EURAP

An International Registry of Antiepileptic Drugs and Pregnancy

Revised January 2004

1. INTRODUCTION

Women with epilepsy are confronted with a number of questions concerning pregnancy, delivery, and the health prospects for their future children. The three main issues are the risks that maternal seizures during pregnancy carry for mother and embryo or foetus, the teratogenic risks of antiepileptic drugs, and the genetic risks of the maternal disease, if caused in part by genetic predisposition. Concern is mainly about pre- and postnatal growth, major malformations, minor anomalies, psychomotor and mental development, and behaviour.

Many doctors and patients are faced with the difficulty in balancing the teratogenic risks resulting from seizures during pregnancy against the risks of taking antiepileptic drugs to prevent these seizures. Antiepileptic drugs of the first generation (phenobarbital, phenytoin, and primidone) and the second generation (valproate, carbamazepine) were all found to be more or less teratogenic. The human teratogenic potential of newer antiepileptic drugs (clobazam, felbamate, gabapentin, lamotrigine, levtiracetam, oxcarbazepine, tiagabine, topiramate, vigabatrin, zonisamide, etc.) is unknown. Adding to this complex problem is the fact that many women with epilepsy need to be treated with more than one antiepileptic drug. This increases the number of different treatment regimens, and decreases the denominators for each medication regimen considerably.

Pre-clinical toxicological studies include testing for teratogenicity in at least two different species. The results of these studies are difficult to extrapolate to the human situation, because of the well-known interspecies differences in teratogen susceptibility, partly determined by differences in pharmacokinetics and pharmacodynamics. Furthermore, combinations of antiepileptic drugs are not tested pre-clinically, although metabolic interactions between individual components of such drug combinations may affect teratogenic risks.

To address these problems, information on outcome of pregnancies following maternal exposure to antiepileptic drugs is necessary to fully evaluate the pros and cons of medication. Such information is also needed to provide pre-pregnancy counselling concerning teratogenic risks, and possibilities for specific prenatal monitoring, including prenatal diagnosis of foetal disorders associated with specific medications. Given the current number of available antiepileptic drugs and combinations, very large numbers of pregnancies have to be evaluated in order to establish the safety of each regimen. Large denominators are also needed because of the qualitative diversity of one of the main endpoints of outcome, major congenital malformations.

A number of European groups with experience and interest in maternal and foetal well-being in association with maternal antiepileptic drug use have decided to form a European consortium to set up a prospective multi-centre study of pregnancies with antiepileptic drugs. Data from all participating groups will be shared in a European Register of Antiepileptic Drugs and Pregnancy (EURAP). This is facilitated by use of

the same protocol and the same data dictionary by all study groups, and will allow for much earlier meaningful safety evaluation.

The protocol takes special account of the possibilities of prenatal diagnosis of embryonic and foetal abnormalities. Ultrasound examination, measurement of alpha-1-foeto-protein, and cytogenetic and molecular genetic analysis of cultured amniotic or chorionic villus cells may be done because of an *a priori* genetic or teratogenic risks for the foetus. On the other hand, it may also be done because of direct or indirect foetal signs presenting already during early pregnancy, leading to selection bias in ascertainment and reporting. Furthermore, an abnormal outcome of prenatal diagnosis would increase the attention paid to specific or potential risk factors in such pregnancies as opposed to pregnancies in which for a number of reasons prenatal diagnosis is not performed. Induced abortions because of prenatally diagnosed foetal malformations are an important endpoint of safety evaluation, but it is difficult to define the denominator for all pregnancies ending in similar early stages for other reasons. These aspects are taken into account in the design of this protocol.

This protocol describes the minimum backbone of the study, and it is primarily focused on optimal ascertainment with respect to risk factors before and during pregnancy, course of pregnancy and delivery, and outcome at birth and early postnatal life.

In addition to the core protocol, extension protocols may be developed to investigate special aspects such as pharmacokinetic changes during pregnancy and puerperium, or long-term postnatal development. It is essential that all participating groups give priority to implementation of the core protocol, and that extension protocols are first submitted to the Central Project Committee (CPC) for review and standardisation before their implementation.

2. STUDY OBJECTIVES

2.1. Primary objective

The primary objective of the study is to evaluate and determine the comparative degree of safety of antiepileptic drugs in the human foetus, with reference to

- New and old antiepileptic drugs
- Individual drugs and drugs in combinations

2.2. Secondary objectives

The secondary objectives of the study are to:

- Establish the pattern of major malformations, if there is any, associated with antiepileptic drugs, individually and in combinations

- Evaluate dose-effect relationships
- Delineate drug-specific syndromes (if any)

2.3. Tertiary objectives

The tertiary objectives of the study are to provide reference data for:
- Use in pre-pregnancy counselling
- Development of guidelines for pre-pregnancy management and counselling.

2.4. Teratogenic endpoints

The teratogenic endpoints of the study are the presence or absence of:
- Major malformations
- Prenatal growth retardation

2.5. Evaluation of risk factors

Evaluation of risk factors will include, among others:
- Maternal age at conception
- Maternal educational level
- Type, dose, and administration schedule of antiepileptic drugs
- Type and aetiology of maternal epilepsy, onset and duration of epilepsy
- Type and frequency of seizures during pregnancy
- Other chronic or intercurrent maternal diseases
- Family history of major malformations, known hereditary diseases, and epilepsy among first-degree relatives of the foetus.
  The complete list of recorded risk factors is reported in the CRF.

3. ORGANISATION OF THE STUDY

3.1. Central and National Registries

All data collection should be done on paper using a standardised Case Record Form (CRF), copy of which is attached. To facilitate data transmission, use of an electronic CRF is also encouraged.
To facilitate collection of data and quality assurance procedures, CRFs are first sent to the national co-ordinator (if available) (see section 3.3) and subsequently transferred to the Central Registry according to the procedure outlined in section 4.6.

3.2. The Central Project Commission (CPC)

The tasks of the Central Project Commission (CPC) (Appendix1) include (i) co-ordination of the activities of national groups; (ii) creation of the Central Registry (EURAP); (iii) evaluation at regular intervals of registry data; (iv) transmission of half-yearly reports to national groups and sponsors; (v) publication of study results. In addition the CPC is responsible for raising funds for the implementation of the study, and for a rational allocation of funds among national groups. The CPC utilises the collaboration of a Central Study co-ordinator and of ad hoc committees (Appendix 2).

3.3. National coordinators

EURAP is open to collaborators in any country provided that they can comply with the study protocol. Each participating country should ideally have a national coordinator, officially appointed by the CPC, although some national coordinators may represent more than one country. Individual centres may under certain circumstances participate under direct coordination from the Central Registry. Reasons may be that a national coordinator has not yet been appointed in the country or that the individual centre for other specific reasons prefer to report directly to the Central Registry.

Specific tasks of national coordinators include the initiation and monitoring of the study in their region through:

- Promotion of the protocol among interested physicians and medical societies;
- Distribution of the protocol to interested individuals and groups;
- Registration of participating physicians/centres and distribution of study material;
- Standardisation of operating procedures at study sites;
- Periodic analysis of data collected in the region of interest;

The national coordinator is also responsible for:

- Assessment of CRF data submitted from participating centres in the national networks (including the search for missing data and the solving of any inconsistencies);
- Implementation of quality control measures to ensure that operating procedures are followed closely throughout all steps from patient enrolment to data collection;
- Transfer of data to the Central Registry;
- Co-ordination of activities with the CPC.

4. OPERATING PROCEDURES

4.1. Registration of individual physicians (centres) willing to participate in the study

Any physician/centre may participate in the study. Interested physicians should contact the coordinators, according to the list in Appendix 3.
The national coordinators will include the registrants in the list of study participants and will provide them with copies of the protocol and CRF and with the identification number of the centre. In countries with more than one national coordinator or in those lacking national coordinators, the Central Registry must make the assignment of the identification number of the centre. Application to take part in the study and

continued participation are subject to acceptance of all procedures/limitations specified in the protocol.

4.2. Responsibilities of individual physicians/centres

- If individual participating physicians are unable or unwilling to follow-up personally the patient, their responsibility is limited to referring the patient to any reference clinical centres identified by the national coordinator.
- If physicians are able and willing to follow-up personally the patient throughout the duration of pregnancy (and to record the results of any investigation carried out outside his/her centre), their responsibility involves careful compilation of the CRF according to the specified time frame and modalities.

The first responsibility of each participating physician is to report immediately the enrolment of the patient by sending the sub-form A of the CRF to the national co-ordinator.

4.3. Inclusion criteria and patient's enrolment

All women exposed to antiepileptic drugs at the time of conception are eligible for entry in the study. The study is not restricted to women with epilepsy. Women who receive antiepileptic drugs for other indications (for example, bipolar disorder, trigeminal neuralgia, etc) are also eligible.

Enrolment of the patient in the study is carried out by filling sub-form A of the CRF and sending it immediately to the national coordinator.

Evaluations of the prevalence of teratogenic events will be based exclusively on cases followed up prospectively and enrolled before foetal outcome is known and in any case not after the 16th week of pregnancy. Cases enrolled after birth, after the 16th week of pregnancy or after prenatal diagnosis will be reported descriptively.

Any additional information collected after completion of individual sub-forms of the CRF will be recorded in a separate file.

4.4. Evaluation of risk factors

Information on several potential risk factors will be collected (section 2.5). Many of these factors have a known effect on pregnancy outcome and their quantification is necessary for data analysis. The list of recorded risk factors is reported in the CRF.

4.5. Evaluation procedures and follow-up

The protocol is purely observational and does not entail any change in prescribing pattern or management policies, which are left to the discretion of the treating physician.

Women should be enrolled as soon as possible. They should then be followed-up and information on progress of the gestation should be entered in the CRF at the end of each trimester of the pregnancy. Follow-up should continue until the infant reaches one year of age. (Follow-up at one year of age may be obtained simply through a

telephone interview of the mother, followed by contact with the relevant physicians if appropriate).

No special evaluation procedure is required at any visit. The data to be entered in the CRF is part of the information that should be generally available during good medical care. In any case, all efforts should be made to provide all the risk factor information that is requested in the CRF. There is no obligation for the reporting physician to examine directly the patient during pregnancy, provided that the necessary information can be obtained reliably and source data are available. The CRF allows the recording of results of tests, which may be indicated in selected patients only (for example, amniocentesis) The CRF provides codes for any of the following situations that should be distinguished from each other:

- results not available because the test, the examination, or the observation is/was not performed (not performed)
- results not available, despite the fact that test, examination, or observation is/was performed (unknown)
- results not available, without knowledge about whether test, examination or observation is/was performed (not ascertained)

and if not, this information should be added as free text including date.

Enrolment

At enrolment, the following information should be entered into sub-form A of the CRF for all patients, irrespectively of the time of enrolment:

- Study site and responsible physician(s):
- Demographics (including ethnic background and social status of parents)
- Family history (including history of epilepsy and birth defects)
- Personal history before pregnancy (including history of epilepsy and birth defects from previous pregnancies)
- Exposure to radiation before pregnancy.

Sub-form A should be sent immediately to the national coordinators.

Follow-up for women enrolled during the first 23 weeks of gestation:

After enrolment (filling of sub-form A) and completion of the first trimester of pregnancy:

The following information should be entered into sub-form B of the CRF:

- Status of pregnancy and any information about foetal status
- Exposure to risk factors during first trimester of pregnancy, with special reference to alcohol, cigarette smoke, radiation, diseases
- Detailed history of exposure to drugs (including folic acid) during the first trimester of pregnancy

- Current pathological conditions. For women having epilepsy, details on type and frequency of seizures must be obtained

Sub-form B should be sent to the national coordinators immediately after its completion.

After completion of the second trimester of pregnancy:

The following information should be entered into sub-form C of the CRF:

- Status of pregnancy and any information about foetal well-being
- Exposure to risk factors during second trimester of pregnancy, with special reference to alcohol, cigarette smoke, diseases
- Detailed history of exposure to drugs during the second trimester of pregnancy
- Current pathological conditions. For women having epilepsy, details on type and frequency of seizures must be obtained

Sub-form C should be sent to the national coordinators immediately after its completion.

After delivery:

The following information should be entered into sub-form D of the CRF:

- Exposure to risk factors during the third trimester of pregnancy, with special reference to alcohol, cigarette smoke and diseases;
- Detailed history of exposure to drugs during the third trimester of pregnancy
- Current pathological conditions. For women having epilepsy, details on type and frequency of seizures during the third trimester of pregnancy and seizures at delivery must be obtained
- Date and site of delivery
- Obstetric complications and mode of delivery
- Clinical status of proband (Apgar score at 1 and 5 min; weight at birth, length at birth, occipital-frontal circumference)
- Detailed description of any congenital abnormality
- Post-mortem examination of proband (if applicable)

Sub-form D should be sent to the national coordinators immediately after its completion and no later than 3 months after delivery.

After proband completed one year of age

(This information may be obtained simply through a telephone interview of the mother, followed by contact with the relevant physicians if appropriate):

The following information should be entered into sub-form E of the CRF:

- Detailed description of any congenital abnormality and time of detection
- Reasons for any hospital admission and/or surgery
- Post-mortem examination of proband (if applicable)

Sub-form E should be sent to the national coordinators immediately after its completion and no later than 14 months after delivery.

Follow-up for women enrolled after the first 23 weeks of gestation:

If enrolment (filling of sub-form A) occurs after 23 weeks of gestation but before birth, sub-form B should be compiled based on retrospective data and the other sub-forms should be compiled sequentially during follow-up. Each sub-form should contain the same information as outlined above for earlier enrolment.

If enrolment (filling of sub-form A) occurs after birth, sub-forms B and C should be compiled based on retrospective data and the other sub-forms should be compiled sequentially during follow-up. Each sub-form should contain the same information as outlined above for earlier enrolment.

CRFs of retrospective cases should be sent to the national coordinator only after all subforms, A-E, have been completed.

4.6. Compilation and processing of the CRF

As outlined above, five sub-forms need to be completed for each pregnancy, irrespectively from the time at which enrolment occurs. Times at which sub-forms should be filled and information to be entered are outlined in section 4.5. Each sub-form contains instructions concerning modalities of compilation.

Sub-form A should be sent immediately to the national co-ordinators at the time of enrolment.

All other sub-forms should be sent after their completion during prospective follow-up . In any case, sub-form D should be sent no later than 3 months after delivery and sub-form E no later than 14 months after delivery

As soon as it is known that the pregnancy involve twins, triples, etc. each foetus will have his/her CRF. Previously completed subforms for that pregnancy are duplicated (one for each foetus) using additional identification numbers.

All sub-forms may be submitted in paper form by mail or by fax or, in electronic form. For electronic transmission, CRFs in FileMaker programme for Windows or Macintosh (or in text file for users of other programmes) will be provided.
Upon receipt, data will be checked by the national coordinators and when found to be satisfactorily completed forwarded immediately to the Central Registry.
Any missing data or inconsistency in the CRF will be discussed, corrected and solved, whenever possible, in collaboration with the reporting physician.

4.7. Description of foetal malformations
All foetal malformations, of any nature and severity, should be described in detail in the appropriate section of the CRF.

4.8. Analysis of data
4.8.1 Evaluation of outcome and classification of malformation
The final assessment and classification of the type of malformations is the responsibility of the Central Project Commission (CPC). Reports of malformations are assessed once a month by an outcome classification commission (OCC), which is appointed by the CPC. Major malformations are classified based on the ICD 9 and Eurocat systems. and include abnormalities diagnosed before or at delivery or termination of pregnancy, or within the first year of life. The assessment is carried out blindly as far as exposure to antiepileptic medication and other risk factors are concerned.

Participating groups may use broader (but not more restrictive) definition criteria, but should always describe such cases in free text, dated and added to the CRF, in order to make analysis on the basis of standardised criteria possible.

Evaluations of incidence and prevalence of teratogenic events will be based exclusively on cases followed up prospectively and enrolled before foetal outcome is known and in any case not after the 16th week of pregnancy. Cases enrolled after birth, after the 16th week of pregnancy or after prenatal diagnosis will be reported descriptively.

Any additional information collected after completion of the individual sub-forms of the CRF will be recorded in a separate file.

4.8.2. Sample size considerations
Due to lack of reliable information about the quantitative and qualitative distribution of individual AEDs and their combinations (risk factors of primary interest) in the population of interest, only a rough estimate of sample size is feasible at the onset. Therefore, determination of sample size will be based on general criteria, after defining of the number and type of risk factors to be assessed stepwise as data collection proceeds.

The general empirical rule being applied (rule of thumb) states that the ratio between the overall number of events (teratogenic events) and the number of explanatory variables (predictors) should be at least equal to 10 (Concato at al., 1993), according to the following equation:

1) Expected Total n° of Events = 10 x {n° of predictors}

Sample size can then be calculated according to equation 2:

2) Total Sample Size = {expected total n° of events} / {incidence of events}

Assuming that the incidence of teratogenic events in the general population is in the order of 5% (Quality Standards Subcommittee of the American Academy of Neurology, 1998) and assuming a minimum number of clinically relevant predictors to be analyzed equal to 25, the Total Sample Size is estimated at about 5,000 pregnancies.
For the above estimate, the following predictors could be evaluated during the first-step analysis: 1) maternal age; 2) familiar history of teratogenic events; 3) exposure to other (non-AED) known teratogens; 4) smoker's status; 5) alcohol consumption; 6) other potential teratogens; 7) individual AEDs as monotherapy (assuming 15 different possible AED monotherapies); 8) AED polytherapy (as a single group); 9) AED dosage (in terms of defined daily dosages or their sums); 10) type of epilepsy (partial or generalized) and 11) frequency of convulsive seizures during the first trimester of pregnancy.
Enlargement of the minimum sample size to about 7,000 patients will allow, as a second step, to assess risk associated with the 10 most frequently used AED combinations, with all remaining combinations being analyzed as a single group.
Further predictors can be analyzed after further enlargements of sample size, as from equation 2 above and on the grounds of the results of a power analysis which will be carried-out by resorting to the SAS macro UnifyPow (O´Brien, 1998).
The final step in the analysis will utilize data from all available AED combinations and will include an evaluation of the effect of dose for each individual AED, and of the interactions between individual drugs. In this analysis, evaluation of risk associated with any individual AED will be derived from both monotherapy and polytherapy exposures. The final sample size cannot be estimated in advance, since no information is available on the distribution of pregnancies in different treatment groups.

4.8.3 Statistics
Baseline demographic variables, risk factors and relevant clinical variables will be summarized descriptively to characterize the study population. For continuous data, statistical description will include arithmetic mean, standard deviation and range, whilst categorical data will be tabulated by frequencies and percentages.
Multiple logistic regression will be used to evaluate AED effects on the incidence of major malformations and intrauterine growth retardation, both as main effects and interactions when administered in polytherapy. The multivariable analysis will allow simultaneous adjustment for different confounding or prognostic factors and

assessment of the impact on prognosis of these factors. Because no control group is available, the AED group with the smaller incidence of teratogenic events will be used as reference for calculation of odds ratios (and associated 95% confidence limits). In particular, multivariable analysis will focus on the assessment of the effects of individual AEDs and their combinations in relation to: 1) maternal age; 2) familiar history of teratogenic events; 3) exposure to other (non-AED) known teratogens; 4) smoker's status; 5) alcohol consumption; 6) other potential teratogens; 7) AED dosage (in absolute terms and in terms of defined daily dosages or their sums); 8) type of epilepsy (partial or generalized) and 9) frequency of convulsive seizures during the first trimester of pregnancy. All computations will be performed by using SAS software procedures.

4. 9. Regulatory and ethical aspects

Informed consent must be obtained from each patient. This will include consent to enter the data in anonymous form in the regional registries and the Central Registry (only the date of birth of the mother and the first three letters of the surname of the mother will identify each case).

The national coordinator will submit the protocol to the Ethics Committee of his/her Institution. Copy of the approval document will be sent to participating individuals/centres for any further action according to local regulations. Copy of the approval document has also to be sent to the Central Registry, in order to justify data collection and the presence of data under its privacy protection rules.

Participation in the EURAP protocol does not exempt reporting physicians from complying with drug surveillance regulations. Any adverse effect, including congenital malformations, should be reported to regulatory bodies or other institutions according to local drug surveillance regulations.

4.10. Conflicts of interest

EURAP complies with the policy on disclosure of conflicts of interest adopted by the International League Against Epilepsy. Thus, members of the CPC and the Central Study Co-ordinator are required to disclose the existence of any financial interest greater than USD 500 or the nature of any other relationship they may have with pharmaceutical companies who develop, produce and market compounds that are subject of this study, or institutions that provide or regulate grants or funding. Members of the CPC have to notify potential conflicts of interest beforehand and deliver a yearly update.

The CPC may decide that conflicts of interest of an individual are of such nature that they are not compatible with a position as a member of the CPC or as Central Study Co-ordinator.

EURAP acknowledges the importance and relevance of information exchange and consultation with the SAB and its individual members. The preceding guidelines concerning disclosure of potential conflicts of interest do not apply to members of the SAB, since the SAB does not have direct or decisive influence on the study results, the interpretation of data, or the publication process. The contribution of members of the SAB will, however, be acknowledged in a separate note in EURAP publications.

5. REPORTS AND PUBLICATIONS

Update reports will be prepared half-yearly (November and May) by the CPC and transferred to national coordinators and sponsors. In addition, to allow the sponsoring pharmaceutical companies a more in-depth safety evaluation, EURAP will provide more detailed but anonymized information on pregnancy outcome after exposure to the sponsor's own product. This will be supplied if requested in conjunction with the semi-annual reports. Such data should be kept strictly confidential and may only be used by the sponsor following the rules set out in the "Agreement on sharing of information from the EURAP database with sponsoring companies."

Individual centres retain the proprietary rights of their own data and they are allowed to publish them without prior approval by the CPC. However, any publication on behalf of EURAP or using the EURAP name in the title or in the authorship/affiliations must obtain prior approval from the CPC.
Any publications (including abstracts using cases included in the EURAP database) should be transmitted for information to the CPC, which shall quote them in any official EURAP publication. This is necessary to avoid the risk that the same dataset reported in different publications be misinterpreted as separate data.

Any submission of EURAP manuscripts including original data will be accompanied by a list of all individual reporting physicians who contribute at least 10 cases to the database.

6. REFERENCES

Centers for Disease Control and Prevention. Metropolitan Atlanta Congenital Defects Program. Surveillance procedure manual and guide to computerized anomaly record. Atlanta, GA: CDC 1998.

Concato J, Feinstein AR, Holford TR. The risk of determining risk with multivariable models. Ann Intern Med 1993; 118: 201-10.

Quality Standards Subcommittee of the American Academy of Neurology. Management issues for women with epilepsy. Neurology 1998; 51: 944-8.

O'Brien R.G. A Tour of UnifyPow: A SAS Module/Macro for Sample-Size Analysis, Proceedings of the 23rd SAS Users Group International Conference, Cary, NC, SAS Institute, 1998; 1346-55.

APPENDIX 1

Central Project Commission

Dina Battino, Milano
Erminio Bonizzoni, Pavia
John Craig, Belfast
Dick Lindhout, Utrecht
Emilio Perucca, Pavia
Anne Sabers, Copenhagen
Torbjörn Tomson, Stockholm, (chair)
Frank Vajda, Melbourne

APPENDIX 2

Central Study Coordinator

Dina Battino, Milan

Scientific Advisory Board

Bernd Schmidt, Freiburg
Martin J Brodie, Glasgow (Eurepa representative)

Outcome Classification Commission

Richard Finnell, Houston
Francesca Faravelli, Genoa

APPENDIX 3

National coordinators

Frank Vajda, Australia - email: vajdafj@svhm.org.au
Gerhard Luef, Austria - email: gerhard.luef@uibk.ac.at
Dick Lindhout, Benelux - email: d.lindhout@dmg.azu.nl (UMCU)
Dinko Vitezic, Croatia - email: vdinko@medri.hr
Jana Zarubova and Robert Kuba, Czech Republic - email: zarubova@ftn.cz; robert.kuba@fnusa.cz
Anne Sabers, Denmark - email: anns@glostruphosp.kbhamt.dk
Noemi Lisanti, Ecuador - email: rodals@agilweb.net
Reetta Kälviäinen, Finland - email: ReettaKalviainen@kuh.fi
Otar Toidze and Sofia Kasradze, Georgia - email: otartoidze@yahoo.com; sofiakas@hotmail.com
Bettina Schmitz, Germany - email: eurap.germany@charite.de
Patrick Kwan, Hong Kong - email: patrickkwan@cuhk.edu.hk
Gábor Barcs, Hungary - email: barcs@opni.hu
Sanjeev V Thomas, India - email: krep@sctimst.ker.nic.in
Miri Neufeld, Israel - email: neufeldm@tasmc.health.gov.il
Daniela Mamoli, Italy - email: dbattino@istituto-besta.it
Masaki Tanaka, Japan - email: tanakama@szec.hosp.go.jp
Ruta Mameniskiene, Lithuania - email: Ruta.Mameniskiene@santa.it
Gordana Kiteva-Trencevska, Macedonia - email: gordanakt@sonet.com.mk
Karl-Otto Nakken, Norway - email: Karl.otto.nakken@epilepsy.no
Weiping Liao, People's Republic of China - email: wpliao@163.net
Piotr Hincz and Joanna Jedrzejczak, Poland - email: phincz@plusnet.pland; office@epilepsy.org.pl
Aline Russell, Scotland - email: aline.russell@sgh.scot.nhs.uk
Dragoslav Sokic, Serbia and Montenegro - email: dsokic@mail.neurologija.bg.ac.yu
Vladimir Safcak, Slovakia - email: lvn@stonline.sk
Bostjan Cebular, Slovenia - email: bostjan.cebular@kclj.si
Mertixell Martinez Ferri, Spain - email: med028321@saludalia.com
Torbjörn Tomson, Sweden - email: torbjorn.tomson@karolinska.se
Barbara Tettenborn and Andrea Jung, Switzerland – email: barbara.tettenborn@kssg.ch; Andrea.Jung@swissepi.ch
Çigdem Özkara, Turkey - email: cigdemoz@istanbul.edu.tr
John Craig, UK - email: john.craig@royalhospitals.n-i.nhs.uk.