Proposal for the “European Protocol for Autism Spectrum Disorder Prevalence” (EPAP)

Background

Autism Spectrum Disorders (ASD) are lifelong neuro-developmental disorders due to neurobiological conditions (Ritvo ER et al, 1990; Courchesne E et al, 2005). Indeed, ASD is a broad concept that includes phenotypes related with the three main characteristics of autism - early onset of impairments in social interaction and communication and unusual, stereotyped behaviours - as defined by L. Kanner in 1943. ASD include Autistic Disorder, Pervasive Development Disorder Not Otherwise Specified, Rett’s Syndrome, Asperger’s Syndrome and Childhood Disintegrative Disorder (Szatmari P, 2000). DSM-IV-TR and ICD10 are the two major classifications that provide some criteria for ASD diagnosis (American Psychiatric Association, 1994; World Health Organization, 1993; Howlin and Moore 1997) although there are some overlaps between them, DSM-IV is more extensively used for clinical practice.

There is ongoing debate over whether a categorical or dimensional conceptualization is appropriate for ASD. The difficulty of such categorical conceptualization, or indeed a bimodal conceptualization, is that the definition of the case may be somewhat arbitrary (Williams JG et al 2006, Williams J et al, 2006). Thus, a dimensional conceptualization of ASD is now commonly invoked and a diagnosis is based on the child’s developmental history and observations of behavioural patterns across at least two observational settings. In any case, a diagnosis may only be made once symptoms are manifest, sufficient evidence of behavioural symptoms has been gathered and usually not before 2 years of age (Baird et al., 2003).

ASD are heterogeneous in terms of aetiology, age of onset, manifestation of symptoms, outcome, and co-morbidity with other disorders and there is no unique risk factor that unifies the understanding of the causation of autism. Genetic studies have been intensively developed during the last 5-10 years but with unequal results. Several markers have been identified in most of the chromosomes although chromosome 2, 7 and 15 and very recently chromosomes 11, p12–p13 (Szatmari P. et al., 2007), 16 and 4 (Abrahams BS and Geschwind DH, 2008) are showing the most prominent and interesting findings. Other studies have been focused on inborn metabolic errors because in some metabolic rare diseases the prevalence of autism features is high (Filipek PA et al., 2000). Other external causes such as chemical exposures to heavy metals as well as persistent organic pollutants (POPs) (Newschaffer CJ et al., 2002) and side effects from virus infectious among others have been suggested as potential causes for autism. In addition, recent research has provided some clarification of how some cases from this spectrum could be explained by the existence of different circumstances, such as perinatal risk factors ( Larsson HJ, 2005, Williams K et al, 2008) and some congenital malformations (Glasson EJ et al., 2004). It is likely that new biotechnological progress in all of these areas, as well as cooperative research, will be a way forward in solving the major challenge of understanding ASD. In this sense, very recently, the Government of the USA has promoted autism research whereby wide-ranging joint efforts among environmentalists and genetic scientists will be set up to research gene-environment interactions (The White House, 2006, Rodier PM. et al, 1998, Newschaffer CJ et al, 2002).

Known estimations of ASD

Incidence studies (Powell JE et al., 2000, Dales L et al., 2001; Kaye JA et al., 2001, Lauritsen MB et al, 2004, Smeth L. et al, 2004, Barbaresi WJ et al, 2005, Newschaffer CJ et al, 2005, Jick, H, 2006, Taylor B, 2006), although fraught with the difficulties of measuring time of onset of the disorder, have reported an increase in incidence estimates over time. Most, if not all, of the reported rise in incidence and prevalence appears to be due to changes in diagnostic criteria and awareness in professionals (Wing L and Potter D, 2002). However, in 2005, a population based study carried out in Yokohama,
Japan provided the first demonstration of incidence increasing (Honda H, 2005a, Honda H, 2005b). In 2007, a study carried out in Denmark showed a statistically significant increase of ASD cumulative incidence across specific birth years (Atladóttir HO et al, 2007). Debate has arisen about both the effects of the age of diagnosis and changes in diagnostic criteria for increasing incidence figures (Parner E, 2008, Shattock et al, 2001) and to date, there is no consensus about the causes of this increase in incidence although these more recent studies could be pointing to the possibility of a real increase of the incidence of ASD in some countries, which is not due to the bias already commented upon.

There has also been considerable variation in prevalence estimates, which may be due either to methodological factors (Medical Research Council, 2001) or to real differences, and two reviews have outlined the methodological barriers to investigating whether there has been an increase in the prevalence of ASD over time and the possible explanations for the apparent increase (Fombonne E, 2005; Wing L and Potter D, 2002). It has been argued that ASD should no longer be considered ‘rare disorders’ (Filipek PA et al., 1999) and also that the burden of disease of these disorders is high (Sánchez-Valle E et al, 2007).

Baird and colleagues (2005), in a study of 16,235 18-month-old children in the South East Thames Health Region, found an estimated prevalence of typical autism of 30.8 per 10,000 (95 percent CI: 22.9–40.6), and of other pervasive developmental disorders of 27.1 per 10,000 (95 percent CI: 19.7–36.4). Bertrand and colleagues (2001) estimated the prevalence of typical autism at 40.5 per 10,000 in a study of 8,896 3- to 10-year-olds in Brick Township, New Jersey. (Chakrabarti S and Fombonne E 2001, Chakrabarti S and Fombonne E 2005) and in a study of 15,500 children aged 2.5 to 6.5 years in Staffordshire, England, an estimated prevalence of 62.5 per 10,000 (95 percent CI: 50.8–76.3) for all pervasive developmental disorders was found.

The estimated prevalence for Asperger’s Syndrome was 8.4 (95 percent CI: 4.5–14.3) per 10,000, and for PDD-NOS was 36.1 (95 percent CI: 27.3–46.9) per 10,000. In one of the few ASD prevalence studies carried out in southern Europe, taking into account the whole population of children between 6 and 9 years old, authors concluded that the prevalence obtained for ASD in children in Portugal was close to 10 per 10,000, (95% CI 8.1–10.0) which was lower than values obtained for the most recent European regional studies. (Guiomar Oliveira G, 2007)

A systematic review of prevalence studies has contributed to explaining some of the influences on variation among prevalence estimates. Over half of the variation among study estimates can be explained by the age of the children screened, the diagnostic criteria used, and the country studied (Williams JG et al., 2006).

ASD prevalence shows a distribution centred at 8 years of age with some standard deviation near to this age (CDC & Prevention, 2007). Prevalence studies published in the past 5 to 10 years were not harmonized with respect to the age and some variation of the estimates could be justified by the different range of age chosen. Prevalence rates have been shown to continue rising within the same birth year when studies were carried in the same population at different points in time, because children with autism up to 10 years of age or older continue to be identified and enrolled in the regional system (California Department of Developmental Services, 2003). Different age ranges could lead to biased prevalence estimates and affect comparability with other studies.

Diagnostic substitution has also been mentioned as a cause of a rise in prevalence. Coo H et al., 2008, showed that diagnostic substitution accounted for at least one-third of the increase in autism prevalence between 1996 and 2004. Other important factors are, for example, whether a study was in a rural or urban location and whether cases were assessed prospectively or retrospectively. The impact of these known factors on prevalence estimates should be further investigated as they may be acting as proxies for other influences on prevalence. For example, the effect of geographical location on prevalence may be due to the services available, or variation in awareness of the disorder (Williams JG et al., 2006).
The most recent publication on prevalence is from a study carried out by the CDC in 2002. This study included approximately 10 percent of U.S. eight-year-old children born in 1994 from 14 states. A total of 407,578 children were involved and 2,685 eight-year-olds were identified as having an ASD. The data were reported by the Autism and Development Disabilities Monitoring (ADDM) Network (Kuehn BM, 2007, Rice CE et al, 2007, Van Naarden Braun K et al, 2007).

The previous study by CDC, developed in 2000, found ASD rates ranged from one in 222 children to one in 101 eight-year old children in the six communities studied. The 2002 study found ASD rates ranging from one in 303 to one in 94 among eight-year old children. The average finding of 6.6 and 6.7 per 1,000 eight-year-olds translates to approximately one in 150 children in these communities. This is consistent with the upper end of prevalence estimates from previously published studies, with some of the communities having an estimate higher than those previously reported in U.S. studies.

Issues for consideration in ASD prevalence studies

All the prevalence studies, including those using more comprehensive and reliable methods lead us to the following conclusions:

• Prevalence is now higher than was previously estimated
• Prevalence is increasing and it is probably not only due to some type of bias or awareness among population and professionals. What this means is still under discussion (Charman T, 2002).
• There is no consensus on an accurate and valid prevalence figure for all regions and all stages. Age of children, case ascertainment procedure and type and level of development of regions explored seem to be the most important variables that influence in this estimate figure.
• There is no consensus with regard to the preferable age at which to measure prevalence, the most frequently chosen ranging from 4 to 11 years. This is due to the fact that 4 years is the age when ASD can be diagnosed without excessive problems and 11 years could be appropriate for diagnosing Asperger’s Syndrome (Howlin P and Asgharing A, 1999, McConachie H et al., 2005). CDC measures the prevalence at the age of 8 years old because that age shows the highest peak of prevalence (Turner LM et al., 2006)
• Case detection or identification procedures vary enormously across studies and are bound to vary across countries and areas due to the differences in the health and educational systems and level of awareness in the areas which have been and will be surveyed. To date there are no recognized harmonised, validated tools for this process.
• Confirmatory case diagnosis demands careful quality control; it is a long and expensive process that requires expertise and the use of validated tools ADI-R and ADOS-G. An informed consent given by the parents or caregivers is needed before starting this procedure.
• A prevalence study needs well trained teams of professionals and the validated tools mentioned above.
• Until now, studies offering more accurate figures on prevalence have been carried out in specific geographical areas where previous surveillance systems or case registers already existed.
• Using data provided exclusively by the health care system is insufficient for getting a good prevalence estimate. Educational and social archives have to be accessible in order to develop a reliable prevalence study. Absolute data confidentiality must be guaranteed.
• The real response rates, as well as reasons for not collaborating, are not well described in most of the studies. In some of them, it is assumed that the lack of response is not related with the outcome (being or not an ASD case).
• Most of the studies do not mention the final cost of the whole strategy for getting an estimated prevalence figure and therefore it is not possible to make a cost-effectiveness analysis. This limitation is also due to the fact that we do not have a gold standard prevalence figure with which to compare our data and estimate the cost in relation to the validated method.

In addition, Rutter M, (2005) pointed out that “valid estimates of the incidence or prevalence of ASD require studies that meet five criteria: 1) a base population of sufficient size to provide a substantial
number of individuals with an ASD (so that the confidence interval will be narrow); 2) a defined epidemiological population that covers all the individuals likely to be at risk for an ASD; 3) systematic standardized screening of the total population; 4) a focus on an age group for which it is known that diagnostic assessments are reliable and valid; 5) diagnosis by trained professionals using high-quality standardized research assessments”. Beside these points, the MRC review of autism (Medical Research Council, 2001) outlined the difficulties of active case ascertainment in a research setting. As far as epidemiology goes, there are different types of ascertainment methods. There are methods for ascertainment where there is very little infrastructure to work with, this is often the case in developing countries; the second is a registry-based approach, which may include linking to biobanks and the third is a service and records-based approach.

**EAIS project**

One of the areas addressed by the European Autism Information System (EAIS) project is the lack of systematic, consistent and reliable data about prevalence and trends of ASD in Europe.

In July 2006, an ad hoc questionnaire was developed within the EAIS project for improving our knowledge about the characteristics of whatever health, education, social or parents’ organisations services, devoted to autism, exist in those countries where the European project is being carried out. Each section of the questionnaire is addressed to one type of services system – health, education and social. There is a section related to parents’ organisations services and another for general aspects of both diagnosis and follow up. Finally, there is a section that summarizes the likelihood of data access in each of the services analyzed. The questionnaire is focused on the regions (also national information) in which EAIS partners function. A total a 65 different questions complete the survey.

The most important conclusions from this survey are:

- It is not clear whether we could get data directly from either health or educational services, except in those countries with an active population registry.
- There are many sources that could provide ASD cases.

**Suggested prevalence design to be developed in the EAIS project**

*Justification of the need to measure European ASD prevalence and study objective*

There is no cure for autism, but research on the efficacy of early, intensive behavioural interventions suggests that developmental trajectories can be positively altered, particularly with respect to language and cognitive development. (Crane JL and Winsler A, 2008, Dawson G and Osterling, J, 1997, Ozonoff S and Cathcart K., 1998, Rogers SJ.1998). This is why, whatever the causes of the rise in prevalence, it is a reality that we now have more cases diagnosed during childhood and adolescence that need care, attention and treatment. This is not exclusively a matter of social justice and/or equity but it is a question of capacity building for bearing the tremendous burden that families and society are going to have to continue accepting if we do not now adopt the necessary decisions for improving the social and communicative capacities of these children and teenagers.

Moreover, if an increasing prevalence is a reality, incidence would have been rising during the previous years, and a real concern about improving research for environmental causes should be incorporated into autism research policy decisions (Jarbrink K. and Knapp M, 2001).

Prevalence is also an important estimate for burden of diseases analysis (Sanchez-Valle E et al, 2007) and for policy-making decisions. In fact, prevalence and some other related measurements are used for defining and designing health, educational and social resources (Rice CE et al, 2007), but the social and economic burdens of ASD have not been as adequately recorded as epidemiological figures, except in some specific situations (Van Naarden Braun K et al, 2007).
Objective

Part of the EAIS project (Work Package 7) is to design a study for ASD prevalence at European level. This has been termed the 'European Protocol for Autism Prevalence (EPAP)'. EPAP will facilitate a common format across the EU and will provide the strongest, most robust evidence available to determine the prevalence of ASD in the EU.

Setting

EPAP will be implemented in different geographic areas across Europe. During the EAIS project, preliminary work was conducted with some Associated and Collaborating Partners towards identification of potential study areas for a European ASD prevalence study. It will be important to select a small number of contrasting areas in which to conduct a pilot study to learn the difficulties of implementation on the ground. Scientists and ASD experts from Ireland, Italy, France, Luxembourg, Malta, Bulgaria, Poland, Czech Republic, Scotland, England, Spain, Denmark, Finland, Cyprus and Portugal have all expressed an interest in participating. Some of these partners have already defined the particular region where the study will be developed but in some other cases the whole country can be the study stage chosen. However, the following criteria should be considered for regions selected:

- well defined and delimited geographical and administrative area;
- stable population (low immigration rate);
- compulsory education system at the ages of the study subjects (see below);
- existence of a Public Health Care System covering near to 100%;
- accessibility to data from educational and special educational sources;
- not a priori selection bias due to the existence of reference services of ASD diagnosis, treatment or special education facilities, which are located outside the area but close enough for children living within the area to access – this could result in missing children within the study area – birth rate should be known or at least it should be available;
- accessibility to general mortality data statistics (mortality rate and mortality by causes);
- parents’ organizations and other regional stakeholders must be in favour of the study;
- accessibility to the clinical records of the potential cases;
- data accessibility from clinics and institutional private services;
- rural and urban settings will be considered.

Design

A cross-sectional design will be performed

Population

- Target population is defined as all children currently living within the target areas selected in the study time period, with age range from 6 to 11 years old, including both genders as well as all ethnic groups. This population will be defined by birth year instead of years of age, once the study starting date is known.
- The population selected should have between 10,000-50,000 children within the age range considered.
- A total of between 100,000-500,000 children could be involved in the whole study population (if all European regions that expressed their interest are finally involved).
- Expected number of ASD cases will be between 600 and 3,000 for all participant countries.
Case definition

For the purposes of this study, a case is defined as a child who fits the definition of the DSM-IV under the Pervasive Developmental Disorders categories, codes F84.0, F84.2, F84.3, F84.5, and F84.9, Autism, Asperger’s Syndrome, Rett’s Syndrome, Childhood Disintegrative Disorder and Pervasive Development Disorder not otherwise specified respectively.

Inclusion criteria

• Children of 6-11 years of age during the designated study year. Eligible children will selected by birth year and special attention will be given to the definition of the birth year, i.e. that it runs from 1st January to 31st December. This definition is relevant for estimating population size and denominator appropriately.
• Children who officially reside in the designated study area during the time of the study.

Sources of information, case ascertainment and procedures

Education, health and social services, both public and private, as well as parents’ organizations, will be used as a sources of information.

Case Ascertainment Procedure

Stage 1 (identification of potential cases)

• A full inventory of private and public mainstream and special needs schools will be drawn up.
• An inventory of social services for children in the age range selected will be also created.
• Previous agreement with schools and other institutions in the survey will be followed up and a schedule of site visits drawn up.
• School site visits will be conducted and each classroom with pupils aged 6-11 years will be checked through the teachers responsible, who will be interviewed about the children. The experience from the Portuguese prevalence study, where this method was applied, is valuable for this aim (Guiomar Oliveira G, 2007). The tool for this interview will be a questionnaire – DSM-IV based - which has been recently used by ourselves (Posada et al, 2008 unpublished paper) for this purpose. A similar questionnaire was used by Goin-Kochel RP and Cohen R, 2008.
• All special needs educational and social services will be checked and all cases described as autistic, Asperger’s or autism-related will be considered.
• Social services and disability registries will also be checked.
• A careful revision will be needed for those children with diagnosis where high frequency of autism is recognized (eg., Down syndrome, etc.) or those with suspected labels regularly used in some countries (eg., High Functional Autistic and Asperger’s syndrome) are not always recognised due to cultural criteria. This point should be considered after discussion with participant partners because there are no general rules that can be applied; this is a regional cultural issue.
• All these services will be asked about their waiting lists and some information about children on the list will be recorded.
• Comprehensive revision of the case records available on socio-educational and parents’ organisations specialised services will be carried out.
• Specific health services (psychiatric and paediatric departments as well as those devoted to language therapies) will be considered as potential sources of ASD children.
• In all of the above services, criteria for selecting potential cases are based on:
  – ASD previous classification documented or related ASD classifications;
  – Non ASD previous classification but special educational needs have been documented;
  – No previous classification nor educational needs documented but teacher’s interview highlighted some DSM-IV characteristics;
Neither ASD previous classification nor educational needs documented but currently undergoing evaluation in either health or education services or parents’ organizations services for language and cognitive problems;

- Children previously diagnosed by ICD-9 codes (speech or language disorders).

**Stage 2 (first approach to diagnosis)**

- Parents of those children identified by the teacher as possible cases will be asked questions using one of these two questionnaires, the Social Responsiveness Scale (SRS). Constatino JN, 2003, Constatino JN, 2004) or the Social Communication Questionnaire (SCQ) (Corsello C, 2007). The final decision will be taken after checking feasibility and reaching some consensus among participant countries.
- A paediatrician will take a detailed developmental history and conduct a comprehensive medical and neuro-developmental examination of all children referred from Stage 1.
- Children will be also observed for their motor skills, attention, listening, speech and language capabilities and any unusual behaviour, particularly sensory stimulation, repetitive behaviours, or motor stereotypes will be noted.
- Hearing and vision will be assessed by specialists.
- At the end of this assessment, a clinical diagnosis of the child’s problem will be suggested and provided to their families by the paediatrician.

**Stage 3. (confirmation of the diagnosis)**

Children with high scores either in the SRS or SCQ questionnaire (see above) or those strongly suspected (by clinical judgement) of having pervasive developmental disorders in previous stages will be further assessed with standardized diagnostic measures (Autism Diagnostic Interview—Revised (ADI-R) and Autism Diagnostic Observation Schedule –Generic (ADOS-G). In cases where the one tool suggests ASD and the other does not, the ADI-R will take precedence as it is based on ICD / DSM criteria whereas the ADOS-G is based on current behaviour.

- The ADI-R and ADOS-G will be managed by a developmental expert, who has been trained in its use.
- Psychometric tests such as WISC IV and/or K-ABC II for cognitive evaluation and Vineland Adaptive Behaviour Scales (VABS) or may be its second version (VABS-II) for social and communicative evaluation will be also considered to be used. Country test costs and feasibility will be assessed in order to take the final decision.
- The final diagnostic determination will be derived from a review of all existing data by an expert team.
- Parents of children from special needs services will be invited to signed an Informed Consent (IC) for accessing records.
- Final diagnosis will be made using the DSM-IV diagnostic criteria for pervasive developmental disorders, including autistic disorder, Asperger’s Syndrome, Rett’s disorder, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified.
- Comorbidity such as mental retardation, cerebral palsy and epilepsy will be checked in those ASD cases finally confirmed. In newly diagnosed cases of ASD, the presence of genetic conditions will be explored to identify secondary ASD cases such as Fragile X, Rett’s Syndrome. If funds allocated are not enough for this purpose, biological samples will be stored.
- Sociodemographic variables like race, gender, maternal age, paternal age, familiar income level, rural/urban residence area, etc will be explored and collected (Karapurkar Bhasin T and Schendel D. 2007).
- Background and family data, whether or not another child is affected in the same family, when was the child identified, or what was the trajectory of the child in preschool years within the health and the educational system will be also recorded. This will be useful for local / national authorities to improve detection and early identification.
• Parental stress measures and other viewpoints of the caregivers about their experiences will be suggested to be also recorded to the local participants partners. Final decision would be taken after discussion of the feasibility at the regional/country level.

To carry out the above two last tasks ad hoc surveys will be developed.

Data collection

Data from all questionnaires will be saved and a quality control of this procedure will be implemented.

In addition to a standard list of demographic variables including race and identifying information, both the earliest and most recent evaluation data relevant to the child’s specific disabilities as well as medical conditions that may be associated with the aetiology of the developmental disability will be recorded.

Instrumentation

An algorithm describing all the steps will be used as the procedure guide for following the whole process.

Training

Most of the activities require specialised professional training. The pilot study areas will select professionals and will create the diagnosis team in each region. This team will be trained in ADI-R, ADOS-G as well as other instruments (such as psychometric tests), where this training is needed.

Quality of diagnosis and reliability analysis

• Quality control of the final diagnosis will be carried out by external experts that will be selected by EAIS project leaders.
• An analysis of agreement among partners will be designed.
• Experts will carry out their evaluation in blind conditions with regard to the final judgment provided by the local team.
• Different languages and countries participating in this project add difficulty to this analysis. To reduce these constraints, evaluators will be referred to the same questionnaires, in the English versions, that were used to map the foreign language versions.
• For viewing videos of children explored during the ADOS-G, a bilingual local expert not initially involved in the local team will help the external experts.

Biological investigations

• All children with a possible diagnosis of pervasive developmental disorder not previously identified will be referred to local health authorities, with the recommendation of undergoing some biological investigations, according to local protocol. Coordination with other partners in the study may be possible for conducting biological investigations abroad if these are not available in certain study areas / countries.
• Parents will be invited to donate a blood sample and they will also be asked for authorization for a sample from their children. All of these samples would be stored in according to the rules of the EuroBioBank strategy.

Statistical analyses

Prevalence estimates and asymptotic 95% CIs will be estimated by race, sex, age and country. The age considered will be the age the child reached in the field study year. A stratified method for calculating the whole prevalence in the participant European countries will be used.
Conventional statistical tests will be performed for categorical and continuous variables. When assumptions for normality are not met, nonparametric analyses will be performed. A p value of 0.05 will be retained as the level of statistical significance.

Comparisons of prevalence rates among countries will be performed by calculating odds ratios and their associated 95% CIs. Statistically significant differences in prevalence rates among countries will be considered if the value 1 is not included in the 95% CI of the ratio.

Challenges and limitations

The main challenges of the EPAP are the multilingual and multicultural nature of the European population, the lack of a biological diagnostic marker, data accessibility issues, institutional differences in health, education and social services between different countries. Among the EU countries, there are marked national and regional differences in the level of awareness and recognition of ASD as a matter of public concern as well as in the development of diagnostic and intervention services. Another important issue is the level of migration between different European regions.

One of the principal limitations of EPAP is that its feasibility has not been previously checked; therefore the EPAP will be tested in an initial phase as a pilot study, where issues on the ground such as costs, professional training, and data accessibility, among others, can be experienced.

Ethical issues

The study must be approved by a local ethical committee and standardized “Informed Consent” for all countries will be used.

Expected results and added value of a European cooperation

It is obvious that where so many countries are involved, many difficulties will have to be overcome. However, this type of large cooperation across Europe will provide added value both in getting to know the ASD reality in Europe as well as capacity building in many countries. Harmonization of methods, information on study costs, burden of disease estimate and also opening the door to setting up a European ASD surveillance programme are some elements of the added value.

References


