

Following Outcomes in Newly Diagnosed Epilepsy
(FONDE)

A PROSPECTIVE OBSERVATIONAL STUDY OF THE PHARMACOLOGICAL AND
LIFESTYLE CONSEQUENCES OF NEWLY DIAGNOSED EPILEPSY

PROTOCOL SYNOPSIS

EUCARE structure

• EUCARE Management Group	Martin J. Brodie, Chair Mike Glynn Michel Baulac Thanos Covanis * Hanneke M. de Boer * John-Kenneth Saké	Glasgow, Scotland, UK Dublin, Ireland Paris, France Athens, Greece Heemstede, The Netherlands Brussels, Belgium
• Programme Manager	Ann Little	Dublin, Ireland
• Data Manager	Dina Battino	Milan, Italy
• Software Manager	Marco DeZordo	Milan, Italy
• Webmaster	Patrick Kwan	Hong Kong, China
• Scientific Advisory Board	Gus Baker Alla Guekht Svein Johannessen Susanne Lund Emilio Perucca Ria Reis Peter Wolf	Liverpool, England, UK Moscow, Russia Oslo, Norway Stockholm, Sweden Pavia, Italy Amsterdam, The Netherlands Copenhagen, Denmark
• External Advisors	John Bowis Allen Hauser Torbjörn Tomson John Norrie	London, England, UK New York, USA Stockholm, Sweden Glasgow, Scotland, UK

* Non-voting members

European Concerted Action and Research in Epilepsy (EUCARE) is a joint initiative of the International League Against Epilepsy (ILAE) and International Bureau for Epilepsy (IBE), supported by an unrestricted educational grant from UCB Pharma. In pursuing its aims, EUCARE follows strategies and policies outlined by ILAE, IBE and the World Health Organisation's (WHO) Global Campaign Against Epilepsy.

1. Introduction

Epilepsy is the most common serious brain disorder, which affects approximately 50 million people worldwide^{1,2}. The therapeutic goal is to control seizures with no or minimal side effects. The aim of epilepsy care, therefore, is to make people seizure free, as only freedom from seizures saves lives, reduces morbidity and ensures a satisfactory quality of life.

Several important European initiatives have been undertaken in an attempt at improving the conditions of people with epilepsy. The report 'Appropriate Standards of Epilepsy Care Across Europe', which was published in *Epilepsia* in 1997 by the Commission on European Affairs (CEA) of the ILAE, outlined a consensus achieved in consultation with European chapters. In 1998, the European Declaration Against Epilepsy was devised and adopted, which led to the launch of the European White Paper on Epilepsy³ at the European Parliament on 22nd March 2001. The European Epilepsy Services Inventory⁴, also undertaken by the CEA, supported a coordinated effort to make effective epilepsy care universally available across Europe regardless of national and economic boundaries.

In order to achieve these goals, it is important to determine what differences exist in different countries with respect to therapeutic practices and clinical outcomes. Recognizing this, the EUCARE initiative set as a primary goal of its new programme the implementation of a prospective observational study aimed at investigating management and lifestyle issues in patients with newly diagnosed epilepsy⁵. Ultimately, this study will identify determinants of medical and social outcomes, and set the basis for targeted interventions according to the needs of individual regions.

The primary goal of this programme is to improve the lives of people with epilepsy.

2. Objectives

The objectives of this study are to assess clinical and social outcomes for people with newly diagnosed epilepsy in relation to a variety of prognostic factors, including age at onset, seizure and syndrome classifications, pharmacological treatment, and socioeconomic background.

3. Study design

This is a prospective, open-label, international, multicentre observational study. Outcomes will be assessed over a number of years under conditions of care that are as near as possible to routine clinical practice.

4. Eligibility criteria

4.1 Inclusion criteria

1. Male or female patients aged 2 years or above
2. Diagnosis of epilepsy made on the basis of clinical and laboratory findings. This can include patients started on treatment following a single unprovoked seizure

3. Patients must either be naïve to antiepileptic drug (AED) treatment or be treated with AED therapy for 14 days or less prior to recruitment.
4. Patients in whom treatment is withheld for any reason (e.g. financial considerations, patient preference) are also eligible for inclusion
3. Informed consent by patient or parents/legal guardian

4.2 Exclusion criteria

1. Current intake of AEDs for more than 14 days. Patients who have been given benzodiazepine as rescue medication for acute seizures, or who take benzodiazepine for indications other than epilepsy may enter the study
2. Previous pharmacological treatment for epilepsy exceeding 14 days. Patients who received prophylaxis against febrile convulsions or as treatment for benign neonatal seizures may enter the study
3. Severe progressive illness not relevant to the epilepsy (for example, metastatic cancer)
4. Subjects unlikely to comply with the protocol, e.g., uncooperative attitude, inability to return for follow-up visits
5. Children with neurodegenerative/neurometabolic disorders

5. Outcome variables

5.1 Primary outcome variable

Proportion of patients remaining seizure-free for at least 1 year

5.2 Secondary outcome variables

1. Proportion of patients remaining on initial treatment (Kaplan-Meier analysis)
2. Proportion of patients remaining free from seizures for 1, 2, 3 and 5 years (Kaplan-Meier analysis)
3. Time to reach 6 months, 1, 2,3 and 5 years' remission
4. Proportion of patients relapsing after at least 1 year's seizure-freedom
5. Proportion of patients discontinuing each drug due to inefficacy or side-effects
6. Incidence and prevalence of side effects with each AED
7. Proportion of patients developing psychiatric symptoms
8. Lifestyle/social parameters: family status (marriage/divorce, birth of children), working and driving status, educational achievements
9. Physical injuries
10. Mortality from any cause
11. New problems related to the diagnosis or treatment

6. Withdrawal

Patients may be withdrawn from the study for the following reasons :

1. At their own request or that of their legally authorized representative
2. If the visits or interviews required by the protocol cannot be guaranteed

7. Sample size

Due to lack of reliable information about the quantitative and qualitative distribution of prognostic variables in the population of interest, only a rough estimate of sample size can

be made at the onset. Therefore, determination of sample size will be based on general criteria, after defining the number and type of prognostic 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 (see Section 5) and the number of explanatory variables (predictors) should be at least equal to 10, according to the following equation⁶:

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}

8. Study procedures

After obtaining informed consent, the investigator will enrol each patient by completing the electronic case record form (CRF) and sending the data to the Milan office. Patients will be provided with charts for recording seizures and will be followed up for a number of years. Although this is an observational study which will mirror clinical practice, it is hoped that follow up will be assiduous. It is suggested that patients are seen a minimum of 6 times: at enrolment (visit 1), after 3 and 6 months (visits 2-3), at 1, 2 and 3 years (visits 4-6) and annually thereafter. More or less frequent assessments will be allowed as clinically indicated. Although it is desirable that all hospital or office visits be documented by the investigator or staff, it will be permissible for up to 2 of the follow-up assessments during the first year and all assessments after the first year to be conducted by telephone interview. The study will be observational, i.e. there will be no interference with routine medical care, except for the minimum frequency of study visits and the recording of information on the electronic CRF. The following information will be obtained at :

Visit 1

- Medical and neurological history and examination
- Demographics and social status
- Educational status
- Profession
- Working status
- Family situation
- Other social status details (e.g. driving)
- Disability status (e.g. learning disabilities)
- Family history of seizures (first degree relatives)
- Perinatal/developmental history
- History of febrile convulsions
- Seizure history (including seizure types and frequency)
- Presumed aetiological factors (may need revision during follow up)
- Epilepsy syndrome classification (may need revision during follow up)
- Investigations (EEG, brain imaging, others)
- Therapeutic plan and drug prescription

Subsequent visits

- Medical and neurological examination (if necessary)
- Seizure status (seizures since the previous visit)
- Drug therapy (current treatment and changes in dose)
- Assessment of compliance (direct questioning and/or serum levels)
- Side effects (by spontaneous reporting)

- Additional information (e.g., serum AED levels, abnormalities on laboratory tests, new EEG or neuroradiology findings)
- New problems caused by the diagnosis/treatment

Flow chart

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	Month 0	Month 3	Month 6	Month 12	Month 24	Month 36
Informed consent	X	X	X	X	X	X
Seizure history	X	X	X	X	X	X
Medical/social history	X	X	X	X	X	X
Aetiology of epilepsy	X	X	X	X	X	X
Details of AED treatment	X	X	X	X	X	X
Routine and other EEG	(X)	(X)	(X)	(X)	(X)	(X)
Brain imaging	(X)	(X)	(X)	(X)	(X)	(X)
Seizure frequency	X	X	X	X	X	X
Seizure types	X	(X)	(X)	(X)	(X)	(X)
Epilepsy syndrome	X	(X)	(X)	(X)	(X)	(X)
Physical examination	X	(X)	(X)	(X)	(X)	(X)
Height and weight	X	X	X	X	X	X
Neurological examination	X	(X)	(X)	(X)	(X)	(X)
Concomitant medication	X	X	X	X	X	X
Side effects		X	X	X	X	X
Serum AED level		(X)	(X)	(X)	(X)	(X)
New problems		X	X	X	X	X

() If clinically indicated

9. Data collection and management

Supervision of study procedures will be the responsibility of the Management Group. All information collected at study visits will be entered into the electronic CRFs and submitted to the Central Data Management Centre (CDMC). The development of the electronic CRFs and the software for data storage, processing and transmission will be responsibility of the software house C.E. Soft s.r.l. in Milan under the leadership of Marco DeZordo.

The CDMC will be responsible for:

- 1) developing the CRFs in paper format
- 2) providing C.E. Soft s.r.l with the instructions to translate paper CRFs into electronic version
- 3) pre-testing the electronic CRFs
- 4) checking each CRF online and liaising with the investigator regarding missing data or inconsistencies
- 5) providing the Management Group every six months with the data analysis to prepare interim reports
- 6) providing the Management Group with the data analysis to prepare the necessary statistical analysis for reporting and publications

10. Investigators/centres

Physicians/centres responsible for the care of patients with newly diagnosed epilepsy can apply for enrolment as a FONDE investigator. Participation will be on a voluntary basis and no direct financial benefit will accrue to the investigator/centre. Investigators/centres will be expected to recruit at least 10 patients per year over a 2 year period and follow them up for as long as possible. Application to join the study can be made by filling the form on the website (www.EUCARE.org). Investigators/centres across a range of medical, neurological and epilepsy services will be recruited.

11. Statistical analysis

Outcome variables must allow assessment of differences as a function of prognostic variables. Baseline demographic variables, prognostic 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 and Kaplan-Meier analysis will be used to evaluate prognostic variables. The multivariable analysis will allow simultaneous adjustment for different confounding or prognostic factors and assessment of the impact on prognosis of these factors. In particular, multivariable analysis will focus on the assessment of the clinical and social outcomes in relation to: 1) age at onset, 2) seizure and syndrome classifications, 3) pharmacological treatment, and 4) socio-economic background.

Patients who are drug naïve and those who have previously received AED treatment for 14 days or less at recruitment will be analysed separately.

12. Publication policy

The results of the study will be promulgated in a series of publications. All research data remain the property of ILAE/IBE and all draft publications require the approval of both Executive Committees prior to journal submission. All papers will list investigators who have recruited

Individual centres or countries will have the opportunity to publish their own data, but must acknowledge that these are part of the FONDE study. Access to these data must have prior

approval of both sponsoring organisations. All draft publications must be endorsed by the Management Group prior to circulation to the Joint Executive Committee of ILAE/IBE requesting permission to submit the paper to a scientific journal.

13. Ethical aspects

This study will be conducted in accordance with the Declaration of Helsinki and in keeping with local ethical regulations. All recruited patients or their parents/guardian (as appropriate) must consent to their participation after the nature and scope of the study have been explained in a form understandable to them. Data collection and processing will be done in a way as to protect confidentiality and privacy.

References

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4. Malmgren K, Flink R, Guekht A et al. Commission of European Affairs Subcommittee on European Guidelines: The Provision of Epilepsy Care across Europe. *Epilepsia* 2003;44:727-31.
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