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EUROCAT Statistical Monitoring Protocol 2012

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EUROCAT PROTOCOL FOR STATISTICAL MONITORING AND INVESTIGATION OF TRENDS AND CLUSTERS

CONTENTS

Acknowledgements:
Alan Kelly and Conor Teljeur (Trinity College Dublin) adapted and implemented the scan technique for statistical monitoring, in discussion with Helen Dolk (EUROCAT Project Leader, University of Ulster) with first results presented to the Registry Leader's Meeting (RLM) in Heidelberg 2003. Subsequently, the statistical code was incorporated into the EUROCAT Data Management Program (EDMP) by James Densem (Biomedical Computing Ltd). Statistical monitoring was co-ordinated by Araceli Busby (LSHTM) until 2005, and by Maria Loane (Central Registry, UU) since then. In 2006, data analysis using the standard software was transferred from Dublin to Central Registry. From 2010, Joan Morris (Queen Mary University of London) has provided statistical expertise. This protocol has been written by all those involved.

1. Background: monitoring strategy and timetable

Statistical Monitoring relates to two of EUROCAT's objectives:

- to provide essential epidemiologic information on congenital anomalies in Europe
- to co-ordinate the detection of, and response to, clusters and early warning of teratogenic exposures

EUROCAT was established in 1979 in the wake of the thalidomide epidemic, and statistical monitoring still aims at early detection of any new teratogenic drug. Since then, interest has also widened to other environmental chemicals as potential teratogens (see EUROCAT Special Report: a Review of Environmental Risk Factors for Congenital Anomaly 2004 http://www.eurocat-network.eu/content/Special-Report-Env-Risk-I-and-II.pdf and http://www.eurocat-network.eu/content/Special-Report-Env-Risk-III.pdf). Statistical monitoring is only one part of surveillance of teratogenic exposures, to identify potential cause for concern where there is no specific prior hypothesis about the exposure. It is essentially a screening method to scrutinise data regularly and systematically, to detect any previously unrecognised increases in frequency. Where there are specified hypotheses about new teratogens (e.g. which drug, when, where), other direct approaches for analysis should be undertaken which are not the subject of this protocol.

The EUROCAT Coding and Classification Committee select EUROCAT congenital anomaly subgroups for statistical monitoring. All subgroups are defined in EUROCAT Guide 1.3 http://www.eurocat-network.eu/content/EUROCAT-Guide-1.3.pdf.

Currently, statistical monitoring is conducted to detect changes in time within each registry and to detect trends across all registries. Future developments will refine data analysis across registries and incorporate the spatial dimension.

Statistical methods have been chosen which are relatively straightforward for public health authorities to understand and communicate, and which can be supplied in the EUROCAT software (EDMP) to member registries for use by non-statisticians.

The elements of the current monitoring strategy are:

- Common user-friendly statistical software for use centrally and locally (EDMP)
- Annual statistical monitoring for trends and clusters at central level, 15 months after last date of birth (e.g. year 2012 births included in monitoring in March 2014).
- More frequent and/or earlier statistical monitoring locally (by member registries)
- Use of EUROCAT communications and special data analyses to respond to news about clusters identified locally or outside the monitoring system
- A clear and prompt system of investigation and reporting of results
- Use of statistical monitoring additionally as a data quality control system

All full member registries able to meet the annual February data transmission deadline (e.g. Feb 2014 for 2012 births) participate in cluster detection monitoring. All full member registries that have data no more than one year behind (e.g. 2011 complete in Feb 2014) are included in trend analysis. Associate members can also request to be included in trend analysis. Associate

member registries are invited to use EDMP locally for cluster detection and report their results to Central Registry.

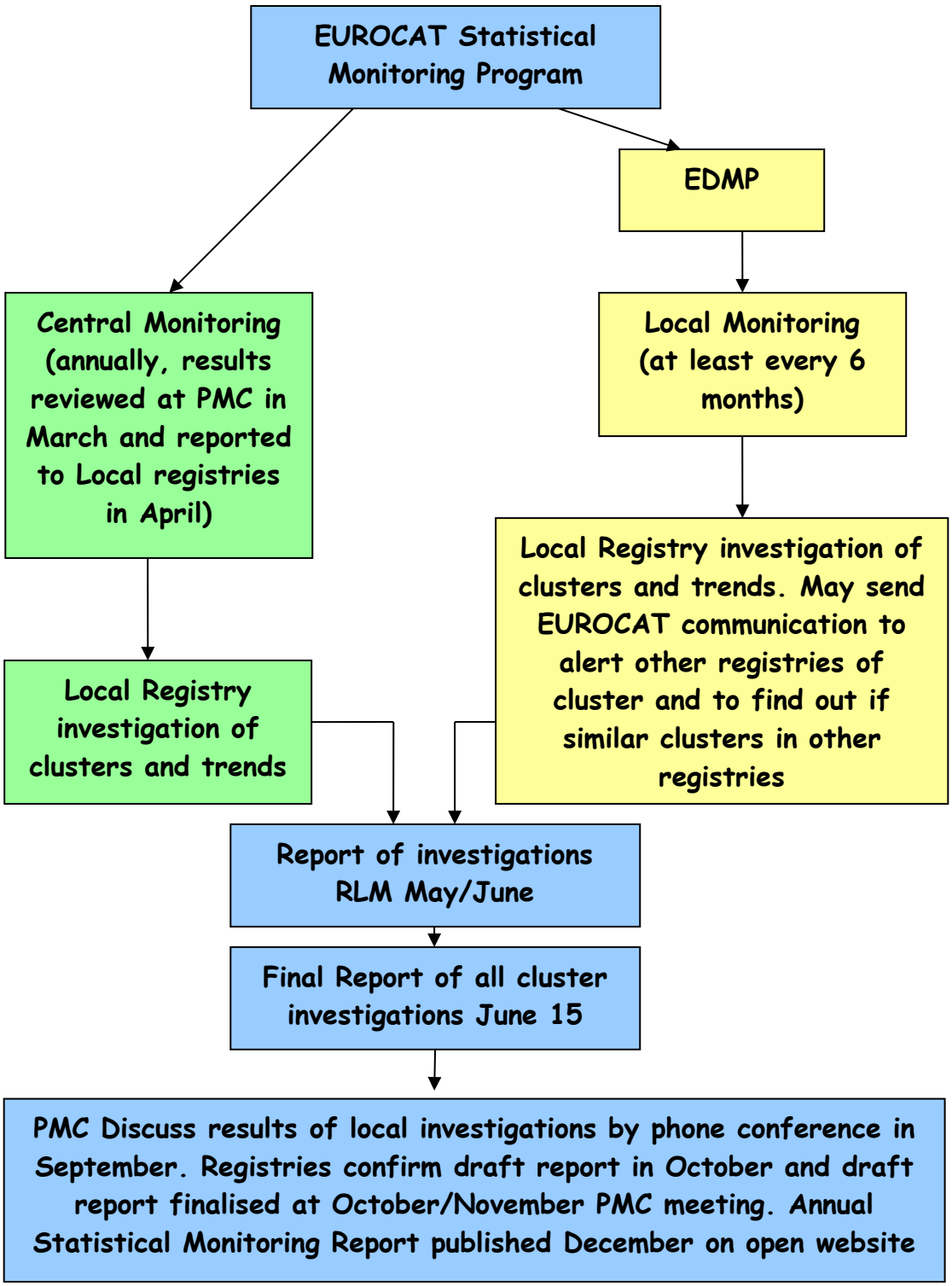


Figure 1: Monitoring and reporting centrally and locally.

2. Statistical Methods

2.1 Statistical methods for the detection of trends

Trend tests are performed for 81 anomaly subgroups (see Appendix 3) for each registry. Currently, Central Registry performs a trend test for the most recent five years of data, as well as a trend test for the most recent 10 years (or 8 years if 10 years are not available). The analysis is based on the number of cases per year of birth and the number of births per year. Data is presented by individual year or grouped by two year intervals if there are too few cases to meet the criterion for testing by single year. A trend test is not performed if the expected number of cases per year (or 2 year interval) is less than 5 and if the observed number of cases in any one year (or 2 year interval) is less than 2.

Change over time is tested with a chi square test for heterogeneity, divided into the trend component ("chi square test for trend") and the non-linear component ("chi square test for non-linear change"). The average annual percentage change in prevalence per year is calculated from a logistic regression. The Chi square test for trend identifies evidence of an increasing or decreasing trend in prevalence. The Chi square test for non-linear change identifies evidence of significant change over time (i.e. the prevalence changes from year to year), in the absence of an increasing or decreasing monotonic trend. The significance level (p-value) for both chi squared tests, direction (upward or downward) and average annual percentage change in prevalence per year (with 95% confidence intervals) are given in the output

Where $p<0.05$ for trend component and $p>0.01$ for non-linear component, the results are identified as an "increasing or decreasing trend". Since overall directional trend is of most concern for investigation, a chi square for trend p-value less than 0.05 is interpreted as a trend even where the p-value for non-linear change is weakly significant also (between 0.05 and 0.01).
Where $p<0.05$ for trend component, $p<0.01$ for non-linear component and the prevalence trend is monotonic, the results are also identified as 'increasing or decreasing trend'.
Where $p<0.05$ for trend component, $p<0.01$ for non-linear component and the prevalence trend is not monotonic, the results are identified as "non-linear change".
Where $p>0.05$ for trend component and $p<0.05$ for non-linear component, the results are identified as "non-linear change".
Where $p>0.05$ for trend component and $p>0.05$ for non-linear component, the results are interpreted as showing no significant change over time.

Since the Chi squared test is based on conventional probabilistic statistics, at a significance level of $p<0.05$, 5% of the test results will be statistically significant by chance. This should be kept in mind in interpretation (see protocol for investigation).

2.2 Adjusting Down syndrome, Edward syndrome and Patau syndrome trends for in-utero survival and maternal age

There is a high fetal loss rate in Down, Edward and Patau syndrome pregnancies and in the absence of prenatal diagnosis the majority of fetal losses prior to 20 weeks gestation are likely to be undiagnosed. Therefore to allow for the increase in prenatal diagnoses and subsequent terminations prior to 20 weeks gestation for each registry, the observed number of terminations

of pregnancy for the 3 trisomic syndromes at less than 20 weeks gestation are corrected for the probability of survival to 20 weeks gestation prior to the trend analysis being performed.

The risk of a Down, Edward or Patau syndrome pregnancy increases considerably with increasing maternal age. Therefore changes in maternal age distribution over time are adjusted for prior to the trend analysis being performed. Both unadjusted and adjusted results are given. Details of the adjustment methodology are given in Appendix 1.

2.3. "Pan-Europe" trend detection.

The "Pan-Europe" analysis repeats the procedures above, but includes data across all eligible registries. This is particularly useful for very rare anomalies which frequently have too few cases per year/2-year interval in individual registries for chi square analysis. The "Pan-Europe" analysis uses logistic regression models with the registries as strata in order to calculate the overall trend across Europe. This model adjusts for the registry effect for example some registries are large while others are small. It can be run on either 9 or 10 years of data. More sophisticated techniques for meta-analysis across registries are under development.

2.4. Statistical methods for the detection of clusters

EUROCAT defines a cluster as:

> "An aggregation of cases of congenital anomaly in time and/or space which appears to be unusual". [1]

This definition includes space as defined by a common activity such as a place of work/ education/ recreation etc. and not just space as defined by residence.

Currently, central statistical monitoring detects temporal clusters within each registry area (region or nation). The EDMP software allows registries locally to detect temporal clusters within subareas of the area covered by the registry.

Cluster detection is based on a moving window test described by Naus and Nagarwalla[2] (see Appendix 2 for statistical details). The method uses a moving window of a given number of cases (window size), measuring the length of time between the first and last case. The method detects whether the given number of cases has occurred in a shorter time than would be expected by chance. The method is not robust with a window size of less than 5 cases. A minimum of 7 cases over the study period of interest is needed to run the analysis. All window sizes from a minimum of 5 to a maximum of the total number of cases minus 2 are tested.

[1] EUROCAT Working Group on the Management of Clusters and Environmental Exposure Incidents, 2003

[2] Naus, J.I. (1965). The distribution of the size of the maximum cluster of points on a line. Journal of the American Statistical Association 60, 532-538

Nagarwalla, N. (1996). A scan statistic with a variable window. Statistics in Medicine 15, 845-850

Each registry and anomaly subgroup is tested independently and the analysis takes into account the number of tests with different window sizes being performed within each registry/anomaly combination to allocate a likelihood to each cluster. The method gives each cluster identified a scan statistic called "lambda", from which a p-value for significance is derived (see Appendix 2).

Many clusters may overlap in time, the inclusion or exclusion of individual cases changing their significance. All significant clusters are identified. The "most significant" cluster (lowest p-value) is then identified. All other significant clusters ($p<0.05$) for which at least 75% of cases overlap with the "most significant" cluster are considered to belong to the same cluster group. The method then looks for the second most significant cluster not already allocated to a cluster group and proceeds similarly identifying the second cluster group. The output identifies the most significant cluster in each cluster group, and the first and last case in time belonging to any cluster within the cluster group.

Following identification of all cluster groups over the time period of analysis, cluster groups overlapping with the last two years of data, and in which the most significant cluster is less than 18 months in length, are chosen for output and investigation. An option is also provided in the software for Central Registry to scan the most significant cluster in all years of data scanned, rather than just the last two years, for research purposes. Similarly, options are available to reset the percentage acceptable for missing gestational age, and cluster lengths greater than 18 months.

Currently Central Registry performs annual cluster analysis using the most recent 5 years of data. More than 5 years may tend to identify trends rather than clusters, and will be computationally slower. Less than 5 years may fail to detect if the most recent years are unusual compared to preceding years.

Since it is exposure during early pregnancy (organogenesis) that is relevant, it is preferable to use estimated date of conception[3] rather than date of birth. Thus cases of different gestational ages (and terminations of pregnancy of low gestational age) are related to a common time when they passed through organogenesis. Cluster detection uses date of conception where gestational age is recorded for more than 90% of cases (for any one anomaly subgroup and registry) allowing its estimation. Where gestational age is missing, it is estimated on the basis of the average gestational age in the registry, by year, anomaly subgroup, and outcome of pregnancy. Gestational age is not estimated if it is missing for more than 10% of cases for the registry and anomaly subgroup, in which case cluster detection is based on date of birth.

Where date of conception is used as a basis for cluster detection, the conception period for statistical monitoring must end 9 months before the last birth month where data collection is complete. Where full years of data are used for surveillance, this means ending the period of the scan at 31 March (date of conception) of the last year of data collected. After this date, some conceptions may result in births in the next year which are not yet included in the dataset. Similarly, the start of the monitoring period must include a complete cohort of conceptions i.e. to detect clusters by date of conception for cases born (or with estimated date of delivery) in the approximate period 2011-2012, the scan routine includes cases with date of conception between 1st April 2010 and 31st March 2012 (24 months). The default monitoring period is set to

[3] EUROCAT date of conception is really the LMP (last menstrual period)

start with estimated dates of conceptions from 1 January of the beginning of the five year period (for simplicity, and to ensure complete coverage of eligible conception outcomes). This means that cluster detection by date of conception is run on 51 months of data (4 complete years: 4 x 12 months = 48 months; and 3 months of the last year included in surveillance). Cluster detection by date of birth is run on 5 complete years of data (60 months).
The Scan method identifies both significant excesses and deficits of cases. Excesses are marked in the output as "clusters", deficits as "deficits".

The Scan method is based on case counts, and results would not be valid if there is large underlying change in population (births) size. There are two types of population change: change in geographical area that the registry covers, and large change in birth rate within the same geographical area. When basing cluster detection on conception cohorts, the latter could be easily taken into account by statistical modifications. However, it is the former type of population change that is more frequent, and a decision was therefore made to exclude registries where population (no. births) change is more than 10% between any two years within the five year period. This is under review.

The data requirements are:

- Full individual dataset including full date of birth (day, month, year), outcome of pregnancy (live/still/TOPFA), gestational age, malformation codes and their derived anomaly subgroups (see EUROCAT Guide 1.3).
- Population change (no. births) must be less than 10% between any two years.

Each dataset used for monitoring should be archived, both by Central Registry and by local registries, as the database is dynamic. Registries should archive a copy of the file transmitted to Central Registry in February of the year of monitoring, and to rename the file eg edmpdata_statmon08. With this file, registries should be able to reproduce Central Registry statistical monitoring results using the EDMP.

The same methodology is used for conducting cluster detection 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. Clusters of interest are circulated to the registries with the country cluster for investigation using the same template as for individual registry investigation.

2.5 History of changes to the statistical software

- Genetic syndromes and skeletal dysplasias are excluded from the statistical monitoring of all other subgroups (year 2011 monitoring onwards). Chromosomal anomalies have already been excluded from monitoring of non-chromosomal subgroups from year 2004 monitoring.
- Forest plots by congenital anomaly subgroup now include individual registry prevalence rates per 10,000 births, to allow comparison between registries and the EUROCAT average (year 2011 monitoring onwards).
- Changes in reporting significant non-linear change. If there is a monotonic increasing or decreasing trend over time, the trend is reported as opposed to the significant variation from linearity (year 2010 monitoring)

- Edward and Patau syndromes: adjusted for maternal age and in utero fetal survival to 20 weeks gestational age (year 2010 monitoring)
- Pan-Europe analysis adjusted for effect of registry (year 2010 monitoring)
- EUROCAT revised subgroups version 2012 were implemented (year 2010 monitoring)
- Forest plots showing the average percentage change in prevalence per year are included in the output for individual registries (year 2010 monitoring)
- Trends: Data is presented by individual year unless there are too few cases to meet the criterion for testing by single year, in which case it is grouped by 2-year intervals (year 2010 monitoring)
- Trend Adobe files: The EUROCAT average prevalence per year (or per 2-year interval) is now plotted on each graph so that a registry can see if it is above or below the average prevalence (year 2010 monitoring)
- Pan-Europe: A Forest plot summarising the pan-Europe trends and the average annual change in prevalence is included (Year 2009 monitoring)
- A new subgroup called "Severe CHD" was included in the list of subgroups (year 2008 monitoring).
- Adjusting Down syndrome trends for probability of in utero survival to 20 weeks gestation of terminations of pregnancy and maternal age (year 2008 monitoring)
- Output of trend analysis. Significant increasing or decreasing trends are only reported where the p-value is <0.05 for the trend component and >0.01 for the non-linear component. Where p<0.05 for trend component and p<0.01 for non-linear component, the results are identified as 'non-linear change'. Where p>0.05 for trend component and <0.05 for non-linear component, the results are identified as 'non-linear change' (year 2008 monitoring onwards)
- Pan-Europe analysis whereby a trend analysis for all registries combined is performed (year 2007 monitoring onwards)
- Trend analysis: in addition to the expected number of cases criterion (i.e. at least an average of 5 per year or 2-year interval), trend analysis is now run if the observed number of cases in each year or 2 year interval is at least 2 (year 2007 monitoring onwards)
- The output of the trend analysis now includes a separate test for trend and a test for non-linearity (Chi square). All significant results are shown (p <0.05) (year 2007 monitoring onwards)
- The Adobe files showing graphical representation of clusters now includes a case list showing estimated date of conception, and ordered by date of conception (year 2006 onwards).
- Trend detection is now run using 10 years of data (where available), as opposed to 5 years of data. (year 2005 monitoring onwards)
- The output of the trend analysis shows observed cases grouped in 2 year intervals, e.g. 1996-97, 1998-99, 2000-01, 2002-03 and 2004-05. A minimum of 5 EXPECTED cases in each 2 year period is needed to be included in the trend analysis. (year 2005 monitoring onwards)
- The cluster output now includes a summary of trend test results run on the same five years of the cluster monitoring, to establish if a cluster could also be described as a trend. (year 2005 monitoring onwards)
- Chromosomal anomalies excluded from the statistical monitoring of non-chromosomal subgroups (year 2004 monitoring onwards)

- Cluster detection run by estimated date of conception, instead of date of birth/delivery, unless date of conception is unavailable. See EUROCAT Statistical Monitoring Protocol http://www.eurocat-network.eu/content/Stat-Mon-Protocol-2004.pdf (year 2004 monitoring onwards)
- Instead of just showing the most significant cluster in each anomaly subgroup, we now show all significant clusters, which may overlap in time (year 2004 monitoring onwards)
- Heterogeneous large subgroups (e.g. digestive system) are not analysed for clusters. (year 2004 monitoring onwards)
- We only report clusters within or overlapping the last two years of data sent by your registry (i.e. "new" clusters), and only clusters of less than 18 months length.(year 2004 monitoring onwards)

3. Use of the EUROCAT Data management Program (EDMP) at local level

Registries should be performing monitoring earlier, and may need to consider smaller geographical areas for monitoring. The EDMP has been designed to facilitate this.

Trend tests.

Registries may wish to use the EDMP to expand the trend tests run centrally e.g. use a different period of years (e.g. since beginning of registry or including a more recent year), or congenital anomaly subgroups outside the selected subgroups for monitoring (these "user defined subgroups" can be defined within the EDMP)

Cluster detection

Local monitoring for clusters can be run more frequently using the most recently ascertained data. As a guide, local registries should run the EDMP statistical monitoring program at least every 6 months and as early as possible after data collection is complete (apart from late diagnosed cases).

Local registries can run cluster detection in geographical sub-areas of their registry area, by using the EDMP "user defined LOCATION subgroup", located under the REPORTS function. Registries must also enter the total births for the user defined registry sub-area.

Local registries can also choose to run cluster monitoring on non-standard anomaly subgroups of interest to them ("user defined subgroups" can be defined within the EDMP).

The time period of the scan is important and may affect the results. The reasons Central Registry has chosen a five year period are given above. Registries scanning more recent data every 6 months are recommended to add the extra months available to the basic 5 year period. Remember that dates of conception end 9 months before the last birth month available. Which clusters are detected and their statistical significance will depend on the number of years scanned, which is an a priori protocol decision to be made before running the software (i.e. do not make the cluster "disappear" or "appear" by trying many different time periods, as this is statistically invalid).

Clusters and trends identified locally should be investigated in the same way as those identified by central monitoring (see section 4), and reported at the following Registry Leaders Meeting and in the Annual Statistical Monitoring Report.

Following preliminary investigations, plausible clusters and trends not resulting from data quality errors can be reported to central registry for communication to all local registries for further investigation (ie. are similar clusters and trends occurring elsewhere). In this way the situation across Europe may be monitored for early detection of possible new teratogens.

4. How to investigate trends and clusters identified by statistical monitoring

See Appendix 5 for examples of the output available describing the results of the statistical monitoring.

The results of all cluster investigations in local registries will be part of our report to the EC and will be available on the open website http://www.eurocat-network.eu/CLUSTERSAndTRENDS/StatisticalMonitoring/StatisticalMonitoring-2007

Note that clusters arising from statistical monitoring are a special situation. Guidelines for investigating clusters more generally (e.g. those reported to you from the community or health professionals) are part of the EUROCAT Cluster Advisory Service http://www.eurocat-network.eu/CLUSTERSAndTRENDS/ClusterAdvisoryService/HowUnusualisanObservedCluster?

4.1 Guidelines for the preliminary investigation of trends

Concentrate your investigations on the increasing trends and also the decreasing trends detected at Pan Europe level in your registry. Report the results of your investigations to the RLM and to Central Registry.

Note also that looking at downward trends and heterogeneity over time can help you with data quality monitoring.
Consider the following, consulting with clinicians or others where appropriate:

- Case verification
    - o Confirmed and accurate diagnoses?
    - o Duplicates?
    - o Resident within region? (truly population-based?)

- Print out a graph of the yearly prevalence (see Appendix 4) - is the trend gradual or a steep change? When does the trend appear to begin?
- Has there been a change in definition or diagnosis, or diagnostic methods e.g. increasing use of prenatal or postnatal ultrasound?
- Have there been changes in how cases are reported to the register?
- Is the trend found across all reporting hospitals?
- Is there a similar trend for any other anomalies?
- Is the trend found in isolated or multiply malformed cases?
- Have there been changes in register population?
- Are there any known changes in the risk factors for this anomaly?
- Have any other registers experienced a similar trend for this anomaly?
- For upward trends; is the prevalence in your registry at the end of the time period above the EUROCAT average?
- For downward trends; is the prevalence in your registry at the end of the time period below the EUROCAT average?

4.2 Guidelines for the preliminary investigation of clusters (see also Appendix 4)

Each year, clusters are divided into "new" clusters, "continuing" clusters and "old" clusters. New clusters are those which have not been detected previously. Continuing clusters are those which were detected the previous year but have continued in time. These are particularly important to investigate. Old clusters are those which were detected and investigated the previous year, but have not continued.
Central Registry alerts you to new and continuing clusters. Make sure that you look at the full 5-year timeline for the congenital anomaly subgroup of interest, as this shows the time distribution of all cases.

- Case verification
  - Confirmed and accurate diagnoses?
  - Duplicates?
  - Confirmed to be resident within region? (truly population-based?)
- Diagnostic dimension:
  - How heterogeneous are the diagnoses? Are cases isolated, multiply malformed, syndromes? Any family history recorded?
  - Do any other anomalies have clusters at the same time?
- Space dimension:
  - Are they clustered near each other within region?
  - Do they come from a single hospital?
  - Do other regions have a cluster at a similar time? (use EUROCAT communication to query other registries).
  - NB. The aim is to describe the cluster in terms of its spatial characteristics, giving clues as to possible causes for further investigation. For example, a new drug on the market may not show spatial concentration, whereas a local chemical pollution accident would be expected to show spatial concentration.
- Time dimension:
  - Is the cluster part of a longer term trend identified by the trend analysis? (if so, investigate as trend rather than as cluster)
  - When does the increased risk appear to start and end – a longer period than the dates of the most statistically significant cluster itself? Look at other clusters in the cluster group to get an idea of the extent of the cluster.
  - Look at the timeline graph (found in the Cluster adobe file). Consider evidence that the cluster started earlier than the last 2 years of data, and observe when the greatest number of excess cases occurred.
  - If cluster is based on date of birth rather than date of conception, is it likely, making assumptions about gestational age of cases within and outside the cluster, that the cluster would also appear if analysed by date of conception?
- Diagnostic & reporting factors:
  - Could a change in diagnostic methods, training, personnel or reporting practice have caused the cluster? This might be particularly suspected if only one hospital is involved, and for anomaly subgroups which vary widely in severity
  - Does the registry have a lower rate before the cluster compared to other registries? Check EUROCAT website for prevalence in other registries (http://www.eurocat-network.eu/ACCESSPREVALENCEDATA/PrevalenceTables)

  - If there are a very large number of cases in the cluster in a very short time period, it is unlikely to be due to diagnostic factors.
- Aetiological factors:
  - Which factors have been investigated?– choice of factors to investigate depends on type of anomaly
  - Which factors have been looked at within the registry database (list variables) and outside the registry database and do any of these appear to explain the cluster?
- Local context:
  - Was there local awareness of the cluster before it was found by central statistical monitoring, either by local EDMP monitoring or other means?
  - Had anyone outside the registry in your region (e.g. local community or health professional) previously been aware of the cluster?
  - Are there any local concerns about environmental exposures which may need investigation?

If investigation of clusters identifies data errors (e.g. incorrect diagnoses, incorrect dates of birth) these errors should be corrected and updated data included in the next data transmission to Central Registry. A record of these errors should be included in the local cluster report sent to Ruth Greenlees at Central Registry (email r.greenlees@ulster.ac.uk).

Recommendation:
Follow up all cluster cases to their current age for further diagnostic information and family history. For clusters of chromosomal anomalies exact karyotype should be reported for all cases in the cluster. If it is not already normal practice, registries should go back to original medical records for cluster cases. When a cluster is confirmed and recommended for continued surveillance registries should organise to do this surveillance earlier than the CR system.

4.3 Reporting the results of investigations to Central Registry

The following templates have been designed to assist registries with initial investigations into clusters and trends.

Cluster Template

Statistical Monitoring Investigations (For 2008-2012 data)
Run at Central Registry, March 2014

< Name of Registry>

Summary of Clusters for your registry		
Anomaly	**Cluster by**	**Comments**
Name of anomaly	Date of Conception or Date of Birth	New or Continuing cluster

Please provide a written report for *each* cluster and send report to Ruth Greenlees at r.greenlees@ulster.ac.uk following the suggested format below: The questions are explained in the "guidelines for the preliminary investigation of clusters" (Section 4.2 of Statistical Monitoring Protocol available at http://www.eurocat-network.eu/clustersandtrends/statisticalmonitoring/statisticalmonitoring-2012 or attached at the bottom of this document for your convenience).

Please type as much as is necessary in the tables below. The boxes will expand to accommodate the text.

If you would like to consult the EUROCAT Taskforce for the Evaluation of Clusters (TEC) about any of the clusters detected in your registry please contact the chair, Vera Nelen at the following address vera.nelen@pih.provant.be with copies to be sent to Nichola McCullough (secretary of the TEC) n.mccullough@ulster.ac.uk and Ruth Greenlees r.greenlees@ulster.ac.uk.

Neural Tube Defects	**Methods and results of case verification**
	Dimensions Diagnostic dimension: Spatial dimension: Time dimension:
	Methods and results of any investigations as to whether changes in diagnostic or reporting practices might have contributed to the cluster.
	Aetiological factors examined and result. Please include the following information: • **Which factors have been investigated?** • **Which of these factors are recorded within the registry database (please list variables)?** • **Which of these factors are NOT recorded within the registry database (please list variables)?** **Do any of these appear to explain the cluster?**
	Local context
	Conclusion: **Do you consider the cluster 'explained' by your preliminary investigation? Yes/No.** **If yes, give a summary of your explanation.** **If no,** **-Does the cluster require a further period of surveillance before a decision is made to investigate further? Why?** **OR**

	-Is there going to be further aetiological/other investigation? Please give details.
	Which public health authorities have been or will be notified about this cluster? Please give details.

Has your registry used the EDMP statistical monitoring function in the last year to look for clusters or trends in more recent data, or for different anomaly subgroups, or any other purpose? Yes/No.

If yes, please give details.

If no, can you please tell us why you do not use the EDMP statistical monitoring function?

N.B. A summary of local monitoring will be included in the next Annual Statistical Monitoring Report.

In last year's statistical monitoring which used 2007-2011* data we detected a new cluster in subgroup <insert name> We would be interested to know what the Public Health Authority response was to this.

*Please note time period

Statistical Monitoring Investigations (up to 2012 data)
Run at Central Registry, March 2014.

Preliminary investigation of trends

Please investigate **the increasing (/) and decreasing (\) trends detected at Pan Europe level** (tables 1a and 2a) using the Guidelines for the preliminary investigation of trends, section 4.1 of the Statistical Monitoring Protocol available on the EUROCAT website or attached here for your convenience. Table 3a contains the trends in your registry not occurring at Pan Europe level.

Increasing Trends

1. Please select an appropriate code from the list below and enter into the appropriate column in Table **1a**

A: Changes in case ascertainment (data quality)
B: Changes in local or central registry methods e.g. definitions and inclusion criteria
C: Changes in diagnostic methods
D: Trend confirmed, due to known demographic changes
E: Trend confirmed, investigation ongoing
F: Trend confirmed, further surveillance proposed before more detailed investigation
G: Not real trend when additional years added or heterogeneous subgroup
H: No report or clear interpretation of preliminary investigations sent

2. Add an explanation

3. Fill in Table **1b** 'To which Public Health authorities will the results of increasing trends be reported?'

Please type as much as is necessary in the questionnaire attached – the boxes will expand to accommodate the text.

Decreasing Trends

Complete this table using the same coding system (A-G) listed under point 1 above.
Please also provide a summary explanation of the decreasing trend.
If any decreasing trends are to be reported to the Public Health authorities complete Table **2b.**

Trends in your local Registry

The increasing and decreasing trends that have been found in your registry (but not listed in the Pan Europe tables) are listed in Table 3a. If these are of particular interest to your registry and you would like to investigate them and share your findings complete Table 3a using points 1 and 2 as above.
If any increasing or decreasing trends are to be reported to the Public Health authorities complete Table 3b.

<Name of Registry> Increasing and Decreasing Trends 2003-2012

1a Increasing trends shown at Pan Europe level

			To be completed by registry	**To be completed by registry**
	Anomaly	**Increasing Trends**	**Code A,B,C,D, E,F,G,**	**Summary Explanation (Please attach full report)**

1b To which Public Health authority will the results of increasing trends be reported. (Please give details of how you will be reporting these results regionally and/or nationally)

2a Decreasing trends shown at Pan Europe level

			To be completed by registry	**To be completed by registry**
	Anomaly	**Decreasing Trends**	**Code A,B,C,D, E,F,G,**	**Summary Explanation (Please attach full report)**

2b To which Public Health authority will the results of decreasing trends be reported. (Please give details of how you will be reporting these results regionally and/or nationally)

3a Trends at individual registry level (not already listed in Pan Europe tables)

			To be completed by registry	To be completed by registry
	Anomaly	**Type of Trend**	**Code A,B,C,D, E,F,G,**	**Summary Explanation (Please attach full report)**

3b To which Public Health authority will the results of trends be reported. (Please give details of how you will be reporting these results regionally and/or nationally)

APPENDIX 1:

Down syndrome, Edward syndrome, Patau syndrome: Adjusting trends for in-utero survival to 20 weeks gestational age and maternal age

Adjusting for in-utero survival

1. Miscarriages occurring prior to 20 weeks are not included in EUROCAT. Down, Edward and Patau syndrome pregnancies are associated with high fetal loss rates. Therefore pregnancies affected with these syndromes that are subsequently terminated prior to 20 weeks gestation may not have survived to 20 weeks gestation. Increasing prenatal screening, diagnosis and subsequent terminations therefore will increase the number of diagnoses of these syndromes.
2. The number of terminations that would have been viable at 20 weeks gestation should be used in trend analysis rather than the observed number of terminations. These are calculated using the Fetal Survival Correction Factors for each trisomy according to maternal age and gestational age that are given in Tables 1-3.
3. The trend analysis is performed on the number of livebirths, still births and terminations that would have been viable at 20 weeks gestation

Table 1 Probability of survival to 20 weeks according to maternal age and gestation for **Down syndrome**
(From G Savva, personal communication)

Maternal	Gestation (weeks)										
age (years)	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
25	0.92	0.93	0.94	0.95	0.98	0.98	0.98	0.99	0.99	1.00	1.00
26	0.91	0.93	0.94	0.95	0.97	0.98	0.98	0.99	0.99	1.00	1.00
27	0.91	0.93	0.94	0.95	0.97	0.98	0.98	0.99	0.99	1.00	1.00
28	0.91	0.93	0.94	0.95	0.97	0.97	0.98	0.99	0.99	1.00	1.00
29	0.91	0.92	0.94	0.94	0.97	0.97	0.98	0.99	0.99	1.00	1.00
30	0.90	0.92	0.93	0.94	0.97	0.97	0.98	0.99	0.99	1.00	1.00
31	0.90	0.92	0.93	0.94	0.97	0.97	0.98	0.99	0.99	1.00	1.00
32	0.90	0.92	0.93	0.94	0.97	0.97	0.98	0.99	0.99	1.00	1.00
33	0.89	0.91	0.93	0.94	0.97	0.97	0.98	0.99	0.99	1.00	1.00
34	0.89	0.91	0.93	0.93	0.97	0.97	0.98	0.98	0.99	1.00	1.00
35	0.89	0.91	0.92	0.93	0.97	0.97	0.98	0.98	0.99	1.00	1.00
36	0.88	0.91	0.92	0.93	0.96	0.97	0.98	0.98	0.99	1.00	1.00
37	0.88	0.90	0.92	0.93	0.96	0.97	0.98	0.98	0.99	1.00	1.00
38	0.88	0.90	0.92	0.93	0.96	0.97	0.98	0.98	0.99	1.00	1.00
39	0.87	0.90	0.91	0.92	0.96	0.96	0.98	0.98	0.99	1.00	1.00
40	0.87	0.89	0.91	0.92	0.96	0.96	0.98	0.98	0.99	1.00	1.00
41	0.86	0.89	0.91	0.92	0.96	0.96	0.98	0.98	0.99	1.00	1.00
42	0.86	0.89	0.91	0.92	0.96	0.96	0.97	0.98	0.99	1.00	1.00
43	0.86	0.88	0.90	0.91	0.96	0.96	0.97	0.98	0.99	1.00	1.00
44	0.85	0.88	0.90	0.91	0.95	0.96	0.97	0.98	0.99	1.00	1.00
45	0.85	0.88	0.90	0.91	0.95	0.96	0.97	0.98	0.99	1.00	1.00
46	0.84	0.87	0.89	0.91	0.95	0.96	0.97	0.98	0.99	0.99	1.00
47	0.84	0.87	0.89	0.90	0.95	0.95	0.97	0.98	0.99	0.99	1.00

48	0.83	0.87	0.89	0.90	0.95	0.95	0.97	0.98	0.99	0.99	1.00
49	0.83	0.86	0.88	0.90	0.95	0.95	0.97	0.98	0.99	0.99	1.00
50	0.82	0.86	0.88	0.89	0.95	0.95	0.97	0.97	0.99	0.99	1.00
Maternal age unknown	0.89	0.91	0.92	0.93	0.97	0.97	0.98	0.98	0.99	1.00	1.00

Table 2 Probability of survival to 20 weeks according to gestation for **Patau syndrome**

Gestation (weeks)										
10	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
0.77	0.79	0.8	0.83	0.85	0.85	0.88	0.9	0.9	0.95	1

Table 3 Probability of survival to 20 weeks according to gestation for **Edward syndrome**

Gestation (weeks)										
10	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
0.73	0.74	0.75	0.76	0.81	0.86	0.87	0.93	0.94	0.96	1

Adjusting for population changes in maternal age

1. The risk of a Down, Edward or Patau syndrome pregnancy increases considerably with increasing maternal age. Therefore changes in maternal age distribution over time need to be adjusted for prior to the trend analysis being performed.
2. For Down syndrome (DS) calculate the expected numbers of DS live births according to the maternal age distribution of mothers by multiplying the age specific live birth rates in Table 4 by the number of births in the population to mothers of that age.
3. For each year calculate the expected numbers of DS live births in any one year divided by the total expected number of DS live births in the whole 5 year time period. This is the DS weight
4. Calculate the total numbers of observed population births in the whole 5 year period
5. Multiply the total population births by the DS weight to obtain an age adjusted numbers of population births for each year
6. The trend analysis is performed on the number of livebirths, still births and terminations that would have been viable at 20 weeks gestation and the adjusted numbers of population births,
7. Repeat steps 2 to 7 for Edward and Patau syndromes using the rates cited in Table 4

Table 4: Livebirth rates per 1,000 births for Down, Edward and Patau syndrome

	Live birth rate per 1000 births		
Maternal age group (years)	Patau Syndrome	Edward Syndrome	Down Syndrome
<20	0.073014	0.111105	0.667844
20-24	0.074271	0.112885	0.699194
25-29	0.081107	0.122263	0.839473
30-34	0.116472	0.170694	1.476398
35-39	0.304307	0.477975	4.705364
40-44	0.877285	2.00049	15.18284
45 +	1.551942	5.326087	30.82091

Table 4 is calculated using formulas in the maternal age-specific live birth prevalence of trisomies 13 and 18 compared to trisomy 21 (Down syndrome)
George M. Savva, Kate Walker and Joan K. Morris (Prenatal Diagnosis 2009) for birth rate plus weighting by births in England and Wales from 1989-2007

APPENDIX 2.

Scan statistic – procedure for calculation

Scan statistic formula based on the formula defined by Nagarwalla (1996).

Data

The date for each case is provided. A start and end date are specified and each case date is represented as a fraction of the period of interest.

$$fraction_{case} = \frac{date_{case} - date_{start}}{date_{end} - date_{start}}$$

Methods

Calculation of lambda

For a given subset of cases, it is possible to calculate the test statistic lambda as follows:

$$\lambda = \left(\frac{n}{r}\right)^{n}\left(\frac{r-n}{n}\right)^{r-n}\left(\frac{1}{d}\right)^{n}\left(\frac{1}{1-d}\right)^{r-n}$$

Where *r* is the total number of cases, *n* is the number of cases in the subset, also called the scanning window, and *d* is the date fraction spanned by the subset of cases. Typically a minimum scanning window of 5 is used. Lambda is calculated for every possible subset of *n* consecutive cases for *n* = 5,…, *r*

The first step is to generate simulated datasets with random numbers. For each simulation, the lambda for each subset is calculated and the largest lambda is recorded. After, for example, 999 iterations the lambdas are ordered by size from smallest to largest and the 95th percentile is noted as λ_{sig}. In order to save computing time, and to give accurate p-values based on sufficient iterations, a look-up table was created for all *r* between 7 and 700 cases, using 100,000 iterations for *r* under 200 cases and 50,000 iterations for *r* over 200 cases. For *r* of more than 700 cases, Monte Carlo simulations (999 iterations) are used to create an array of lambdas.

For the real dataset, the lambda for each subset of cases is calculated. If the lambda is greater than or equal to λ_{sig} then the cases are designated as a significant cluster and the details of the cluster, such as start date and duration, are recorded. The p-value is recorded as the position of lambda within the simulated lambdas.

As a first step, a 'quick' check is performed to test whether the most significant cluster is significant at p<=0.1. If no significant cluster, then move on to next anomaly subgroup. If significant cluster is found then a full check is performed for all clusters with a p-value less than 0.06.

Group allocation

The final step is to allocate clusters to groups based on their overlap. The cluster with the largest lambda is identified and is allocated to the first group. Each ungrouped cluster is then tested for overlap with the first cluster. Overlap is calculated as the number of cases appearing in both clusters divided by the number of cases appearing in either cluster. If the overlap is greater than or equal to 0.75 then both are given the same group label. If any clusters remain ungrouped then the cluster with the largest lambda is identified and given a new group label and the procedure is repeated until all clusters are grouped.

Nagarwalla, N. (1996). A scan statistic with a variable window. Statistics in Medicine 15, 845-850

APPENDIX 3.

List of congenital anomaly subgroups for monitoring.

The EUROCAT congenital anomaly subgroups are defined in EUROCAT Guide 1.3, Chapter 3.3 (http://www.eurocat-network.eu/content/EUROCAT-Guide-1.3.pdf), and are analysed in the following ways:

1. Prevalence by outcome of pregnancy, by registry and year (or combined registries/years). All cases and All cases excluding genetic conditions[4].
2. Analysis of trends, all outcomes of pregnancy combined. Genetic conditions are excluded from the statistical monitoring of all other subgroups.
3. Detection of clusters, all outcomes of pregnancy combined. Genetic conditions are excluded from the statistical monitoring of all other subgroups.

EUROCAT Subgroups	**Prevalence by pregnancy outcome, registry, year**	**Include in monitoring of trends**	**Include in monitoring of clusters**
All anomalies	✓	✓	**NO**
All anomalies excluding genetic conditions	✓	✓	**NO**
Nervous system	✓	**NO**	**NO**
Neural Tube Defects	✓	✓	✓
Anencephalus and similar	✓	✓	✓
Encephalocele	✓	✓	✓
Spina Bifida	✓	✓	✓
Hydrocephalus	✓	✓	✓
Microcephaly	✓	✓	✓
Arhinencephaly / holoprosencephaly	✓	✓	✓
Eye	✓	**NO**	**NO**
Anophthalmos / microphthalmos	✓	✓	✓
Anophthalmos	✓	✓	✓
Congenital cataract	✓	✓	✓
Congenital glaucoma	✓	✓	✓
Ear, face and neck	✓	**NO**	**NO**
Anotia	✓	✓	✓
Congenital heart defects (CHD)	✓	✓	**NO**
Severe CHD	✓	✓	✓
Common arterial truncus	✓	✓	✓
Transposition of great vessels	✓	✓	✓
Single ventricle	✓	✓	✓
VSD	✓	✓	✓
ASD	✓	✓	✓
AVSD	✓	✓	✓

[4] Genetic syndromes/ microdeletions, skeletal dysplasias chromosomal anomalies

Tetralogy of Fallot	✓	✓	✓
Tricuspid atresia and stenosis	✓	✓	✓
Ebstein's anomaly	✓	✓	✓
Pulmonary valve stenosis	✓	✓	✓
Pulmonary valve atresia	✓	✓	✓
Aortic valve atresia/stenosis	✓	✓	✓
Hypoplastic left heart	✓	✓	✓
Hypoplastic right heart	✓	✓	✓
Coarctation of aorta	✓	✓	✓
Total anomalous pulm venous return	✓	✓	✓
PDA as **only** CHD in term infants (GA +37 weeks)	✓	✓	✓
Respiratory	✓	**NO**	**NO**
Choanal atresia	✓	✓	✓
Cystic adenomatous malf of lung	✓	✓	✓
Oro-facial clefts	✓	**NO**	**NO**
Cleft lip with or without cleft palate	✓	✓	✓
Cleft palate	✓	✓	✓
Digestive system	✓	**NO**	**NO**
Oesophageal atresia with or without tracheo-oesophageal fistula	✓	✓	✓
Duodenal atresia or stenosis	✓	✓	✓
Atresia or stenosis of other parts of small intestine	✓	✓	✓
Ano-rectal atresia and stenosis	✓	✓	✓
Hirschsprung's disease	✓	✓	✓
Atresia of bile ducts	✓	✓	✓
Annular pancreas	✓	✓	✓
Diaphragmatic hernia	✓	✓	✓
Abdominal wall defects	✓	**NO**	**NO**
Gastroschisis	✓	✓	✓
Omphalocele	✓	✓	✓
Urinary	✓	**NO**	**NO**
Bilateral renal agenesis including Potter syndrome	✓	✓	✓
Renal Dysplasia	✓	✓	✓
Congenital hydronephrosis	✓	✓	✓
Bladder exstrophy and/or epispadia	✓	✓	✓
Posterior urethral valve and/or prune belly	✓	✓	✓
Genital	✓	**NO**	**NO**
Hypospadia	✓	✓	✓
Indeterminate sex	✓	✓	✓
Limb	✓	**NO**	**NO**

Limb reduction	✓	✓	✓
Upper limb reduction	✓	✓	✓
Lower limb reduction	✓	✓	✓
Complete absence of a limb	✓	✓	✓
Club foot - talipes equinovarus	✓	✓	✓
Hip dislocation and/or dysplasia	✓	✓	✓
Polydactyly	✓	✓	✓
Syndactyly	✓	✓	✓
Other anomalies/ syndromes			
Skeletal dysplasias	✓	✓	**NO**
Craniosynostosis	✓	✓	✓
Congenital constriction bands/amniotic band	✓	✓	✓
Situs inversus	✓	✓	✓
Conjoined twins	✓	✓	✓
Congenital skin disorders	✓	✓	✓
Teratogenic syndromes with malformations	✓	✓	**NO**
Fetal alcohol syndrome	✓	✓	✓
Valproate syndrome	✓	✓	✓
Maternal infections resulting in malformations	✓	✓	✓
Genetic syndromes + microdeletions	✓	✓	**NO**
Sequences	✓	**NO**	**NO**
Chromosomal	✓	✓	**NO**
Down syndrome	✓	✓	✓
Patau syndrome/trisomy 13	✓	✓	✓
Edward syndrome/trisomy 18	✓	✓	✓
Turner syndrome	✓	✓	✓
Klinefelter syndrome	✓	✓	✓
Down syndrome Adjusted	**NO**	✓	**NO**
Patau syndrome Adjusted	**NO**	✓	**NO**
Edward syndrome Adjusted	**NO**	✓	**NO**

APPENDIX 4

Investigating a cluster of birth defects
Elisabeth Robert-Gnansia, Lyon FRANCE

Investigations vary according to the anomaly of interest and local conditions. Elisabeth Robert has prepared notes to guide investigations of clusters arising from statistical monitoring, based on long experience in the Central East France register and elsewhere.

A cluster can be defined as a space-time aggregation of occurrences, in this context of birth defects. An example of such a cluster is the occurrence of 5 infants with a given malformation born in a geographic area during 4 months and with 3,000 annual births. If the overall rate for this malformation in the region is 1/6,000, it means that the expected number of cases during the 4 months is 0.17, and 5 were found. Such aggregations can have many causes. The reason for being interested in them is that the cases may have been caused by some local source of exposure. One often thinks of industrial pollution as a cause, but other factors may explain the cluster, including many artefactual events.

Clusters may be identified as a local observation by people living in a specific area, by health care workers, or by the routine surveillance of congenital malformations or other pregnancy outcomes. In rare cases, the detection of a cluster is forwarded from the news media, or a pressure group who may perceive that a specific source of pollution may cause birth defects and therefore a cluster must have occurred around that source. It then becomes our responsibility to investigate the identified cluster. Some review articles and papers on statistical methodology have questioned the usefulness of investigating clusters, and of monitoring programs in general for the detection of a newly introduced teratogen.

There are many arguments against cluster investigations. First, there is a great statistical probability that many clusters occur by chance alone, because there are many serious congenital malformations monitored routinely and repeated evaluations. Second, in evaluating situations in which an environmental agent has been evidenced as harmful, it appears that most clusters have occurred in areas where no registry was operative or where the hypothesis came from observations made by astute clinicians. Third, clusters are often alleged in relationship to a perceived environmental hazard, such as a toxic waste site, and the investigating team often must extend the investigation far beyond what is indicated scientifically in order to respond to community concerns.

Among the possible explanations for a cluster, one thinks first of a local harmful factor, but the actual cause may be different: local temporal variations in diagnosis, in ascertainment, local aggregation of genes, e.g. due to population migrations, demographic or socioeconomic variations, and finally a random phenomenon. Clusters are different to long time trends: a steep increase of urinary flow anomalies has occurred from the early 1980s, obviously due to better and earlier diagnosis through fetal ultrasonography. After having excluded all artefactual explanations, sometimes one nevertheless may be unable to answer the question "Is there a cluster?"

Examples can be given of surveillance events that may or may not be clusters: a marked increase in the prevalence at birth of hypospadias was observed in several registries in the world from

the end of the 1980s, but no clear cut explanation can be given: improved ascertainment of minor forms or real increase? An sharp increase of the incidence of gastroschisis has been observed as well in many western registries since the beginning of the 90s, the reality of which is much less questionable than the one of hypospadias, but no explanation has been found so far.

When a cluster is considered as likely, other questions are to be answered:

1. To follow up or not to follow up? The decision to follow-up means spending time and money, and run the risk of spreading rumours.

2. How to follow up?

This should be performed in 4 stages, which might be called (a) nosodetermination, (b) chronodetermination, (c) geodetermination, (d) etiodetermination.

The first stage (*nosodetermination*) consists in confirming the case status, with exact diagnoses, and definition of inclusion and exclusion criteria: it should be checked that the cluster is not due to inclusion of minor forms of the studied malformations, which were not included in the baseline data. This is especially true for limb reduction defects (inclusions of missing phalanges?) or hypospadias (distal forms). Also diagnostic methods or medial personnel might have changed (e.g. more trained ultrasonographist or neonatologist), and explain an increased number of cases.

The second stage (*chronodetermination*) consists in checking the clustering in time: dates of birth or of termination of pregnancy are to be clearly assessed. Gestational ages are to be taken into consideration, especially when dealing with a cluster arising over a short period of time.

The third stage (*geodetermination*) should check the clustering in space. Some malformed babies might be transferred in utero for a better management of a surgical malformation at birth. One should then eliminate the possibility of a concentration of cases in university hospitals that attract patients with rare malformations, by assessing correctly the place where the child's family actually lived during pregnancy.

The fourth stage (*etiodetermination*) is the most difficult one, and consists in collecting detailed exposure information on cluster cases. A more detailed form than the routine one is to be used in order to collect all this information. If an environmental exposure is suspected, one should try to study similarly exposed areas, and to set up a case-control study within the area (3). In any case, it is essential to continue the surveillance.

The experience of registries that have investigated numerous clusters of congenital malformations shows that:

- Clusters will occur and will be found if looked for
- Most clusters have technical explanations or are artefacts
- Most clusters will go away when you look them “in the eyes”
- Nevertheless, clusters may be important for the identification of hazards in the environment and we have to investigate them

To decide whether one should follow up a cluster or not is difficult and depends mainly on available resources. If one investigates a cluster, most likely no explanation will be found. A unique example of a routine cluster investigation that led to an environmental factor as a possible explanation is given by a study led in the county of Östergötland, in Sweden. A higher prevalence at birth of congenital malformations was noticed (1), and looking at data revealed that cardiovascular malformations (CVM) explained the differences in rates. A case-referent study was performed (2), which retrieved several known risk factors for CVM (maternal diabetes, body mass index over 29, involuntary childlessness, previous spontaneous abortion, first trimester exposure to thyroid drugs and NSAIDs). All the significantly high ORs were higher in the studied county than in the rest of Sweden. Geographic comparisons of CVM were made within the county (3), and the hypothesis arose that the clustering in time and space showed that drinking water chlorination might be a mild risk factor for CVM (4).

Acknowledgement
This summary was adapted from a lecture by Pr Bengt Källén (Lund), with permission.

References
1. Blomberg M, Selbing A, Kallen B.Congenital malformations in the southeast of Sweden--a registry study with validation. Acta Paediatr. 2000 Oct;89(10):1238-43 2. Cedergren MI, Selbing AJ, Kallen BA. Risk factors for cardiovascular malformation--a study based on prospectively collected data. Scand J Work Environ Health. 2002;28:12-7.
3. Cedergren M, Selbing A, Kallen B. Geographic variations in possible risk factors for severe cardiac malformations. Acta Paediatr. 2002;91:222-8.
4. Cedergren MI, Selbing AJ, Lofman O, Kallen BA. Chlorination byproducts and nitrate in drinking water and risk for congenital cardiac defects. Environ Res. 2002;89:124-30.

APPENDIX 5.

EUROCAT Data Management Program (EDMP) output – an explanation

For each registry, the results are output in:

I. An EXCEL file containing 7 worksheets (Read me, Summary, Trend, Long Term Trend, Clusters, Forest Plot Ordered by anomaly subgroup, Forest Plot ordered by percentage change estimate) . This must be examined first. See Figure 1a.
II. An Adobe file ("Long Trend_Registry name) containing graphs of anomaly subgroups with significant trends. See Figure 2
III. An Adobe file ("cluster_Registry name") containing a full case list of cases within the subgroup where a cluster was identified. See Figure 3.

I. EXCEL file:

It is important to read the EXCEL "Read me" instructions (first Sheet, see Figure 1a), as this explains some of the key elements of the Statistical Monitoring exercise.

The second sheet "Summary" lists all the significant results detected for the registry (see Figure 1b):

- Significant trend results (5 year period)
- Significant trend results (10 year period)
- Significant clusters (5 year period)

The third sheet "Trend" shows the five year trend results. Output is in the same format as explained below for "Long Term Trend".

Long-term (10 year) trend analysis results are in the fourth sheet "Long Term Trend" (see Figure 1c) – output shows:

i. The number of cases per subgroup per individual year, and the total number of cases over the time period.
ii. A Chi square test for trend giving the direction (slope increasing or decreasing) and percentage change per year of any linear trend, and the statistical significance (p value).
iii. A Chi square test for non-linear change reporting the Chi square statistic and the statistical significance (p-value).
iv. The last column presents the overall description of the identified trend/linear change.

Forest plots showing the average percentage changes in prevalence per year are included in the sixth and seventh sheets (see figures 1d and 1e)-the outputs show:

I. The estimated average annual percentage change in prevalence and 95% confidence intervals ordered by EUROCAT anomaly subgroup (figure 1d)
II. The estimated average annual percentage change and 95% confidence intervals for anomaly subgroups ordered by rate of change (figure 1e)

Cluster analysis results are in the fifth sheet "Clusters" (Figure 1f).

i. Type of cluster analysis run (date of conception or date of birth), the number of cases in the most significant cluster, the start and end date of most significant cluster, the

number of expected cases in the time period of the most significant cluster, and the level of statistical significance (p-value and lamda)

ii. The total number of valid cases within the subgroup (i.e. must have valid date of birth) and the proportion of cases with missing gestational age is presented.

iii. The next column explains if an excess of cases was reported (cluster) or if less cases than expected were reported (deficit)

iv. The last column shows the trend test result run on the same five years of the cluster monitoring, to establish if the cluster may be part of an overall trend.

II. Adobe file "Long Trend_Registry name" shows graphical displays of significant trends. The EUROCAT average prevalence per year (or per 2-year interval) is plotted on each graph so that a registry can see if it is above or below the average prevalence See Figure 2 below.

III. Adobe file "cluster_Registry name" gives more detail on all significant clusters. See Figure 3.

i. ALL cases in the anomaly subgroup both within and outside cluster are listed with local ID, date of conception, date of birth, gestational age (GA), estimated GA, and day case occurred.

ii. Lambda values for the most significant cluster are listed, along with the lambda values for all possible overlapping clusters. The highest lambda value indicates the most unusual cluster.

iii. Many clusters may overlap in time, with the inclusion or exclusion of individual cases changing their significance. The "most" significant cluster (highest "lambda" value) is listed first, followed by all significant clusters, with "cluster group" showing groups of highly overlapping clusters.

iv. A timeline shows the occurrence of all cases within the anomaly subgroup over the time period. A solid line displays the most significant cluster within the time period with a dotted line on either side showing the longest extent of the cluster group.

v. It is important to remember that if a cluster is detected using DATE OF CONCEPTION, the timeline represents the date of conception of those cases.

Figure 1a: Brief explanation of the key elements of Statistical Monitoring.

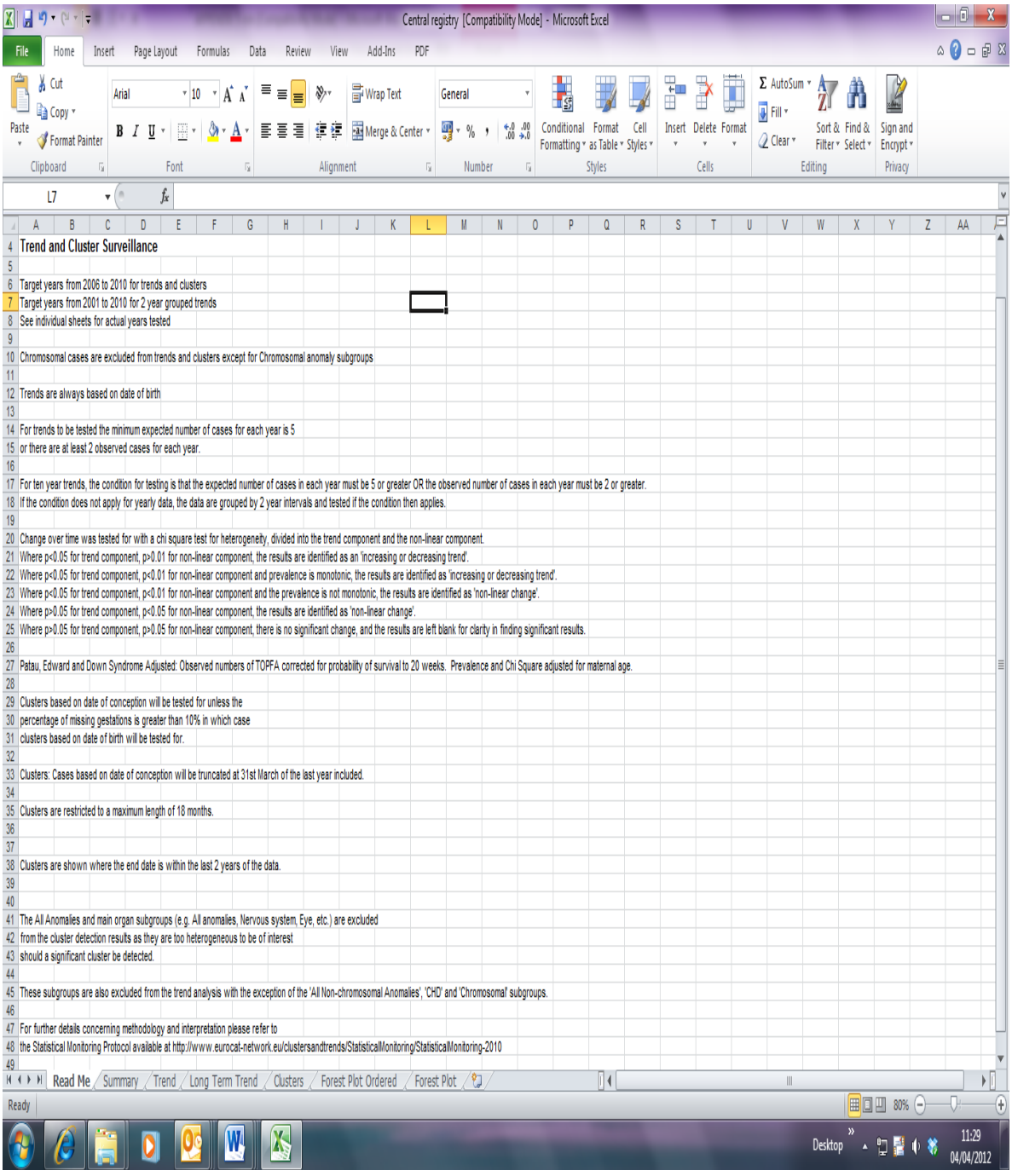
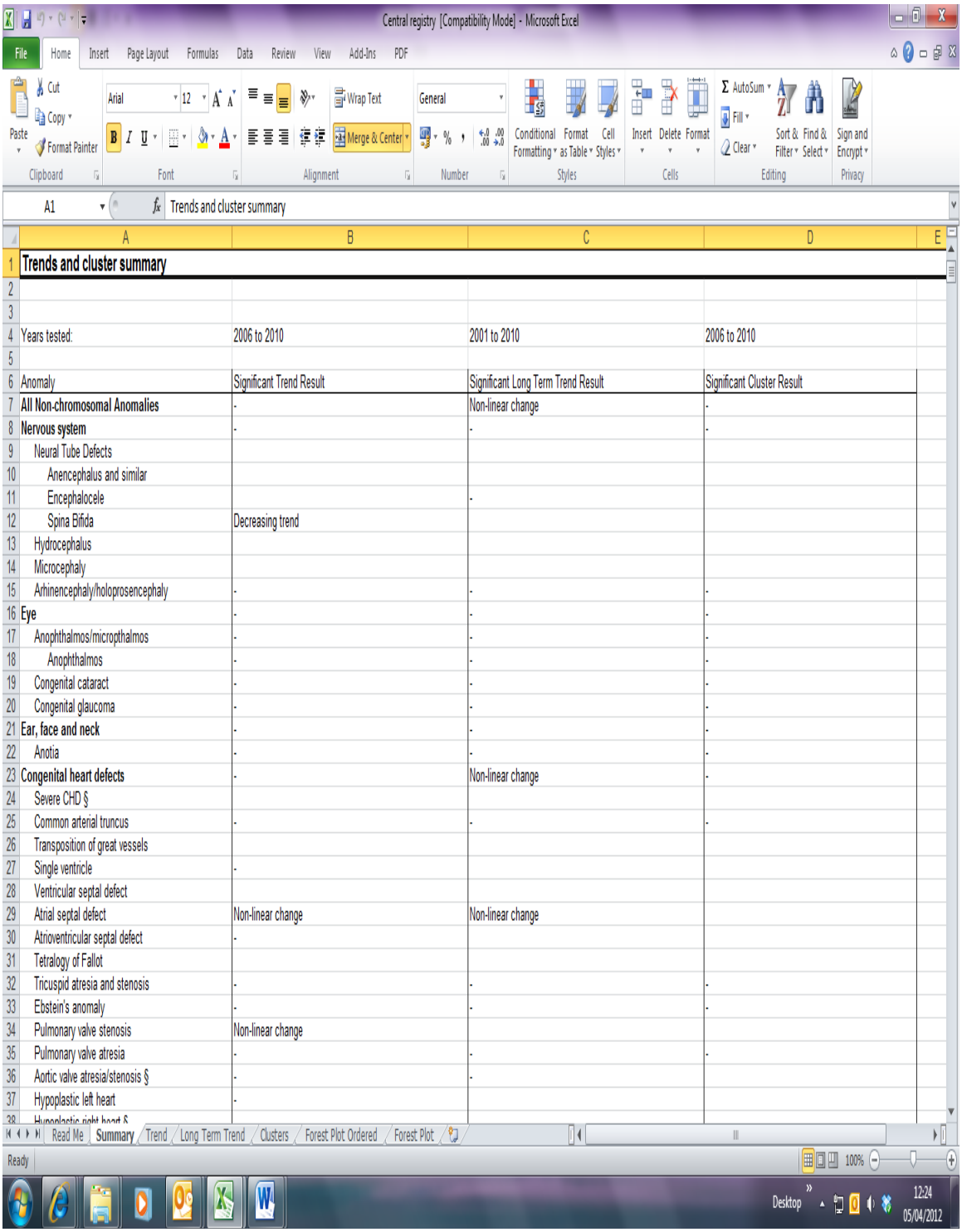


Figure 1b: Output lists all the significant trends and clusters identified in Statistical Monitoring.



Central registry [Compatibility Mode] - Microsoft Excel

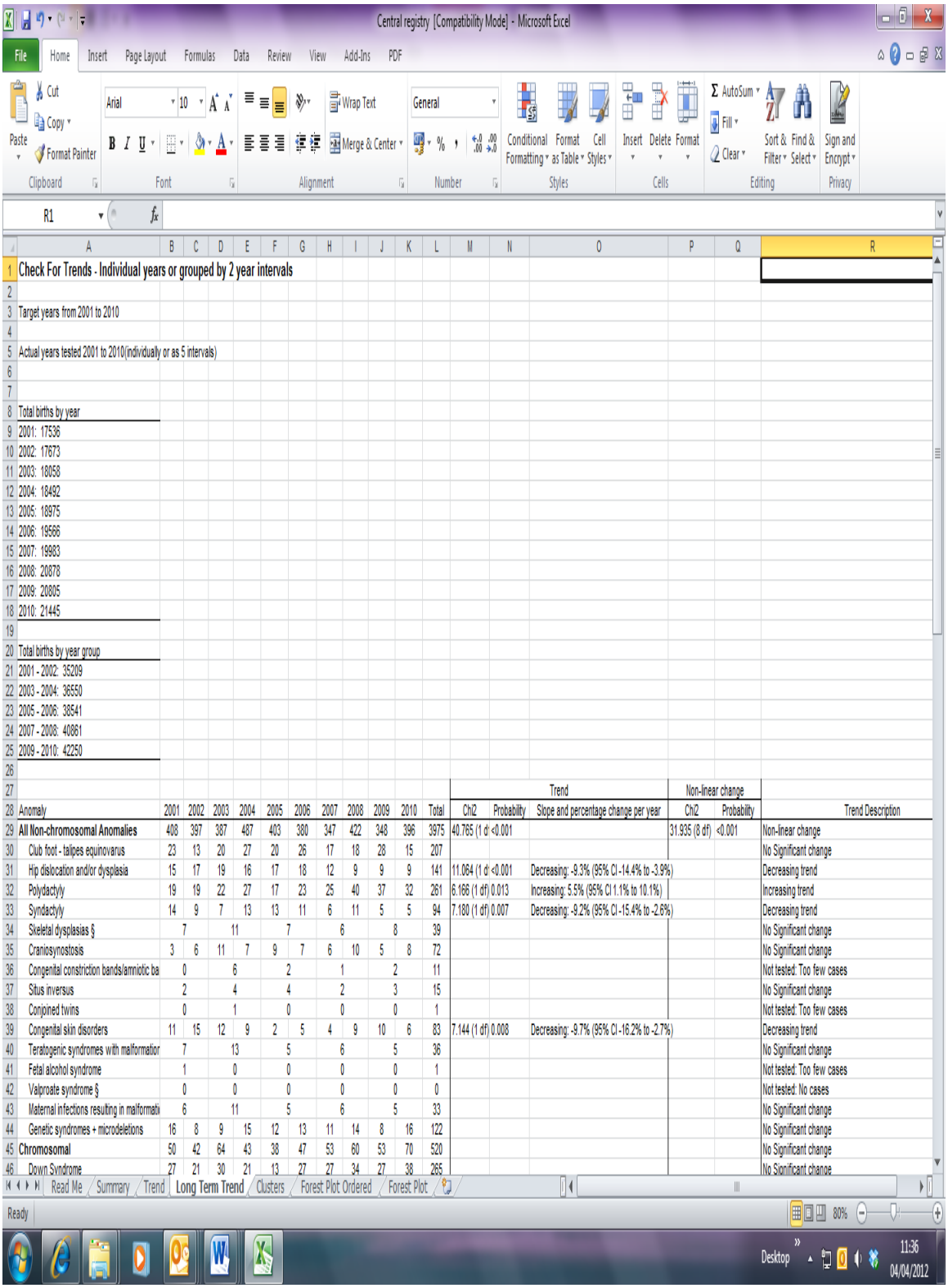
A1: Trends and cluster summary

	A	B	C	D
1	**Trends and cluster summary**			
2				
3				
4	Years tested:	2006 to 2010	2001 to 2010	2006 to 2010
5				
6	Anomaly	Significant Trend Result	Significant Long Term Trend Result	Significant Cluster Result
7	**All Non-chromosomal Anomalies**	-	Non-linear change	-
8	**Nervous system**	-	-	-
9	Neural Tube Defects			
10	Anencephalus and similar			
11	Encephalocele		-	
12	Spina Bifida	Decreasing trend		
13	Hydrocephalus			
14	Microcephaly			
15	Arhinencephaly/holoprosencephaly	-	-	-
16	**Eye**	-	-	-
17	Anophthalmos/micropthalmos	-	-	-
18	Anophthalmos	-	-	-
19	Congenital cataract	-	-	-
20	Congenital glaucoma	-	-	-
21	**Ear, face and neck**	-	-	-
22	Anotia	-	-	-
23	**Congenital heart defects**	-	Non-linear change	-
24	Severe CHD §			
25	Common arterial truncus	-	-	-
26	Transposition of great vessels			
27	Single ventricle	-		
28	Ventricular septal defect			
29	Atrial septal defect	Non-linear change	Non-linear change	
30	Atrioventricular septal defect	-		
31	Tetralogy of Fallot			
32	Tricuspid atresia and stenosis	-	-	-
33	Ebstein's anomaly	-	-	-
34	Pulmonary valve stenosis	Non-linear change		
35	Pulmonary valve atresia	-	-	-
36	Aortic valve atresia/stenosis §	-	-	
37	Hypoplastic left heart	-		
38	Hypoplastic right heart §			

Read Me | Summary | Trend | Long Term Trend | Clusters | Forest Plot Ordered | Forest Plot

Ready

Figure 1c: Output showing the results of the long term trend test analyses.



Central registry [Compatibility Mode] - Microsoft Excel

Check For Trends - Individual years or grouped by 2 year intervals

Target years from 2001 to 2010

Actual years tested 2001 to 2010(individually or as 5 intervals)

Total births by year

2001: 17536
2002: 17673
2003: 18058
2004: 18492
2005: 18975
2006: 19566
2007: 19983
2008: 20878
2009: 20805
2010: 21445

Total births by year group

2001 - 2002: 35209
2003 - 2004: 36550
2005 - 2006: 38541
2007 - 2008: 40861
2009 - 2010: 42250

												Trend			Non-linear change		
Anomaly	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	Total	Chi2	Probability	Slope and percentage change per year	Chi2	Probability	Trend Description
All Non-chromosomal Anomalies	408	397	387	487	403	380	347	422	348	396	3975	40.765 (1 df)	<0.001		31.935 (8 df)	<0.001	Non-linear change
Club foot - talipes equinovarus	23	13	20	27	20	26	17	18	28	15	207						No Significant change
Hip dislocation and/or dysplasia	15	17	19	16	17	18	12	9	9	9	141	11.064 (1 df)	<0.001	Decreasing: -9.3% (95% CI -14.4% to -3.9%)			Decreasing trend
Polydactyly	19	19	22	27	17	23	25	40	37	32	261	6.166 (1 df)	0.013	Increasing: 5.5% (95% CI 1.1% to 10.1%)			Increasing trend
Syndactyly	14	9	7	13	13	11	6	11	5	5	94	7.180 (1 df)	0.007	Decreasing: -9.2% (95% CI -15.4% to -2.6%)			Decreasing trend
Skeletal dysplasias §	7		11		7		6		8		39						No Significant change
Craniosynostosis	3	6	11	7	9	7	6	10	5	8	72						No Significant change
Congenital constriction bands/amniotic ba	0		6		2		1		2		11						Not tested: Too few cases
Situs inversus	2		4		4		2		3		15						No Significant change
Conjoined twins	0		1		0		0		0		1						Not tested: Too few cases
Congenital skin disorders	11	15	12	9	2	5	4	9	10	6	83	7.144 (1 df)	0.008	Decreasing: -9.7% (95% CI -16.2% to -2.7%)			Decreasing trend
Teratogenic syndromes with malformatior	7		13		5		6		5		36						No Significant change
Fetal alcohol syndrome	1		0		0		0		0		1						Not tested: Too few cases
Valproate syndrome §	0		0		0		0		0		0						Not tested: No cases
Maternal infections resulting in malformati	6		11		5		6		5		33						No Significant change
Genetic syndromes + microdeletions	16	8	9	15	12	13	11	14	8	16	122						No Significant change
Chromosomal	50	42	64	43	38	47	53	60	53	70	520						No Significant change
Down Syndrome	27	21	30	21	13	27	27	34	27	38	265						No Significant change

Figure 1d: Output showing the Forest plot representing estimated average annual percentage change in prevalence and 95% confidence intervals ordered by EUROCAT subgroup

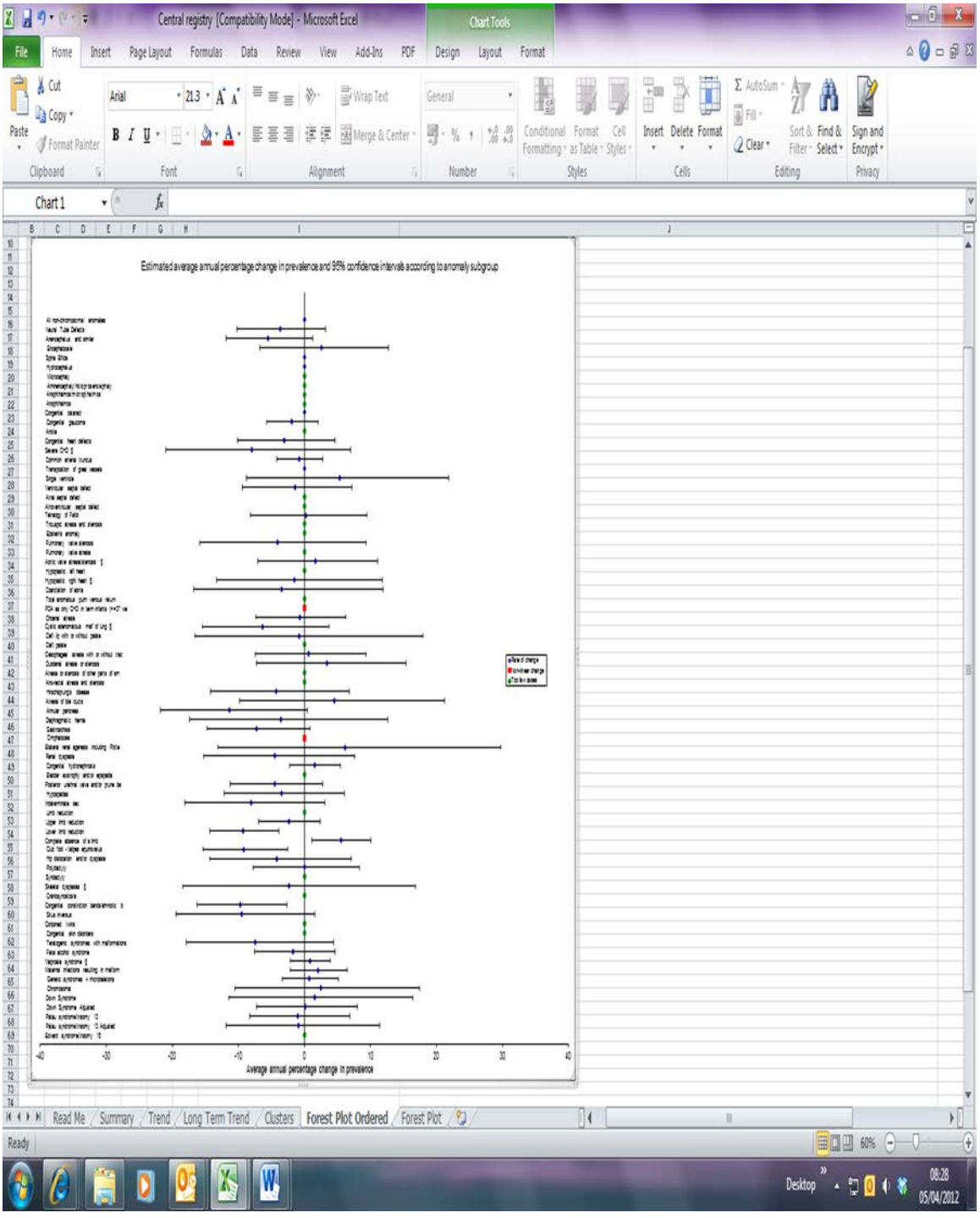


Figure 1e: Output showing the Forest plot representing estimated average annual percentage change and 95% confidence intervals for anomaly subgroups ordered by rate of change

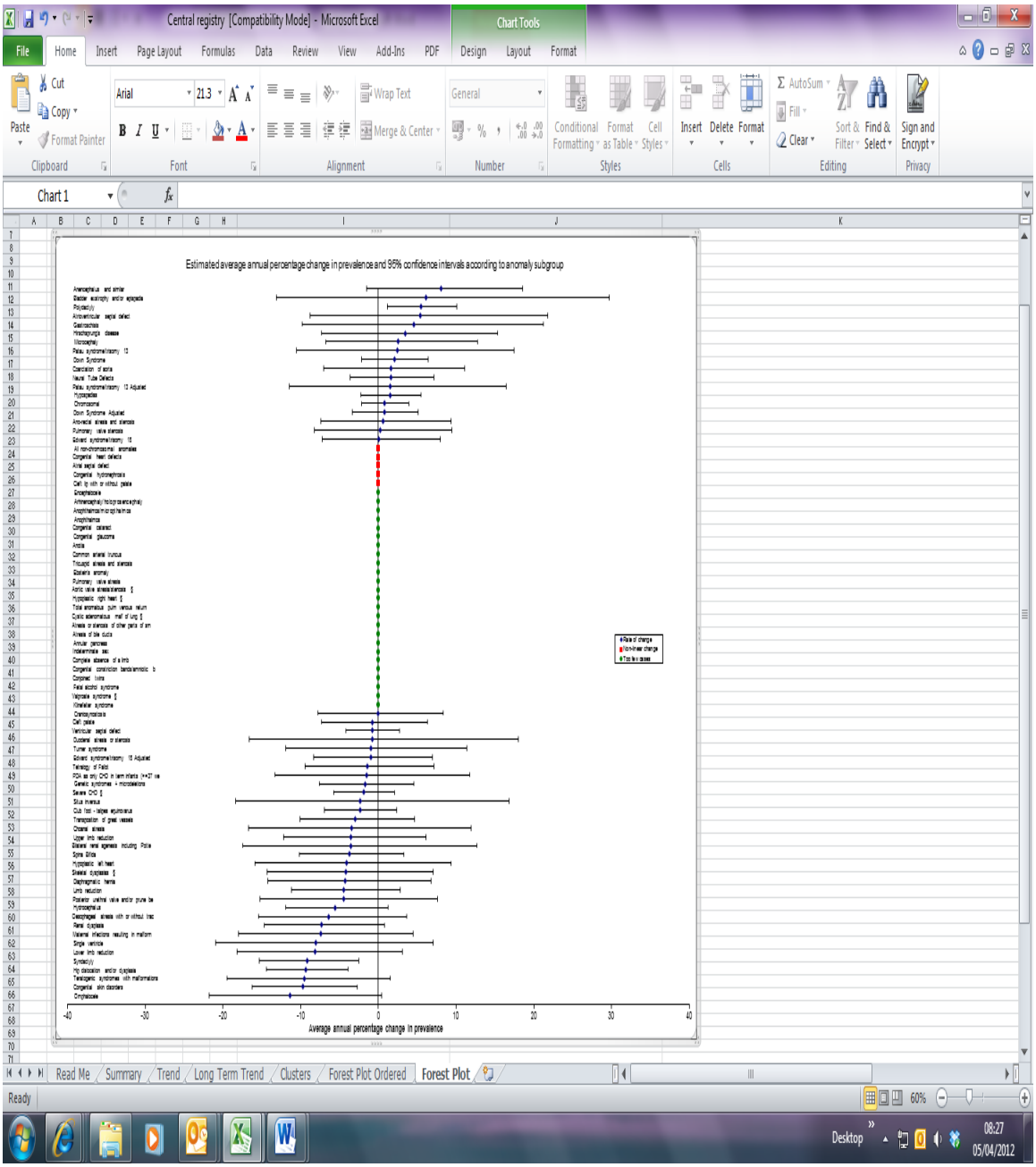
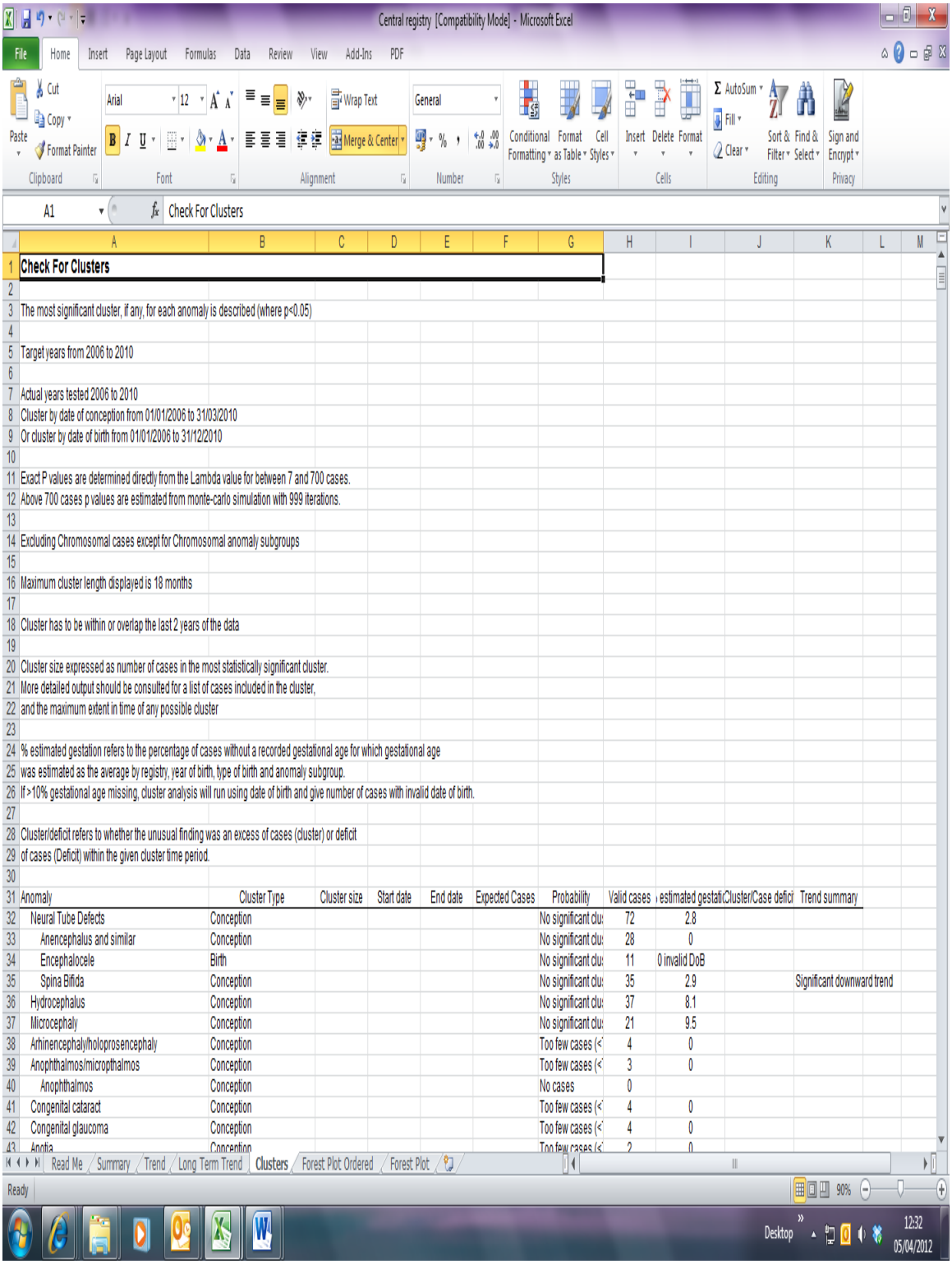


Figure 1f: Output showing the results of the cluster monitoring



Central registry [Compatibility Mode] - Microsoft Excel

A1: Check For Clusters

Check For Clusters

The most significant cluster, if any, for each anomaly is described (where p<0.05)

Target years from 2006 to 2010

Actual years tested 2006 to 2010
Cluster by date of conception from 01/01/2006 to 31/03/2010
Or cluster by date of birth from 01/01/2006 to 31/12/2010

Exact P values are determined directly from the Lambda value for between 7 and 700 cases.
Above 700 cases p values are estimated from monte-carlo simulation with 999 iterations.

Excluding Chromosomal cases except for Chromosomal anomaly subgroups

Maximum cluster length displayed is 18 months

Cluster has to be within or overlap the last 2 years of the data

Cluster size expressed as number of cases in the most statistically significant cluster.
More detailed output should be consulted for a list of cases included in the cluster,
and the maximum extent in time of any possible cluster

% estimated gestation refers to the percentage of cases without a recorded gestational age for which gestational age
was estimated as the average by registry, year of birth, type of birth and anomaly subgroup.
If >10% gestational age missing, cluster analysis will run using date of birth and give number of cases with invalid date of birth.

Cluster/deficit refers to whether the unusual finding was an excess of cases (cluster) or deficit
of cases (Deficit) within the given cluster time period.

Anomaly	Cluster Type	Cluster size	Start date	End date	Expected Cases	Probability	Valid cases	estimated gestatic	Cluster/Case deficit	Trend summary
Neural Tube Defects	Conception					No significant clus	72	2.8		
Anencephalus and similar	Conception					No significant clus	28	0		
Encephalocele	Birth					No significant clus	11	0 invalid DoB		
Spina Bifida	Conception					No significant clus	35	2.9		Significant downward trend
Hydrocephalus	Conception					No significant clus	37	8.1		
Microcephaly	Conception					No significant clus	21	9.5		
Arhinencephaly/holoprosencephaly	Conception					Too few cases (<	4	0		
Anophthalmos/microphthalmos	Conception					Too few cases (<	3	0		
Anophthalmos	Conception					No cases	0			
Congenital cataract	Conception					Too few cases (<	4	0		
Congenital glaucoma	Conception					Too few cases (<	4	0		
Aniridia	Conception					Too few cases (<	2	0		

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Figure 2: Graphical representation of trend surveillance

Significant trends found between 2002 and 2009

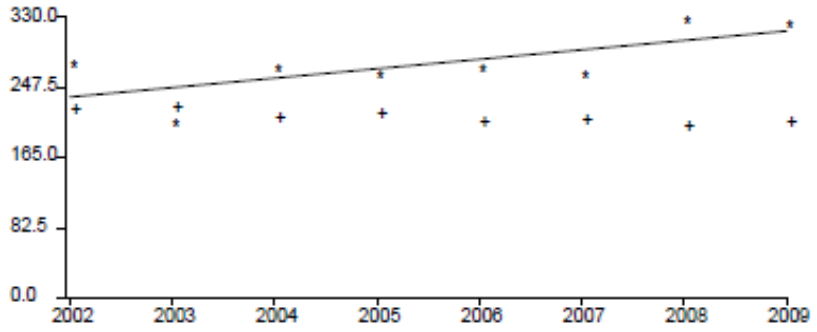
Anomaly Subgroup: **All Non-chromosomal Anomalies**

Increasing trend

Test for Trend			Test for non-linear change
Chi2	186.071	(1 df)	Not significant
p value	<0.001		
Slope	Increasing		
Rate of change	4.1% per year [95% CI 3.5% to 4.7%]		

Year:	Cases:	Total births:	Registry rate (per 10,000 births):
2002	2689	97334	276.27
2003	1960	95177	205.93
2004	2579	95613	269.73
2005	2577	98002	262.95
2006	2723	100360	271.32
2007	2577	98098	262.70
2008	3277	99580	329.08
2009	3132	96961	323.02

Trend plot Y axis: Rate per 10,000 births X axis: Year of birth



* = Registry prevalence, + = EUROCAT average prevalence (25 registries)

Figure 3: Adobe File “cluster_Registry name”. Graphical representation of detected clusters.

Anomaly Subgroup: **Choanal atresia**
Cluster type: Cluster by date of conception
Date range: Clusters between 01/01/2003 and 31/03/2007
Most significant cluster
Number of cases: 6 Expected number of cases: 0.89 p value: 0.021
Start date: 14/08/2006
End date: 07/12/2006

Record	Date of conceptior	Days	Date of birth	Gestation	GA estimated	Local ID
1	08/05/2003	127	15/01/2004	36	☐	2004027
2	06/09/2003	248	10/04/2004	31	☐	2004252
3	25/02/2004	420	08/12/2004	41	☐	2004695
4	22/05/2004	507	26/02/2005	40	☐	2005061
5	26/06/2004	542	02/04/2005	40	☐	2005784
6	07/04/2005	827	29/12/2005	38	☐	2005763
7	14/08/2006	1321	28/05/2007	41	☐	2007482
8	15/08/2006	1322	15/05/2007	39	☐	2007427
9	22/09/2006	1360	11/05/2007	33	☐	2007402
10	26/10/2006	1394	19/07/2007	38	☑	2007233
11	17/11/2006	1416	10/08/2007	38	☐	2007652
12	07/12/2006	1436	23/08/2007	37	☐	2007244

Lambda:	No cases:	expected:	Start case:	Start date:	End date:	p value:	cluster group:	Type
2324.46	6	0.9	7	14/08/2006	07/12/2006	0.021	1	Cluster

Distribution of cases

* = cases with gestation entered, ? = cases with estimated gestation

Tick marks for the 1st of each month.
Solid line represents span of most significant cluster, dotted lines indicate span of cases in clusters of the same group.