the summer, the revised documents for subgroups and minors were written and approved by committee members. After approval, the coding was checked in the central database and send to BioMedical Computing Ltd for implementation in the ECD and EDMP. New versions of ECD and EDMP were in use by the end of 2014, information on new subgroups was circulated in a Communication and website prevalence tables were updated.

Surveillance of multiple malformations
More years for review were uploaded to the website and classification agreed through the web-based review system. The years 2005, 2008-2012 are now finished with all cases classified according to the multiple malformation algorithm.

Coding documents
All coding documents were reviewed in autumn 2014 to be sure that everything was correct and updated before the transfer to JRC. A section describing coding committee work was written for the EUROCAT Procedural Manual.

Monogenic syndrome prevalence table
The prevalence table was discussed at a Steering Committee meeting and it was decided to use the same inclusion criteria as for the EUROCAT papers on syndromes. The table was updated in autumn 2014.

Coding queries
Questions from EUROCAT registries or from outside EUROCAT (Christof Schaefer, ENTIS and others) had been received by email throughout the year. Replies had been given to all.

Review of prevalence data
Prevalence tables (A1 tables) from Finland, Auvergne, Rhone-Alp, Pleven, Hungary and Brittany had been reviewed and commented during 2014. Case list from the statistical monitoring had been reviewed and commented, mainly in relation to isolated/multiple classification of cases and presence of heterogeneity.
Members of Coding and Classification Committee
Ester Garne (Chair)
Ingeborg Barisic
Elisa Calzolari
David Tucker
Diana Wellesley

7. Provision of Accessible documentation of EUROCAT Procedures

As part of its normal operation, EUROCAT has been keeping extensive procedural documentation. For the transfer to JRC, this was indexed into a Manual, supplemented with personal delivery of Part I to JRC offices in early October 2014 and a week of training on Part II in the University of Ulster offices for JRC staff in late October 2014. The EUROCAT Network Procedural Manual parts I & II (Annex 9) is a unified document to guide the reader through EUROCAT processes from membership application, registration of cases, use of EDMP software, coding and classification, data security, data transmission, maintenance of the central database, production of prevalence information, running surveillance for clusters and trends, website updating, support of registries, access to research data and authorship of papers.

8. Provision of Essential Epidemiologic Information on congenital anomalies in Europe/

To assess the impact of changes in prenatal screening

Following receipt of data at the biannual deadlines (15 February 2014 and 15 October 2014), data and birth denominators were imported into the central database (ECD). ECD then produced epidemiologic tables showing prevalence for 89 congenital anomaly subgroups by pregnancy outcome, prenatal diagnosis and perinatal mortality rates for all and selected congenital anomalies for each member registry. The tables were first uploaded to a secure test website where member registries checked and confirmed their own data. Only then were the epidemiologic tables released to the EUROCAT main website for open view. Data for cases born in 2012 were new to the website in March 2014. Updates to 2012 and all previous years were uploaded in November 2014. Six new anomaly subgroups were introduced in 2014 and amended tables (to include these six) were uploaded in December 2014.

Geographic Inequalities in Public Health Indicators related to Congenital Anomalies were the focus of a EUROCAT Special Report. This report focussed on six indicators: perinatal mortality [an indicator of mortality burden], prenatal diagnosis [an indicator of the degree to which prenatal screening services are detecting cases of congenital anomaly], TOPFA [an indicator of the degree to which TOPFA is the choice following prenatal diagnosis, and the degree to which TOPFA may be affecting perinatal mortality and livebirth prevalence], Down Syndrome [an indicator of the combined effect of prenatal screening policy and termination of pregnancy for fetal anomaly], Neural Tube Defects [an indicator of the success of preventative programs] and pediatric surgery [an indicator of the overall public health burden in terms of need for surgery]. A paper for a peer reviewed journal will be derived from the report.

A subset of epidemiologic tables (2012 and 2008-2012), together with the Geographical Inequalities report, form part of the Annual Surveillance Report (Annex 10). A full set of tables can be found in the appropriate sections on the website http://www.eurocat-network.eu
9. **Facilitation of early warning of new teratogenic exposures/Evaluate Effectiveness of Primary Prevention/ Act as an information and resource centre for the population, health professionals and policy makers regarding clusters, exposures and risk factors of concern.**

**Statistical Monitoring**
EUROCAT annually performs statistical monitoring for both trends and clusters in time in order to detect any previously unrecognised increases in frequency of congenital anomalies which may be associated with exposure to teratogenic drugs or environmental chemical pollutants. The EUROCAT Statistical Monitoring Report 2012 (Annex 11) (http://www.eurocat-network.eu/clustersandtrends/statisticalmonitoring/statisticalmonitoring-2012) publishes details of the trends and clusters detected in individual registries and in all registries combined (pan-Europe) for the ten year period 2003-2012. Monitoring included analysis of pan-European trends covering over six million births in 25 registries, 2003-2012 and cluster detection in 18 registries covering almost one million births in 2011-2012. Cluster monitoring at country level i.e. countries with more than one registry were also monitored to detect clusters at a national as well as at a regional level.

Key findings were: two new increasing trends oesophageal atresia with or without trachea-oesophageal fistula and maternal infections resulting in malformations (namely rubella, cytomegalovirus and toxoplasmosis). Increasing trends over time were again detected for three types of severe congenital heart defects (single ventricle, tetralogy of Fallot and atrioventricular septal defects), some digestive system anomalies, craniosynostosis and cystic adenomatous malformation of the lung. No decreasing trend in neural tube defects was observed, again emphasising the failure of primary prevention by periconceptional folic acid supplementation policy. Overall, prevalence of all anomalies excluding genetic conditions decreased over time. Investigation of clusters in the last two years (2011-2012) identified no clusters of immediate public health concern.

A study investigating long-term trends and geographical differences in the prevalence of non-chromosomal anomalies over 30 years from 1983 to 2012 using data from 25 registries was conducted. A paper is currently being circulated for approval before being submitted to a journal for publication.

A paper describing the methodology adopted by EUROCAT for routine cluster detection and a second paper describing the results including outcomes of registry investigations into clusters detected over seven years using this methodology have been accepted for publication in the European Journal of Epidemiology.


**Congenital Rubella**
European Centre for Disease Prevention and Control (ECDC) analysed EUROCAT data in relation to the target for elimination of congenital rubella from the European Region by 2015. Congenital rubella is among the 52 diseases and health issues under
surveillance in the EU covered by a Commission Decision for epidemiological surveillance (Commission Decision No 2119/98/EC)). Cases of rubella infections in pregnant women are currently reported to the European Centre for Disease Control (ECDC) through the rubella case-based monthly reporting scheme. However, reporting of the outcome of pregnancy and potential complications to the newborn is not actively followed-up by ECDC. The reporting of CRS data from EU Member States to WHO-EURO is established and operational through the annual WHO/UNICEF Joint Reporting Form. ECDC would like to further support EU Member States in their attempt to identify CRS cases and estimate the prevalence of CRS. Data on CRS cases is registered by the EUROCAT network and this source of information could constitute an additional source of data in the EU to document the burden of CRS. A study was therefore performed which covered the CRS cases (livebirths, stillbirths or terminations of pregnancy following prenatal diagnosis (TOPFA)) with a date of delivery during the period 2000 to 2012.

In the period 2000 to 2012, 19 cases classified by EUROCAT registry leaders as congenital rubella syndrome were reported from nine registries out of 34 registries participating in the study. Seventeen cases were livebirths, the others TOPFA. EUROCAT registries reported some cases that were not known to national authorities, but a complete comparison was not possible. Thirteen cases were born to mothers who had a previous pregnancy, suggesting that an opportunity to establish non-immune status during care of the mother for her previous pregnancy had been lost, and possibly reflecting the increased risk of contracting rubella by contact with small children. The report recommends better links between EUROCAT registries and national authorities responsible for CRS surveillance. The Full Report will be made available early in 2015 pending ECDC approval, and a draft paper for publication is in preparation.

As a result of this collaboration, EUROCAT registries and national authorities have begun working together in Spain, Italy and Ireland.

10. Expansion of EUROCAT network and operation of Registry Advisory Service

At the start of 2014 EUROCAT had 31 full members and six associate members, covering an average annual birth population of 1.6 million, with over 465,000 cases of CA registered in the central database. The activities of Registry Advisory Service (RAS) during EUROCAT Operating Grant in 2014 were as follows:

- Organisation of RAS workshop for new applicant and affiliate members on June 26 in Belfast, UK. The topics of the workshop were: definition and coding of complex cases with multiple congenital anomalies, data quality indicators and coding exercise. The workshop was attended by 10 participants from different EU countries/regions that are not yet included in EUROCAT network (Cyprus, Greenland) or already have an affiliate membership.
- Organisation of the roundtable discussion with new/applicantaffiliate members on 27 June 2014, Belfast, UK. The aim of the meeting was to determine ways in which the EUROCAT/JRC could help the sustainability and improve the quality of new registries in the future. The participating registries presented their organisation/structure, main activities and problems they encounter in their work. As Dr Katya Kovacheva, the registry leader of the Pleven Registry, was not able to attend, Dr Barisic has presented in her name the accomplishments and challenges confronted in the work of the Pleven registry. Dr Anna Pierini from Tuscany Registry presented the activities undertaken in Italy in order to facilitate and to improve the work of the new register of the new
Italian registries. The main conclusion of the roundtable discussion was that the work of the new registries will be significantly helped by organising workshops for the registries’ staff at the JRC, and by local organisation of EUROCAT symposia in order to raise the visibility and to popularise the activity of the registries within the respective health systems and in the general population.

- One-year follow-up and evaluation of first datasets for new affiliates was done by Dr Ester Garne for Auvergne, Brittany and Pleven Registries.
- Pleven Registry (Bulgaria) has started using EUROCAT Data Management Programme software (EDMP) in September 2014 with the help of Central Registry. In October 2014 the head of the registry in Pleven, Dr Katja Kowacheva, and her collaborator, Dr Zornitsa Kamburova, visited the registry in Zagreb in order to get training in coding, use of EDMP software and registry management. Despite difficulties in collecting data and funding, the registry in Pleven collected valuable data on congenital anomalies that can be found on the EUROCAT website. The dataset was evaluated by Dr Ester Garne.
- At the invitation of the French EUROCAT registries Dr Ester Garne organised the workshop on coding and classification of congenital anomalies at the regional meeting in Paris (see Annex 7). All existing and new French registry members were present, including Dr Veronique Goulet, the leader of the new Central registry in France.
- Contacts with Italian part of Switzerland, Latvia, Slovenia and Ukraine are ongoing and assistance with coding queries has been provided by Central Registry and RAS members.
- Czech Republic is starting to send individual dataset in order to progress from associate to full membership. This status change needs evaluation from Registry Advisory Service in the next period.
- The interest to join EUROCAT from non-European registries of congenital anomalies, "World Affiliate" membership is continuing. In 2014 RAS has received two new expressions of interest (Malaysia and Fiji).

11. To conduct pharmacovigilance based on EUROCAT database

EUROCAT pharmacovigilance activities included three separate signal evaluation studies using a case-malformed control design. The fifth and final update lamotrigine study investigating maternal first trimester lamotrigine exposure and risk of orofacial clefts using data from 21 EUROCAT congenital anomaly registries covering over ten million births, 1995-2011 found no evidence of an increased risk of orofacial clefts relative to other malformations associated with lamotrigine exposure. The report was submitted to the co-funder GlaxoSmithKline (GSK) in March 2014, who, in turn, have passed it on to the appropriate Regulatory authorities.

A second study involving 12 EUROCAT registries covering almost four million births 1995-2011 assessed whether maternal first trimester exposure to methadone is associated with risk of Pierre Robin Sequence (PRS) and found a strong association between methadone exposure and PRS.

A third study involving 15 EUROCAT registries covering over three million births 1995-2011 found an association between maternal mental health conditions/medication use and the severe congenital heart defect, Ebstein’s anomaly. All three studies are currently being drafted into papers for publication in peer-reviewed journals. These studies highlight the importance of congenital anomaly registries for evaluating signals reported in the literature.
EUROCAT is registered on the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) website as a research resource and the lamotrigine studies are listed on the register of studies
http://www.encepp.eu/encepp/resourcesDatabase.jsp

In the 2014 DQI, 23 out of 31 full member EUROCAT registries recorded medication exposures using ATC codes, which was one more compared to the previous year and 82% of the ATC codes had seven digits and were in the correct format which was the same as reported in 2013 (http://www.eurocat-network.eu/aboutus/datacollection/dataquality/dataqualityindicators).

The Report on Sources of Information on Medication Use in Pregnancy was updated http://www.eurocat-network.eu/content/Special-Report-Medication-Use-In-Pregnancy.pdf.

12. Annual EUROCAT Registry Leaders’ Meeting (Deliverable 04)

The 29th EUROCAT Registry Leaders’ Meeting (RLM) was hosted in Belfast, Northern Ireland (UK) on the 26-27 June 2014 by EUROCAT Central Registry (University of Ulster: Operating Grant holder and organisers of the event). This was the first time it had been held in Belfast, as the RLM moves between members of the network in order to raise the profile of EUROCAT in each country. The RLM was attended by 62 individuals. EUROCAT Central Registry was represented, 22 Full Member Registries from 13 European countries were represented (Austria, Belgium, Croatia, Denmark, France, Hungary, Ireland, Italy, Netherlands, Norway, Poland, Spain, UK), three Associate Member Registries from three European countries were represented (Finland, Poland, Sweden), five Affiliate Member Registries from five European countries were represented (France, Greenland, Latvia, Slovenia, UK), one World Affiliate Member Registry from New Zealand was represented and eight external guests (external to the EUROCAT Network) were present including representation from DG-Sanco, the Joint Research Centre Ispra, the International Clearing House for Birth Defects Surveillance and Research and EUROPLAN.

The minutes of the RLM accompanied by all presentation slides delivered at the RLM have been made available to EUROCAT members on the EUROCAT website (Agenda and minutes have been provided in Annex 12).
Evaluation

All tasks mentioned in Annex 1 were completed. Steering Committee meetings monitored the process and performance of annual activities as documented in the minutes (Annex 1).

As an extensive Evaluation report was produced at the end of the EUROCAT Joint Action 2011-2013, a move of Central Registry was impending and the Project Manager left her post in October 2014 due to the impending move, we contacted EAHC to reduce the evaluation activity and its associated budget, including not engaging an external subcontractor for an external evaluation but instead using a small portion of that budget to engage a Communications consultant to follow-up recommendations of the previous Evaluation Survey to consider the website design. Valuable guidance was given as to how investment could be made in a more public-facing website for the future (see Evaluation Report, Annex 13).

The EUROCAT website had 12,000+ visitors per month, from 152 countries, mainly professionals.

EUROCAT guidelines and prevalence data continue to be highly valued and cited.

The web-based Evaluation survey, completed in late 2013 by a variety of stakeholders in European countries as part of the EUROCAT Joint Action 2011-2013 Evaluation, was extended in 2014 to EC Expert Group on Rare Diseases members. The web link was forwarded to EC Expert Group on Rare Diseases members by Dr Jaroslaw Waligora, DGSanco. 15/60 (25%) EC Expert Group on Rare Diseases members filled out the survey which can be found in Annex 13. It is evident that not all EC Expert Group on Rare Diseases members are acquainted with the activities of EUROCAT and more communication would be needed. We recommend more engagement between EC Expert Group on Rare Diseases and EUROCAT at European level. We recommend the invitation of the EUROCAT President to one EC Expert Group on Rare Diseases meeting per year to report on progress. We also recommend that the email addresses of EC Expert Group on Rare Diseases members be made available to EUROCAT members (they are currently withheld) so that EUROCAT registries can find and communicate with their national representatives.
Dissemination

See Section 3 under Operating Grant Implementation above.

The EUROCAT website is www.eurocat-network.eu

All EUROCAT publications are listed below and can also be accessed on the EUROCAT website at the following link: http://www.eurocat-network.eu/aboutus/publications/publications. The peer reviewed papers that have been published in open-access can be seen in Annex 6. Due to the delay between paper submission and publication, 2014 journal publications may relate to work done under the EUROCAT Joint Action.

Peer-Reviewed Papers (18)


EUROCAT Reports (4)

EUROCAT (2014). EUROCAT Special Report: An Archive of the Cluster Advisory Service Content of the EUROCAT Website. EUROCAT Central Registry, University of Ulster.

EUROCAT (2014), Future Development of EUROCAT, EUROCAT Central Registry, University of Ulster


Conference Presentations
A copy of conference presentations can be found in Annex 7.

Coding in EUROCAT - Homogeneous Coding for Comparing Data Coding Workshop for French Registries, Paris, France Ester Garne (November 2014)

Congenital Anomalies as Preventable Rare Diseases EPIRARE 3rd International Workshop Rare Disease and Orphan Drug Registries Amanda Neville (November 2014)

Congenital Anomalies as Preventable Rare Diseases International Conferences for Rare Diseases and Orphan Drugs Amanda Neville (October 2014)

Maternal first trimester lamotrigine exposure and risk of orofacial clefts: analysis using data from EUROCAT congenital anomaly registries British Isles Network of Congenital Anomaly Registers Biennial Scientific Meeting, Wales Maria Loane (October 2014)
The prevalence and risk of Down Syndrome in monozygotic and dizygotic multiple pregnancies in Europe: implication for prenatal screening
British Isles Network of Congenital Anomaly Registers Biennial Scientific Meeting, Wales
Breidge Boyle (October 2014)

Update on EUROCAT: Surveillance of Congenital Anomalies
ICBDSR Annual Meeting, Helsinki, Finland
Helen Dolk (September 2014)

Selective Serotonin Reuptake Inhibitor Antidepressant Use in First Trimester Pregnancy and Risk of Congenital Anomalies: A European Register-based Study in 12 European Countries
International Marcé Society for Perinatal Mental Health Biennial Conference in Perinatal Mental Health, Swansea, Wales
Breidge Boyle (September 2014)

Teenage mothers and risk of congenital anomalies
MFIR Healthy Pregnancy Seminar Series, University of Ulster
Maria Loane (June 2014)

The effect of maternal age on the risk and prevalence of congenital anomalies in Europe: design and analysis of a collaborative database
INHR, University of Ulster
Maria Loane (May 2014)

**Participation in EU actions (if applicable)**

EUROCAT participated in the preparation of funding applications for the Rare Diseases Joint Action, and the HORIZON2020 INFRADEV-1-2014 on Rare Diseases (see description under activity 2 above).

15 EUROCAT Registries are involved in the Framework 7 funded EUROmediCAT Project: Safety of Medication Use in Pregnancy in relation to risk of congenital anomaly, funded 2011-2015, Grant No: HEALTH-F5-2011-260598 co-ordinated by Ulster University.
Further remarks

The EUROCAT Central Registry has operated at Ulster University for 15 years from 2000-2014.

The move to JRC, Ispra, from 1 January 2015, to be part of the Rare Diseases Platform which is being developed at JRC, is a landmark for EUROCAT’s sustainable future, and should ensure that congenital anomaly surveillance and prevention is given the visibility at both European and Member State level that it deserves, and is given due prominence in rare disease policy.

EUROCAT at Ulster University has had six contracts with DG Sanco/EAHC Public Health Programme since 2000. Each of these has been conducted with transparency and accountability. All activities and budgets are approved by the Steering Committees and registries as part of the preparation of the funding application, on which basis registries agree to continue transmitting their data to a central database. Depending on the funding contract (Project, Joint Action, Operating Grant), registries have been partners or collaborators, but the working model of collaboration has remained the same.

The team at the WHO Collaborating Centre for the Surveillance of Congenital Anomalies at University of Ulster, where EUROCAT Central Registry has been sited since 2000, thank the EUROCAT registries warmly for their excellent collaboration, and wish EUROCAT well for its future.
Annexes

1. Agenda and Minutes of EUROCAT Steering Committee, April 2014, June 2014, October 2014 and December 2014
2. Future Development of EUROCAT (Deliverable 9)
3. Registries’ Decisions re JRC Data Transfer
4. Promotional Leaflet (produced September 2014) (Deliverable 2)
5. EUROCAT Newsletters (produced September and December 2014) (Deliverable 3)
7. Conference Presentations
8. External email Enquiry Log
10. Annual Surveillance Report (Deliverables 1, 5 and 6)
12. Agenda and Minutes of Registry Leaders’ Meeting, June 2014 (Deliverable 4)
13. Evaluation Report