EURAP EXTENSION PROTOCOL N. 2

shortened version

See amendments on page 6 and regarding paragraph 3.6. on page 7 (in red)
New amendment decided upon in London on Oct 1,2012 on page 5 (in blue)

NEUROCOGNITIVE EXTENSION PROTOCOL (NCEP) FOR CHILDREN EXPOSED TO ANTIEPILEPTIC DRUGS IN UTERO

International, multicentre, semi/prospective evaluation of children exposed to carbamazepine, lamotrigine or valproate monotherapy during the prenatal period

Authors

Kai Eriksson
Pediatric Research Centre
Medical School
FinnMedi 3, 3.fl., r. 3-119
33014-University of Tampere
FINLAND
+358-3-31166125 (Tel)
+358-50-3370830 (Mobile)
+358-3-31164390 (Fax)
kai.eriksson@uta.fi
kai.eriksson@pshp.fi

Eija Gaily
Hospital for Children and Adolescents
Helsinki University Hospital
Helsinki, Finland
00029-HUS
FINLAND
+359-9-47180420 (Tel)
+358-50-4270742 (Mobile)
+358-9-47180413 (Fax)
eija.gaily@hus.fi
eija.gaily@fimnet.fi

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Introduction

1.1. Major malformations

Epilepsy is a common neurological disorder, affecting approximately 1% of the population – equally men and women. Prenatal exposure to antiepileptic drugs (AEDs) is also a common clinical situation since 0.3-0.5% of all pregnant women have epilepsy (Olafsson et al. 1998, Viinikainen et al. 2005) and most of them use AEDs during pregnancy because maternal and fetal risks associated with seizures are considered to outweigh potential adverse drug effects on embryonal development (Meador et al. 2004). The association between first trimester AED exposure and major congenital malformations in the offspring has been widely studied (e.g. Wide et al. 2004, Artama et al. 2005, Morrow et al. 2005) but methodologies vary greatly between studies and many confounding factors (e.g. pre- and perinatal factors, genetic and family history of malformations and variables related to the mother's epilepsy) have not been adequately controlled for.

AEDs, which may be associated with potentially greater teratogenic risk based on results of available studies, include valproate (e.g. neural tube defects)(Samren et al. 1999, Morrow et al 2005) and phenobarbital (e.g. heart defects)(Waters et al. 1994). High AED doses (Kaneko et al. 1999) and polytherapy (Holmes et al. 2001, Artama et al. 2005) also seem to be associated with increased risk. Information on teratogenic risk related to exposure to newer AEDs is still scarce.

1.2. Dysmorphic features

Dysmorphic features have been associated with exposure to virtually all major AEDs, and in particular with phenytoin (Hanson et al. 1976) and valproate (Clayton-Smith and Donnai, 1995). These syndromes, however, lack specificity. Prospective studies examining mothers and case reports from twins and siblings indicate that genetic vulnerability plays an important role in their expression.

1.3. Mental deficiency

Population-based evaluator-blinded comparative prospective studies have not identified a significant increase in the prevalence of mental deficiency in children of mothers with epilepsy (Gaily et al. 1988, Gaily et al. 2004), although larger studies are needed. According to the available studies, prenatal exposure to phenytoin or carbamazepine monotherapy does not appear to impair intelligence (Shapiro et al. 1976, Gaily et al. 1988, Wide et al. 2001, Gaily et al. 2004).

The question whether children of mothers with epilepsy have specific cognitive defects compatible with normal intelligence has been addressed in a prospective, evaluator-blinded population-based study; an increased risk was found but it was not attributed to AED exposure (Gaily et al. 1990). In a population-based, evaluator-blinded, controlled study from Finland (Eriksson et al. 2005), the neurological and cognitive functioning of school-aged (≥6 years) children exposed to valproate monotherapy in utero was compared to matched non-exposed and carbamazepine exposed children. The prevalence of low intelligence was increased in valproate exposed children but also the mothers using valproate scored significantly lower in intelligence quotient (IQ) tests and also had a significantly lower educational level, which may largely explain the results.

In addition to population-based data, there are four prospective clinic- or registry-based studies investigating the effect of phenytoin, phenobarbitone, primidone and carbamazepine (Fujioka et al. 1984, Scolnik et al. 1994, Ornoy et al. 1996, Koch et al. 1999). The results have been contradictory, with some studies showing and others not showing impaired cognition in AED-exposed children. No data have been published on the effects of newer-

generation AEDs such as lamotrigine, levetiracetam, oxcarbazepine, topiramate or gabapentin.

1.4. Verbal intelligence, need for educational support

A retrospective postal questionnaire by Adab et al. (2001) included 56 school-aged (4 – 18 y) children exposed to valproate monotherapy. The need for additional educational support at school was significantly increased in valproate-exposed children compared to unexposed and carbamazepine-exposed children. Since then, two further studies have suggested that exposure to valproate (alone or in combination therapy) may impair verbal IQ.

The prospective study by Gaily et al. (2004) was limited by the small number (13) of valproate monotherapy exposed children and by the confounding effects of low maternal education and possibly also maternal epilepsy characteristics. In the retrospective study by Adab et al. published in 2004 – largely from the same cohort as the one previously cited – children aged 6 years or older exposed to valproate had a mean verbal IQ which was significantly lower than that found in unexposed children and children exposed to other monotherapies.

1.5. Confounding factors and how to control them

The most important factors confounding the effect of in utero AED exposure on neurocognitive performance in children include:

- Genetic traits
  - associated with different epilepsy syndromes and etiologies
    - controlled by re-evaluation of mothers epilepsy when considered necessary (see section 3.6.)
- Severity of mother's epilepsy
  - seizure control during and after pregnancy, number and doses of AEDs
    - controlled by collection and analysis of adequate data from core EURAP database and through the NCEP CRFs
- Maternal and paternal intelligence
  - family history of developmental delay and specific cognitive dysfunction
    - controlled by assessment of maternal IQ (see section 3.6.)
- Psychosocial and family environment
  - socioeconomic status, psychiatric disorders, race, language spoken, mother's ability to care for the child (i.e. developmental support, stimulating social environment)
    - controlled by collection and analysis of adequate data from core EURAP database and through the NCEP CRFs
- Pre-, peri- and postnatal co-morbidity of the child
  - chromosomal/genetic syndromes, prematurity, birth weight, Apgar score
    - controlled by collection and analysis of adequate data from core EURAP database and through the NCEP CRFs

2. Objectives and rationale of the study

The main objective of this EURAP neurocognitive extension protocol (NCEP) is to compare developmental outcome in children exposed prenatally to carbamazepine (CBZ), lamotrigine (LTG) or valproate (VPA) monotherapy. Prospective recording of exposure data and adequate follow-up time are essential requirements in this study. The rationale for including the above AEDs in this first part of the study is as follows:

a) CBZ, LTG and VPA are the only AEDs, which at this time have sufficient numbers of prenatal exposures in the EURAP core protocol to meet the sample size required (see section 4.1.) to identify significant differences in the primary endpoint (see section 3.3.)
b) In the second phase of the study (from year 2009 onwards, see section 3.1.) other AEDs may be included provided that magnitude of exposure will be sufficient to allow meaningful statistical power
    - the second phase of the study could be important because it is likely that type of epilepsy in women treated with VPA will differ compared with women exposed to LTG and CBZ, which may prevent assessment the impact of this confounder on observed outcome

Specific aims of the present study are:

a) To evaluate the association between exposure to CBZ, LTG and VPA monotherapy in utero and long–term neurocognitive development
b) To assess any pattern of neurocognitive dysfunction associated with prenatal exposure to these AEDs
c) To identify the role of other possible risk factors and confounders in the assessed outcomes
d) To provide reference data for use in pre-pregnancy counselling and development of guidelines

Cognitive defects other than mental deficiency cannot be reliably assessed before the age of 5 – 6 years. Longer follow-up periods, on the other hand, will increase the likelihood of loss to follow-up and the impact of confounders. Standardized endpoint measurements will be used to control for factors relevant for the study objectives.

3. Methods

3.1. Design

- International, multicenter, EURAP registry-based semi/prospective study
- Identification of eligible mother – child pairs and retrieval of exposure data on maternal AED treatment and seizures during pregnancy, type and etiology of maternal epilepsy from the prospectively collected database of the core EURAP study
    - follow-up will be semi-prospective for the neurocognitive protocol in those cases as the written consent will be obtained from the mother after the child's birth
- Tentative time window 2009-2013
    - the number of mother – child pairs required to ensure the desired statistical power (see section 4.1.) for this first part will be 95 in each study group, altogether 285
    - the number of centres needed to enrol these mother – child pairs is estimated to be app. 10 (ten) according to the numbers from EURAP database (Appendix C.)

3.2. Inclusion / exclusion criteria

- Inclusion criteria will be as follows:
    - the study will aim at enrolling mother – child pairs meeting the eligibility criteria outlined below and enrolled semi-prospectively in the participating centres in the EURAP core study
    - eligibility must be checked with the central registry in Milan (Dina Battino or Bibiana, email dbattino@istituto-besta.it) before enrolling the mother –child pair for NCEP (to avoid enrolling cases that have been rejected by the central registry prior to NCEP)
    - for minimising selection bias

        - every effort will be made to enroll all consecutive mother – child pairs and information about the reason for not enrolling will be recorded and analyzed to minimise the possible selection bias
        - criteria for centres eligible for the study include e.g. sufficient number of cases in each exposure group and ascertainment rate
    - written informed consent will be required from the mother and /or father according to national legal requirements
    - exposure of the child to CBZ, LTG or VPA monotherapy during the entire period from conception to birth
        - exposed children aged at the time of the neurocognitive examination; 6 (six) years ±3 (three) months (see section 3.5.)
- Exclusion criteria will be:
    - mother's inability to take care of the child (e.g. due to severity of the epilepsy)
    - significant pre-, peri- and postnatal neurological co-morbidity of the child; e.g. known chromosomal/genetic syndromes, prematurity (gestational age less than 37 weeks)
    - mother – child pairs in whom information to estimate the impact of factors other than AED exposure modifying significantly development of the child cannot be reliably assessed, i.e. is missing or unavailable

3.3. Endpoints

-
- verbal IQ of the child at age 6 years (±3 months), however, children may be tested up to age 7 years
- nonverbal and full scale IQ of the child at age 6 years (±3 months), up to 7 years
- Secondary end-point
    - other specific cognitive functions of the child at age 6 years (±3 months), up to 7 years(see section 3.5.)

3.4. Assessment of the child at 6 (up to 7) years of age

- Structured interview of the parents, see Appendix C for variables
- WISC-III
    - neuropsychologist, blinded
    - verbal, nonverbal and full scale IQ
    - referral to more extensive assessment (see section 3.7.) if
        - VIQ, PIQ or FSIQ less than 70
        - Mother-child difference over 15 points
        - VIQ-PIQ difference over 15 points
- NEPSY (Korkman et al. 1998) Developmental Neuropsychological Assessment (short version)
    - 15 subtests covering the essential domains of neurocognitive development: attention, language skills, visuospatial skills, manual fine motor skills, memory and learning

3.5. Assessment of the mother

- At the same time as the visit described in section 3.5 (child 6-7 years)
- Intelligence
    - neuropsychologist, blinded
    - WAIS-III (shortened)
- Re-evaluation of the mother's epilepsy
    - when considered necessary

- national EURAP coordinator and/or neuropediatrician
- re-review of existing relevant data on maternal epilepsy diagnosis
  - hospital charts, EEG and MRI reports, family history
  - in uncertain cases: review of EEG recordings, MRI images, possibly also mother's interview

3.6. Extended assessment of children = referral to a neuropediatric department for further evaluation

- This will be required only for children who have significant abnormal test results (as defined in section 3.5.) at 6-7 years of age and who have not been appropriately diagnosed already.
- It is estimated that the extended evaluation will involve a maximum of 15-20 % of all participating children
- Extended evaluation is aimed at understanding the type, severity and probable etiology of the cognitive problems in the child.

4. Statistical analysis *(Erminio Bonizzoni)*

4.1. Power calculations

- Significant verbal IQ difference is set at 7.5 points with an estimated SD = 15 points
- The number of children or sample size needed in each AED exposure group, in order to achieve a power of 80% to detect a difference at a familywise type I error rate equal to 0.05 (two-tailed) for each three individual pairwise comparison of one AED exposure group against another is equal to 85.
- Computations carried-out using the Tukey probability function
- Assuming an attrition rate equal to 10%, a minimum of 95 children will be needed for each monotherapy group

4.2. Descriptive analysis

- Baseline demographic variables, risk factors and relevant clinical variables will be descriptively summarized to characterize the study population
- In general, continuous data will have statistical description with arithmetic mean, standard deviation, median and range, whilst categorical data will have the absolute and percentage frequencies tabulated

4.3. Analysis of end points

- Stratified One-Way ANOVA models followed by pairwise linear contrasts between AEDs groups will be employed to evaluate the effects on IQ scores of AED-exposed children of mothers with epilepsy, adjusting by the following stratification variables (=main confounding factors) e.g. maternal IQ, maternal epilepsy type, severity and etiology
- Multiple Pairwise Comparisons between AED groups will be carried-out by means of the Westfall-Young closed testing procedure with Bootstrap Resampling (Westfall and Young, 1993). Computations will be performed by resorting to the MULTTEST SAS procedure (SAS version 9.1; SAS Institute, Cary, NC)

5. Study organization and operating procedures

5.1. Central Project Commission, External Scientific Advisory Board *(Appendix A)*

Needed for

- Coordination of the study

- Raising and allocating funds for implementation of the study
- Creation and management of the NCEP database
- Ascertainment of the quality of the data
- Responsibility for analysis and reporting
- Decisions about publication of the study results

5.2. National EURAP coordinator *(Appendix B)*

- Neurologist / epileptologist
- Works in close collaboration with the core EURAP local reporting physicians (who have personal contacts with the eligible families) and the national NCEP coordinator (see section 5.3.) to identify mother – child pairs eligible for the study
- Re-evaluates (or delegates the re-evaluation of) the type/syndrome and etiology of maternal epilepsy when necessary
- Is available for counselling for the families participating in the study, especially regarding questions about maternal epilepsy and its treatment

5.3. National NCEP coordinator (= study physician) *(Appendix B)*

- Neuropediatrician
- Recruits and ensures the commitment of the participating local centres
- Organizes the study locally and nationally, recruits personnel (see below) in collaboration with national EURAP coordinator, when necessary
- Collects and completes developmental CRFs from local centres
- Sends complete CRFs to Central Study Coordinator
- Supervises and consults local teams
- Is available to counsel the families participating in the study, especially regarding questions about the child's test results, development and need of further investigations

5.4. Local personnel

- Study nurse
  - keeps track of study subjects, arranges visits, sends invitations and information
  - interviews parents by phone and during the visits
  - enters data from interviews into the CRF
  - counsels parents
- Neuropsychologist
  - conducts the developmental testing of the child, blinded for exposure
  - tests mothers
  - enters the test data into the CRF
  - refers children with abnormal results (see section 3.7.) to the extended evaluation phase
  - does the complete neuropsychological evaluation of the children referred to the extended evaluation phase
  - informs parents of test results
- Study physician (may be the national coordinator)
  - pediatric neurologist, pediatrician, dysmorphologist
  - receives and signs written informed consent form (mother an/or father)
  - examines all children
  - enters data in CRFs
  - refers children for further clinical investigations and treatment, when necessary
  - informs parents of the results of the study and is available to counsel the families participating in the study, especially regarding questions about the child's health, development and need of further investigations

6. Data operating procedures

6.1. Data recording and management

Data will be collected by using standardised Case Record Forms (CRFs) filled on paper forms and submitted by mail/fax or in electronic (excel, access) form. Electronic CRF linking the NCEP data to the core EURAP database may be possible in the future.

CRFs are first sent to the national NCEP coordinator who assures the quality of the data and forwards them to the Central Study Coordinator.

6.2. NCEP database

The Central Study Coordinator will be responsible for creating and maintaining the central NCEP database. The data will be transferred to the central coordinator either as an Access or Excel file or alternatively in a printed form by mail.

7. Ethics

7.1. Informed consent and ethics committee approval

Informed consent will be obtained from every study subject; mother and/or father according to national laws and regulations. Parent/s will sign the consent form on behalf of their children. The data will be kept anonymous by using codes consisting of dates of birth and first letters of first and surname for identification of the study subjects only. National EURAP and NCEP coordinators will collaboratively submit the study protocol to their local or national Ethics Committees according to national practises. Copy of the approval document will be sent to all local centres and to the Central Study Coordinator to justify data collection from that centre/country.

7.2. Conflict of interest

EURAP complies with the policy on disclosure of conflicts of interest adopted by the International League Against Epilepsy. Members of the CPC and the Central Study Coordinator are required to disclose the existence of any financial interest greater than USD 500 or the nature of any other relationship they (or their family) may have with commercial entities, who develop, produce and market medical products that are used in the treatment of epilepsy. 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 Coordinator.

7.3. Concerns, benefits

Every effort will be made to answer the questions and concerns that may arise within the families by the information given to them before consent or during the study, or by the test results. The participating families and children may benefit from the study, if previously undiagnosed developmental problems are discovered. The child will then be guided to necessary further medical investigations and/or to get the help she/he needs, such as special education or therapy. Also this study brings benefit to the community by providing critically important information for rational treatment selections in women of childbearing age.

8. Reporting and publications

The study results will be reported by the CPC only after the completion of the study. In addition, EURAP may provide more detailed but anonymized information on the results regarding to the sponsor's own product but such data shall 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 would 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 have contributed to the database.

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Appendix A.

NCEP CPC – Central Project Commission

E. Gaily (FI) – Central study coordinator
D. Battino (I) – Core EURAP database representative
Elisa Kantola-Sorsa (FI) – Central study neuropsychologist*
T. Tomson (S) – Core EURAP representative
E. Bonizzoni (I) – Central study statistician

NCEP ESA – External Scientific Advisors

G. Baker (UK)
D. Lindhout (NL)
E. Perucca (I)

*elisa.kantola-sorsa@hus.fi

Appendix B.

National EURAP and EURAP NCEP coordinators

Country	EURAP coordinator	E-mail	NCEP coordinator	E-mail
Benelux	Lindhout, Dick	d.lindhout@umcutrecht.nl	Lindhout, Dick	d.lindhout@umcutrecht.nl
Denmark	Sabers, Anne	anns@glostruphosp.kbhamt.dk	Nikanorova, Marina	KFMANK@vestamt.dk
Finland	Kälviäinen, Reetta	reetta.kalviainen@kuh.fi	Gaily, Eija	eija.gaily@hus.fi
Germany	Schmitz, Bettina	eurap.germany@charite.de bettina.schmitz@vivantes.de	Schmitz, Bettina	eurap.germany@charite.de bettina.schmitz@vivantes.de
Italy	Mamoli, Daniela	dbattino@istituto-besta.it	Vignoli, Aglaia	aglaia.vignoli@ao-sanpaolo.it
Norway	Nakken, Karl-Otto	Karl.otto.nakken@epilepsy.no	Eriksson, Ann-Sofie	Ann-Sofie.Eriksson@ epilepsy.no
Sweden	Tomson, Torbjörn	torbjorn.tomson@karolinska.se	Åmark, Per	per.amark@ karolinska.se

Appendix C.

Prospective, monotherapy pregnancies by country, AED and gender (on 24.10.2006)

COUNTRY	Valproate				Carbamazepine				Lamotrigine				VPA	CBZ	LTG	TOTAL
	Female		Male		Female		Male		Female		Male					
	N	Age (y) mean (range)	N	Age (y) mean (range)	N	Age (y) mean (range)	N	Age (y) mean (range)	N	Age (y) mean (range)	N	Age (y) mean (range)				
Austria	15	3,9 (1,8-7,0)	26	3,6 (1,6-6,5)	15	3,5 (1,9-5,7)	12	4,3 (2,0-6,3)	7	2,9 (1,9-4,0)	7	3,2 (1,7-4,6)	41	27	14	82
Denmark	5	4,5 (3,0-5,6)	10	4,2 (2,8-5,4)	11	3,8 (2,2-6,2)	11	5,1 (2,8-6,2)	48	3,8 (2,3-5,6)	47	3,7 (1,7-5,7)	15	22	95	132
Finland	6	2,2 (1,2-3,1)	3	1,6 (1,4-1,7)	8	2,2 (1,5-2,7)	10	2,2 (1,2-2,7)	1	1,3	1	1,3	9	18	2	29
Germany	24	2,8 (1,4-5,4)	31	2,9 (1,2-5,1)	26	2,7 (1,3-5,1)	16	3,3 (1,8-5,0)	33	2,4 (1,1-3,5)	34	2,4 (1,1-4,6)	55	42	67	164
Italy	51	3,8 (1,1-7,0)	64	3,9 (1,3-6,8)	90	3,7 (1,1-6,4)	95	4,2 (1,1-6,8)	3	2,3 (1,4-3,0)	9	3,2 (1,0-5,8)	115	185	12	312
Netherland	22	2,3 (1,0-4,2)	12	2,6 (1,2-3,6)	33	2,6 (1,1-7,0)	22	3,0 (1,1-7,1)	15	2,2 (1,1-4,5)	21	2,4 (1,2-5,2)	34	55	36	125
Norway	13	3,3 (1,5-5,9)	17	3,2 (1,7-4,3)	40	3,4 (1,2-6,0)	26	3,6 (1,2-5,8)	30	3,0 (1,2-4,7)	37	2,8 (1,0-5,0)	30	66	67	163
Spain	12	4,2 (1,9-7,0)	14	3,5 (2,1-6,0)	23	3,7 (1,9-6,2)	24	3,8 (1,6-7,0)	10	3,4 (1,6-4,9)	6	3,9 (2,6-6,0)	26	47	16	89
Sweden	35	3,7 (1,6-6,7)	34	4,0 (1,4-6,5)	47	4,0 (1,8-6,9)	53	3,7 (1,4-6,7)	36	3,5 (1,3-5,8)	28	3,3 (1,4-5,2)	69	100	64	233
TOTAL	183	-	211	-	293	-	269	-	183	-	190	-	394	562	373	1329

Appendix D.

EURAP / NCEP CRF variables

0. Identification data

- Country (Finland, Benelux, Denmark, Germany, Italy, Norway, Sweden)
- EURAP no. / mother
- EURAP initials / mother
- NCEP initials / child
- Date of birth / child (ddmmyy)
- Gender / child (M/F)
- Date of assessment (ddmmyy)

1. Background data / child, mother

- Health of the child
  - Malformations noted after the age of one year (Y/N)
    - If yes, describe _____
  - Epilepsy / seizures (Y/N)
    - If yes, what type _____
  - Developmental delay / mental retardation (Y/N)
    - If yes, describe _____
  - Other neurological diagnoses or illnesses (Y/N)
    - If yes, which _____
  - Current long-term medications (Y/N)
    - If yes, which _____
- Maternal and paternal health
  - Mother
    - Seizure / epilepsy / syndrome type _____
    - Number of seizures in the past 12 months ___
    - Current long term medication (include also non-AED-drugs)
    - History of learning disorders (if yes, describe)
    - Family history of epilepsy, 1st or 2nd degree relatives (Y/N)
  - Father (biological)
    - Seizure / epilepsy / syndrome type _____
    - Number of seizures in the past 12 months ___
    - Current long term medication (include also non-AED-drugs)
    - History of learning disorders (if yes, describe)
    - Family history of epilepsy, 1st or 2nd degree relatives (Y/N)
- Education, mother
  - Years of education; how many _____
  - Educational level; basic schooling, vocational training, high school/college, university; which _____
- Education, father (biological)
  - Years of education; how many _____
  - Educational level; basic schooling, vocational training, high school/college, university; which _____
- Socioeconomic status
  - Employment outside household, mother (Y/N)
    - If yes, occupation _____
  - Employment outside household, father (pesent in the family) (Y/N)
    - If yes, occupation _____
  - Single or two parent or other type of family, which_____
  - Number of siblings; how many_____

2. Assessment of the mother

2.1. WAIS-III (shortened = 7 subtests)
Variables:
- VIQ (subtests: Information, Similarities, Arithmetics, Digit Span)
- PIQ (subtests: Digit Symbol, Block Design, Picture Completion)
- FSIQ

2.2. Re-evaluation of the mother's epilepsy – *only when considered necessary*
- Re-review of existing relevant data on maternal epilepsy diagnosis
  - hospital charts, EEG and MRI reports, family history
  - in uncertain cases: review of EEG recordings, MRI images, possibly also mother's interview

3. Assessment of the child at 6 (up to 7) years of age
3.1. WISC-III – 6 subtests:
Variables:
Information raw score
Information standard score
Similarities raw score
Similarities standard score
Comprehension raw score
Comprehension standard score
Picture Completion raw score
Picture Completion standard score
Block Design raw score
Block Design standard score
Object Assembly raw score
Object Assembly standard score
VIQ (subtests: Information, Similarities, Comprehension)
PIQ (subtests: Object Assembly, Block Design, Picture Completion)
FSIQ
3.2. NEPSY – 14 subtests:
Variables:
Tower raw score
Tower standard score
Auditory attention and Response set raw score
Auditory attention and Response set standard score
Visual Attention raw score
Visual attention standard score
Phonological Processing raw score
Phonological Processing standard score
Speeded Naming raw score
Speeded Naming standard score
Comprehension of Instructions raw score
Comprehension of instructions standard score
Design Copying raw score
Design Copying standard score
Arrows raw score
Arrows standard score
Fingertip tapping raw score
Fingertip tapping standard score
Imitating Hand Positions raw score
Imitation Hand Positions standard score
Visuomotor Precision raw score
Visuomotor Precision standard score
Memory for Faces raw score
Memory for Faces standard score
Memory for Names raw score
Memory for Names standard score
Narrative Memory raw score
Narrative Memory standard score
3.3. Referred for extended evaluation: yes/no

Appendix E1.

INFORMED CONSENT FORM – *MOTHER*

EURAP EXTENSION PROTOCOL N. 2

NEUROCOGNITIVE EXTENSION PROTOCOL FOR CHILDREN EXPOSED TO ANTIEPILEPTIC DRUGS IN UTERO

Semi/prospective evaluation of 300 children exposed to valproate (VPA), carbamazepine (CBZ) or lamotrigine (LTG) monotherapy

The use of antiepileptic drugs during pregnancy is needed because seizures may be harmful for both mother and fetus and therefore the benefits of drug treatment are probably greater than the risks of these drugs for the development of unborn child.

The purpose of this study is to determine to what extent the medicines that mother has been taking to control epilepsy during pregnancy may influence the neurocognitive development of the child as assessed with the methods used in this study.

This consent does not involve any change in the medical treatment of me or that of my child. This study will involve cognitive and neurological examination of me and my child and study physician will also collect information about my socio-economic, family and medical history that may be shared with other research personnel. This information, however, will not be disclosed to third parties. No data that identify me will be published although law may require some information to be disclosed to health authorities.

My doctor has answered any questions that I may have had. My consent is free, and I may withdraw it at any time without this affecting in any way my treatment or the relationship with my doctor.

I, undersigned, _____, born in ____/____/_____
Name (Family name, First name) Date (DD/MM/YYYY)

on _____
Place of birth (Country, City)

give my consent to take part in the above described study from which I have received both written and oral information.

Informed consent received,

Study physician, _____, date ____/_____/_____
Name, Degree DD/MM/YYYY

Place _____
Country, City

Appendix E2.

INFORMED CONSENT FORM – *CHILD*

EURAP EXTENSION PROTOCOL N. 2

NEUROCOGNITIVE EXTENSION PROTOCOL FOR CHILDREN EXPOSED TO ANTIEPILEPTIC DRUGS IN UTERO

Semi/prospective evaluation of 300 children exposed to valproate (VPA), carbamazepine (CBZ) or lamotrigine (LTG) monotherapy

The use of antiepileptic drugs during pregnancy is needed because seizures may be harmful for both mother and fetus and therefore the benefits of drug treatment are probably greater than the risks of these drugs for the development of unborn child.

The purpose of this study is to determine to what extent the medicines that mother has been taking to control epilepsy during pregnancy may influence the neurocognitive development of the child as assessed with those methods used in this study.

This consent does not involve any change in my medical treatment. This study will involve my cognitive and neurological examination of me and study physician will also collect information about my socio-economic, family and medical history that may be shared with other research personnel. This information, however, will not be disclosed to third parties. No data that identify me will be published although law may require some information to be disclosed to health authorities.

My doctor has answered any question that I may have had. My consent is free, and I may withdraw it at any time without this affecting in any way my treatment or the relationship with my doctor.

I, undersigned, _____, born in ____/____/_____
Name (Family name, First name) Date (DD/MM/YYYY)

child, _____, born in ____/____/_____
Name (Family name, First name) Date (DD/MM/YYYY)

on _____
Place of child's birth (Country, City)
give my consent on behalf of my child for him/her to take part in the above described study from which I have received both written and oral information.

Informed consent received,

Study physician, _____, date ____/____/_____
Name, Degree DD/MM/YYYY

Place _____
Country, City