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FULL-LENGTH ORIGINAL RESEARCH

An international pilot study of an internet-based platform to facilitate clinical research in epilepsy: The EpiNet project

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Summary

Purpose: We created an epilepsy patient database that can be accessed via the Internet by neurologists from anywhere in the world. The database was designed to enroll and follow large cohorts of patients with specific epilepsy syndromes, and to facilitate recruitment of patients for investigator-initiated clinical trials.

Methods: The EpiNet database records physician-derived information regarding seizure type and frequency, epilepsy syndrome, etiology, drug history, and investigations. It can be accessed from any country by approved investigators via a secure, password-protected Website. All data are encrypted. The database is for both research and clinical purposes. Investigators were invited to register any patient with epilepsy, but were particularly encouraged to register patients when uncertain of the optimal management. Participation required approval from investigators' ethics committees and institutional review boards, and all patients or their caregiver provided written informed consent. Patients were not enrolled in clinical trials in this pilot study.

Key Findings: The international pilot study recruited patients from September 2010 to November 2011. Sixty-four investigators or research assistants from 25 centers in 13 countries registered 1,050 patients. Patients with a wide range of epilepsy syndromes and etiologies were registered. Patients' ages ranged from 2 weeks to 90 years.

Significance: The Website was successfully used by doctors working in different health systems. The pilot study confirmed that this low-cost, collaborative approach to research has great potential. Large, multicenter cohort studies will commence in 2012, and randomized clinical trials are being planned. All epileptologists are invited to join this project.

KEY WORDS: Internet, Epilepsy database, Clinical trials, International collaboration.

There is currently little evidence to guide the choice of antiepileptic drugs (AEDs) or other aspects of the management of epilepsy (Glauser et al., 2006). Despite this, very few patients are enrolled in clinical trials, and there is concern that many trials do not accurately reflect real life, since many trials are designed primarily for regulatory purposes (Mohanraj & Brodie, 2003). Most clinical trials demonstrate that drugs are more effective than placebo (Wilby et al., 2005; Beyenburg et al., 2010), but few studies have compared AEDs (Costa et al., 2011). When comparative studies have been performed, sample size considerations have only enabled these to be powered to demonstrate equivalence rather than superiority (Mohanraj & Brodie, 2003; Glauser et al., 2006). In addition, most studies have focused on patients with refractory focal seizures on polytherapy, and relatively few on patients early in the course of their disease (Kwan & Brodie, 2003; Marson et al., 2007a,b, Sachdeo, 2007), or with specific epilepsy syndromes (Wilby et al., 2005). Patients with different etiologies may have different responses to specific drugs or drug combinations (Gayatri & Livingston, 2006), or other treatment modalities. There is a

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real dearth of information regarding optimal management strategies with drug-resistant epilepsy (Karceski et al., 2001, 2005; Costa et al., 2011). This is due in part to the difficulties in recruiting sufficient patient numbers, the costs associated with trials of this size, and excessive bureaucratic requirements (Yusuf et al., 1984; Califf, 2005; Duley et al., 2008; Yusuf, 2010). The Institute of Medicine recently recommended that new approaches to randomized controlled trials in epilepsy be developed (Committee on the Public Health Dimensions of the Epilepsies, 2012).

The EpiNet project was established to address some of these issues (Bergin et al., 2007, 2010a). The ultimate goal of EpiNet is to provide a platform from which international, investigator-led, pragmatic, low-cost clinical trials in epilepsy can be performed. We have created a multipurpose epilepsy patient database that can be accessed via the Internet and can allow patients from multiple international sites to participate in clinical trials. It also provides a database for epileptologists to follow patients in large, prospective registries.

This project was initiated by the New Zealand chapter of the International League Against Epilepsy (ILAE), and a New Zealand pilot study demonstrated good patient recruitment from multiple sites nationally (Bergin et al., 2010b). Herein we report an international pilot study that was undertaken to assess the feasibility of this approach on a global scale.

The aims of the pilot study were the following:

1 To determine whether there is sufficient interest internationally for this approach to clinical research to be viable;
2 To ensure that the Internet platform is efficient, reliable, secure, and user-friendly for doctors from different health care systems and cultures.

Methods

A secure epilepsy patient database has been created by a New Zealand information technology company, ''Enigma.'' The database is held on a server that is housed in a secure data center inside a locked, metal cabinet in Auckland, New Zealand. The server is not accessible directly from the Internet, and is protected by a secure hosting environment (firewall).

The database can be accessed by approved investigators via a secure, password-protected Website from anywhere in the world. All data are encrypted (128 bit encryption). (A demonstration copy of the database can be accessed at http://www.epinet.co.nz).

Information is collected according to multiple axes: epilepsy overview; seizure history; electroclinical syndrome; etiology; investigations; drug treatment; miscellaneous (including intercurrent illnesses). Seizures and electroclinical syndromes are organized according to the document published by the ILAE classification commission in 2010 (Berg et al., 2010).

There are different levels of accreditation to access the database. Research assistants can enter data into the forms, but the data are not formally entered into the study database until it has been reviewed by an investigator.

The database has been designed to be versatile. New forms and new fields can be added as required.

Forms are generally designed as a series of expandable trees. They can rapidly collect precise information, but users are not overwhelmed at the outset by too many options. Drop-down lists are presented whenever possible to ensure that there is uniformity of data collection. Some fields are mandatory, but most are optional.

Examples of the forms used to collect information are presented as Data S1. Investigators receive a searchable online database of their patients.

The information contained in the records is owned by the investigators who submit it, and they control who can access the information. Deidentified data can be accessed by other investigators if the primary investigator agrees. A steering committee is the guardian of the database.

Although primarily for research, the platform has also been designed to improve clinical care of patients. For this reason, some personal details are transmitted to the central server: name, date of birth, gender, ethnicity, and health record number. (Transmission of this data is not mandatory and coded information can be entered into these demographic fields if desired.) Information in a record is immediately made available to clinicians in a printable, user-friendly summary, which is automatically updated when new information is entered. Because the records are accessed by way of the Internet, they can potentially be accessed by doctors from different hospitals and from different parts of a country. The investigator who enters the information (the primary investigator) determines who can access a record. Individual records cannot be accessed by anyone outside a patient's own country.

For the pilot study, investigators were encouraged to register patients for whom they were uncertain of the optimal management, since these patients may be suitable for subsequent trials. However, any patient with epilepsy could be registered. Patients were not actually entered into trials in this study.

Approval was obtained from all appropriate ethics committees and institutional review boards. All patients gave their written informed consent before information about them was entered into the database; consent for children was obtained from a parent or caregiver.

Results

The pilot study ran from September 2010 to November 2011. Neurologists needed to obtain approval from their institutional review board and ethics committee before they could join the collaboration. Centers joined until November 2011 (See Table 1). By 30 Nov, 2011, 1,050 patients had been registered in the EpiNet database.

Table 1. Participating centers

Month joined	Center	City, Country	Total
2010 – September	Auckland City Hospital	Auckland, New Zealand	302
	Wellington Hospital	Wellington, New Zealand	42
2010 – October	Whangarei Hospital	Whangarei, New Zealand	7
	Austin and Repatriation Hospital	Melbourne, Australia	7
	ULB-Hôpital Erasme	Brussels, Belgium	28
2010 – November	Palmerston North Hospital	Palmerston North, New Zealand	10
	National Epilepsy Centre	Karachi, Pakistan	58
2010 – December	Christchurch Hospital	Christchurch, New Zealand	13
2011 – January	Waikato Hospital	Hamilton, New Zealand	8
2011 – March	Montefiore Medical Center	New York, NY, U.S.A.	18
2011 – April	San Gerardo Hospital	Monza, Italy	48
2011 – May	Royal Melbourne Hospital	Melbourne, Australia	9
	All India Institute of Medical Sciences	New Delhi, India	198
	London Health Sciences Centre	London, Ontario, Canada	16
2011 – June	Otago Hospital	Dunedin, New Zealand	7
	St Vincent's Hospital	Melbourne, Australia	67
	Severance Hospital	Seoul, Korea	24
2011 – July	CHU Mont-Godinne	Yvoir, Belgium	64
2011 – August	Istituo Giannina Gaslini	Genoa, Italy	25
2011 – September	Lady Ridgeway Hospital	Colombo, Sri Lanka	15
	Bharati Vidyapeeth Deemed University Medical College	Pune, India	28
	Royal Adelaide Hospital	Adelaide, Australia	10
	UKM Medical Centre	Kuala Lumpur, Malaysia	39
2011 – October	King's College Hospital	London, Great Britain	6
2011 – November	Hospital de Sta Luzia	Viana do Castelo, Portugal	1
			1,050

Patients were registered by 64 investigators or research assistants from 25 centers in 13 countries. Investigators participated from: Australia, Belgium, Canada, Great Britain, India, Italy, Korea, Malaysia, New Zealand, Pakistan, Portugal, Sri Lanka, and the United States. (see Table 1). All investigators and research assistants who registered patients in the EpiNet database are listed in Appendix 1. The rate of enrollment increased steadily as more centers joined the collaboration (see Fig. 1).

Patients' ages ranged from 2 weeks to 90 years. Five hundred seventy-seven patients were male and 473 were female. Thirty-three patients were entered after a first seizure, 38 after a second seizure, and 957 had had more than two seizures. In 946 patients the diagnosis of epilepsy was certain (i.e., a seizure had been recorded on electroencephalography [EEG]) or beyond reasonable doubt. In a further 88 patients the diagnosis of epilepsy was considered likely or possible.

Patients with a wide range of different epilepsy syndromes and etiologies were registered. (Note that it was not mandatory to fill in these particular forms and some investigators entered data into only one or other of these forms.) Entries were made on the etiology form for 775 patients. A specific etiology (other than idiopathic/presumed genetic) was made for 374 patients, and the etiology was unknown for 278 patients (Table 2). Entries were made on the electroclinical syndrome page for 675 patients, but many of these were to record that the patient had a structural or metabolic cause for their epilepsy, or to state that the syndrome was unknown. ILAE-approved electroclinical syndromes or constellations were diagnosed in 187 patients. Investigators reported that 616 of these patients would be suitable for randomized controlled trials.

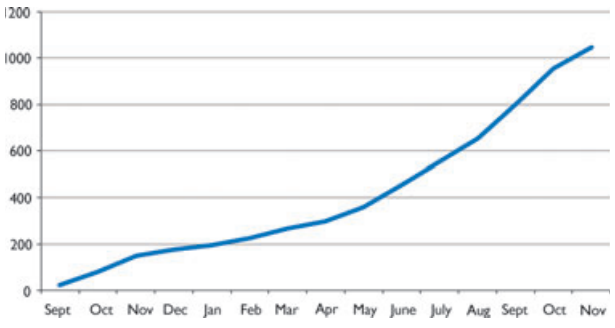


Figure 1.
Cumulative enrollment of patients into the EpiNet database during the international pilot study.
Epilepsia © ILAE

Discussion

The aims of this pilot study have been achieved. The pilot study has confirmed that this low-cost, collaborative

Table 2. Etiology

Congenital/genetic/developmental disorder	99
Nonprogressive encephalopathy due to prenatal or perinatal ischemia	34
Malformation of cortical development	30
Unilateral polymicrogyria	1
Schizencephaly	4
Focal or multifocal cortical dysplasia	4
Isolated lissencephaly	3
Periventricular nodular heterotopia/focal heterotopia	5
Microdysgenesis	2
Nature of malformation not determined/not specified	11
Neurocutaneous disorders	11
Tuberous sclerosis complex	9
Neurofibromatosis	1
Sturge-Weber syndrome	1
Chromosomal abnormalities	5
Down syndrome	3
Other chromosomal abnormality	2
Monogenic mendelian diseases with complex pathogenic mechanisms	5
Rett syndrome	2
Other	3
Acquired structural disease	241
Mesial temporal sclerosis	56
Tumor	44
Meningioma	5
Ganglioglioma	2
Dysembryoplastic neuroepithelial tumor	9
Hypothalamic hamartoma	1
Other low-grade primary cerebral tumor	6
High-grade tumor or metastasis	14
Nature of tumor undetermined/not specified	7
Poststroke	30
Cerebral infarct	19
Cerebral venous sinus thrombosis	1
Intracerebral hemorrhage	9
Subarachnoid hemorrhage	1
Vascular malformation	24
Cavernous hemangioma	11
Arteriovenous malformation	8
Other vascular malformation	5
Posttraumatic	36
Infective (postencephalitic/postmeningitis)	45
Viral encephalitis (presumed or definite)	17
Bacterial meningitis	8
Neurocysticercosis	10
Cerebral abscess	1
Other infectious cause or exact cause not specified	9
Other CNS inflammatory disease	3
Multiple sclerosis	3
Degenerative disease	1
Metabolic	10
Acquired metabolic disorders	3
Hypoglycemia	1
Hepatic encephalopathy	1
Electrolyte disturbance	1
Inherited metabolic disorders	5
Homocysteinemia	1
Mitochondrial disorder	3
Peroxisomal disorder	1
Not specified if acquired or inherited	2
Drug toxicity	7
Medicinal drug	2
Recreational drug	5
Other defined disease	17
Idiopathic (presumed genetic)	123
Unknown	278

CNS, central nervous system.

approach to research has great potential. More than 1,000 patients were registered by neurologists, epileptologists, and research assistants from 13 countries spanning three continents. Investigators were not paid anything to register the patients, and the immediate benefits to the investigators were rather nebulous.

The second aim was also met. The Website was successfully used by doctors working in different health care systems in different countries, and patients registered were from varied cultural backgrounds.

We had previously undertaken a smaller study in which 137 people with epilepsy in New Zealand were registered in a simpler online epilepsy database (Bergin et al., 2010b). Following feedback from the neurologists who participated in that study, a new database was built for this study, which is considerably more sophisticated, and further security measures have been introduced. Although the same axes are used to collect information, more fields are available in the new database. This database has been constructed in a way that will enable new fields and forms to be added relatively easily, since a modular approach has been developed for many of the forms. For instance, information on positron emission tomography (PET) scanning and single photon emission computed tomography (SPECT) scanning is not currently collected, but subforms to collect this data can be easily added (and this is planned). There are now different levels of accreditation, so that information can be entered by research assistants, but the information is not entered into the formal database until it has been verified by an approved investigator. Multiple further levels of accreditation can be added, so that some users (e.g., primary health physicians or emergency physicians) may be able to enter data into specific fields, but will have read-only access of other forms.

Patients with a wide range of seizure types, electroclinical syndromes, ages, and etiologies were registered during the international pilot study, which is the subject of this report (Table 2). We recognize that this is not an epidemiologic study, and no conclusions can be drawn regarding the frequency of particular syndromes. However, the information does provide some preliminary indication regarding the types of patients who are potentially available for clinical trials.

As the use of the platform increases, the number of patients in the database who have specific epilepsy

syndromes or etiologies is likely to grow, and we hope that it will eventually be possible to conduct focused studies. Indeed, we hope that the use of the EpiNet platform will enable the identification of relatively large groups of patients with uncommon or rare syndromes, so that research in these patient groups can be facilitated.

Limitations

Enrollment of patients into trials

Although the EpiNet project is being developed to facilitate clinical trials, no patients were actually enrolled in trials during this international pilot study, although over half of these patients were considered by their doctors to be suitable for clinical trials. In the earlier study, performed in New Zealand, we demonstrated that this approach can be used to recruit patients for trials. In that proof-of-principle study, patients were randomized online to receive a different AED immediately after they were registered into the database (Bergin et al., 2010b). Patients were not randomized during this study, since the focus was on ensuring that the database itself is as user-friendly as possible for clinicians from different countries. Further changes are now being undertaken as a result of feedback we have received from investigators in this study.

We recognize that conducting large, multicentre randomized controlled trials across multiple countries will not be easy, although this remains our ultimate goal. We are aware that it will be difficult and time-consuming to obtain approval from ethics committees and institutional review boards in multiple countries. We therefore intend to work toward this target in several steps. In 2012, registries of patients who have had a first seizure, and of patients who commence a first AED will be launched. Follow-up data on these patients will be collected prospectively, with the expectation that many of these patients will eventually be suitable for trials. This will be made explicitly clear in the consent forms for patients who are enrolled into these registries. During this phase of the project, we will obtain further information on the feasibility of running trials, since we will be able to determine if investigators actually provide follow-up data as required. At the same time, we hope to expand the collaboration, so that there will be more investigators familiar with the EpiNet platform when trials are eventually commenced. When randomized-controlled trials are commenced, they will be pragmatic trials of AEDs that are already in use, so some information required for regulatory purposes will not need to be collected. This will simplify the data collection, as much less information will be collected than is the case for trials of new AEDs. In addition, we have designed the database in such a way that we expect it to be of clinical value for investigators, and we anticipate that investigators will enter much of this data into the database to assist with the clinical care of patients, regardless of the research component. Much of this information can be entered directly into the database while the patient is with the investigator at a routine clinic. Paper forms are not being used. As a result, we anticipate that the extra costs of collecting this data will be much less than is the case for conventional trials.

Security issues

It is critical that patient data are kept confidential. Many investigators were doubtful that their ethics committees and institutional review boards would approve the transmission of clinical information into a database in another country. However, approval *was* granted by the relevant authorities in all 13 countries from which data were transmitted. In all cases, the ethics committees and institutional review boards were satisfied that patient information was secure and confidential, and that the encryption processes used in transmission of the information were adequate, and that transmission of the data was justified.

Time taken to enter data

Most doctors are already very busy. If doctors are going to enter information into a database, then they have to give this priority over some other task. Although doctors may be supportive of research in theory, there may need to be some immediate benefit before doctors will spend even a few minutes entering data. We have therefore designed this database so that there is immediate and ongoing clinical benefit in entering a patient's data. It is to enhance the clinical utility of the database that we suggest that investigators enter patients' personal demographic details, although it is not essential that these data are transmitted. Not all of the clinical information collected is needed for research purposes, although this was not always clear to investigators during this pilot study. We are therefore developing a ''Minimum Dataset'' presentation for the questionnaire. This will present the mandatory fields only. (Investigators will be able to enter other information at a later date if they so choose.)

Accuracy of data entry and validation of database

The success of this approach depends on having a large number of participants who are prepared to enter accurate information and provide reliable follow-up data. For this reason, epileptologists and neurologists from any country are welcome to join the project. However, we did not have any way of verifying that the data entered into the database during the pilot study were accurate. For this approach to be valid, there needs to be some way of ensuring that information entered is accurate and reliable. To achieve this, we intend to construct checklists to ensure that the information entered into an individual patient's record is internally consistent. (For instance, if mesial temporal sclerosis is identified as the etiology for a patient's epilepsy, there will be an internal check that this has either been identified on the magnetic resonance (MR) scan or histologically; if generalized epileptiform discharges are identified on EEG, then

a ''red-flag'' would be raised that the patient may not be eligible for a trial or a cohort study.) We will also request that investigators keep source documents so that these can be checked as required.

A validation study is also planned to ensure that investigators are sufficiently knowledgeable about epilepsy, and that all investigators ''speak the same language''; a series of case histories that highlight key aspects of diagnosis of epileptic seizures and syndromes will be circulated. Investigators will enter the relevant information into the database, and the results will be compared. Interrater accuracy and reliability will be determined. Investigators who do not participate in this study will still be able to use the EpiNet database, but the information they submit will not be entered into the formal research component of the database, and they will not be able to enrol patients into clinical trials.

Future Directions

During 2012 we will be launching the first two multicenter registries within the EpiNet database. Subsequently, other registries will also be established, including a registry of patients who are discontinuing AEDs. We would like to follow these patients to learn more about the risk of relapse in particular epilepsy syndromes, and the predictive value of the EEG. Other members of the collaboration are welcome to propose registries of other patient groups. We plan to then commence investigator-initiated therapeutic trials in patients for whom there is clinical equipoise.

We can see many other ways in which this project could develop. Records could be used to provide emergency management plans for patients that could be accessible by doctors from multiple hospitals. Point-of-care guidance could be given to investigators who are uncertain regarding the optimal treatment of a particular patient if the patient is not being entered into a trial. Records that have been used for the validation study could be used for training purposes for residents and fellows. The EpiNet platform could be used to study nonmedicinal treatments and management decisions that do not involve drugs. Patients could potentially enter some data into their own records, and the platform could be used to undertake Internet-based studies of behavioral interventions. Clearly, not all of these developments can be undertaken simultaneously, and some of them will require some external funding. However, those of us who are involved in this project see enormous potential to improve the care of patients with epilepsy.

We invite all interested epileptologists to join the EpiNet study group. More information can be obtained at http://www.epinet.co.nz.

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References

Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, Engel J, French J, Glauser TA, Mathern GW, Moshé SL, Nordli D, Plouin P, Scheffer IE. (2010) Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia*, 51:676–685.

Bergin P, Frith R, Walker E, Timmings P. (2007) How to get the answer to nearly everything: using the internet for epilepsy research. *Epilepsia*, 48:1415–1417; discussion 1417–24.

Bergin P, Beghi E, Egbuji J. (2010a) The EpiNet project—Invitation to participate in investigator-led clinical research. *Epilepsia*, 51:1919–1920.

Bergin PS, Ip T, Sheehan R, Frith RW, Sadleir LG, McGrath N, Ranta A, Walker EB. (2010b) Using the Internet to recruit patients for epilepsy trials: results of a New Zealand pilot study. *Epilepsia*, 51:868–873.

Beyenburg S, Stavem K, Schmidt D. (2010) Placebo-corrected efficacy of modern antiepileptic drugs for refractory epilepsy: systematic review and meta-analysis. *Epilepsia*, 51:7–26.

Califf RM. (2005) Simple principles of clinical trials remain powerful. *JAMA*, 293:489–491.

Committee on the Public Health Dimensions of the Epilepsies, I. O. M.. (2012) *Epilepsy across the spectrum; promoting health and understanding [Online]*. The National Acadamies Press, Washington, DC.

Costa J, Fareleira F, Ascenção R, Borges M, Sampaio C, Vaz-Carneiro A. (2011) Clinical comparability of the new antiepileptic drugs in refractory partial epilepsy: a systematic review and meta-analysis. *Epilepsia*, 52:1280–1291.

Duley L, Antman K, Arena J, Avezum A, Blumenthal M, Bosch J, Chrolavicius S, Li T, Ounpuu S, Perez AC, Sleight P, Svard R, Temple R, Tsouderous Y, Yunis C, Yusuf S. (2008) Specific barriers to the conduct of randomized trials. *Clin Trials*, 5:40–48.

Gayatri NA, Livingston JH. (2006) Aggravation of epilepsy by anti-epileptic drugs. *Dev Med Child Neurol*, 48:394–398.

Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Chadwick D, Guerreiro C, Kalviainen R, Mattson R, Perucca E, Tomson T. (2006) ILAE treatment guidelines: evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia*, 47:1094–1120.

Karceski S, Morrell MJ, Carpenter D. (2001) Treatment of Epilepsy (The Expert Consensus Guideline Series). *Epilepsy Behav*, 2:A1–A50.

Karceski S, Morrell MJ, Carpenter D. (2005) Treatment of epilepsy in adults: expert opinion, 2005. *Epilepsy Behav* 7(Suppl. 1):S1–S64; quiz S65–7.

Kwan P, Brodie MJ. (2003) Clinical trials of antiepileptic medications in newly diagnosed patients with epilepsy. *Neurology*, 60:S2–S12.

Marson AG, Al-Kharusi AM, Alwaidh M, Appleton R, Baker GA, Chadwick DW, Cramp C, Cockerell OC, Cooper PN, Doughty J, Eaton B,

Gamble C, Goulding PJ, Howell SJ, Hughes A, Jackson M, Jacoby A, Kellett M, Lawson GR, Leach JP, Nicolaides P, Roberts R, Shackley P, Shen J, Smith DF, Smith PE, Smith CT, Vanoli A, Williamson PR; SANAD Study group. (2007a) The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial. *Lancet*, 369:1000–1015.

Marson AG, Al-Kharusi AM, Alwaidh M, Appleton R, Baker GA, Chadwick DW, Cramp C, Cockerell OC, Cooper PN, Doughty J, Eaton B, Gamble C, Goulding PJ, Howell SJ, Hughes A, Jackson M, Jacoby A, Kellett M, Lawson GR, Leach JP, Nicolaides P, Roberts R, Shackley P, Shen J, Smith DF, Smith PE, Smith CT, Vanoli A, Williamson PR; SANAD Study group. (2007b) The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. *Lancet*, 369:1016–1026.

Mohanraj R, Brodie MJ. (2003) Measuring the efficacy of antiepileptic drugs. *Seizure*, 12:413–443.

Sachdeo R. (2007) Monotherapy clinical trial design. *Neurology*, 69:S23–S27.

Wilby J, Kainth A, Hawkins N, Epstein D, McIntosh H, McDaid C, Mason A, Golder S, O'Meara S, Sculpher M, Drummond M, Forbes C. (2005) Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation. *Health Technol Assess*, 9:1–157, iii–iv.

Yusuf S. (2010) Damage to important clinical trials by over-regulation. *Clin Trials*, 7:622–625.

Yusuf S, Collins R, Peto R. (1984) Why do we need some large, simple randomized trials? *Stat Med* 3:409–420.

Appendix 1

Participating investigators (RA = Research Assistant)

Australia: (*Adelaide*) Michelle Kiley; (*Melbourne*) Patrick Carney, Georgie Scales (RA), Wendyl d'Souza, Michael Tan, Terry O'Brien, Darren Germaine.

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India: (*New Delhi*) Manjari Tripathi, Nitika Dang; (*Pune*) Kavita Srivastava.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Demonstrations of forms from EpiNet Website.

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