We are very grateful for the opportunity to respond to these commentaries.

We are delighted with the generally positive responses. We acknowledge that there are difficulties with the proposal we have put forward; it is possible that some of these will prove insurmountable, but we do not think this is likely. Our view is that with enthusiasm, ingenuity and hard work, all the problems outlined by the various commentators can be overcome. We do not have all the answers at present, and we agree with Devinsky that the fruits of success are likely to lie in subsequent versions of the project. It will be a challenge to get the project up and running and giving us useful information, but we will certainly not succeed if we do not make an attempt. We believe that it is worth the attempt, because this approach gives the opportunity to answer questions that are very unlikely to be answered in any other way.

We are not proposing that all epilepsy research should be conducted in the manner we have outlined here. We accept that a double-blind randomised controlled trial is the optimal way of comparing two or more alternative treatments. We encourage researchers who are able to organise such trials to address specific questions to do so. We accept, as Cooper asserts, that many questions may be able to be answered via alternative approaches. However, if a condition is relatively uncommon, and one needs to recruit, say, 500 patients, then it is surely easier and quicker to have 500 doctors who recruit one patient each than 10 doctors who have to recruit 50 patients each. The approach we propose would enable researchers to select quite specific patient groups. We think it may well be possible to perform pharmacogenetic studies in the future using the approach we outline here, though we do not ourselves have any plans to organise such a study.

We disagree with Burneo’s assertion that, because the doctors and patients are not blinded, that randomisation may not succeed in its goal of achieving groups with similar prognosis. Randomisation cannot be guaranteed to produce groups with similar prognosis, but this is the case even when the patients and doctors are blinded. It is the randomisation, rather than the blinding, that gives prognostically balanced groups. If enough patients are randomised, then it is statistically very unlikely that the groups will differ in any substantial way at the outset. Doctors will not know before randomisation which arm of the study patients are going to be allocated to. Some doctors might recruit only sicker or less sick patients than those recruited by other doctors (referral bias), but these patients will still be allocated to the different arms in a random manner; this same referral bias may also be present in conventional double blind randomised controlled trials. We accept that if patients in one treatment arm were more likely to drop out than those in another arm, then the groups who finish the study may no longer be comparable. However, this will be clear to everybody, since the patients have been recruited and their participation has been recorded. There would not be any attempt to hide this information; indeed, the rate of dropping out would be one of the endpoints being monitored, and one of the analyses would be on an intention to treat basis. There is the possibility of bias, if doctors are less likely to record a particular end-point in patients who receive one form of treatment than another, but we cannot see why this should actually happen, and could envisage methods to prevent or document this (such as monitoring of randomly chosen patients, or independent endpoint adjudicators). It is also worth emphasising that we are not suggesting that this approach be used to conduct placebo-controlled trials. We suggest that it is used to compare different active treatments. If a doctor believes one treatment is certainly better than another, or if a patient is only prepared to use one of the proposed alternatives, then the patient should not be recruited for a trial; indeed, we believe it would be unethical to do so.

We have emphasised these points because we believe that the major benefit of the proposal we have made is precisely that it would enable the epilepsy community to rapidly perform randomised controlled trials. We note that the recently published SANAD trial (Marson et al, 2007), which compared various drugs in the management of patients with newly diagnosed epilepsy, was conducted in precisely the manner that we are proposing, except that the study was limited to predetermined researchers, and the internet was not used as a tool. We think this is a very impressive study, which has answered one of the many questions that needed to be addressed. However, we note that it took the SANAD investigators 4 1/2 years to recruit the required number of patients. It is also apparent that the researchers analysed patients as if they were a homogenous group. One of the advantages of the project we are proposing is that it would be possible to compare drugs in highly selected patient groups; we do not know whether patients with complex partial seizures due to cerebrovascular disease will respond to different drugs compared with patients who have post-traumatic epilepsy or epilepsy following meningitis, but we think this possibility should be considered.

We agree with Fisher and Burneo that the internet could be used to create registries of patients with different epilepsy syndromes. These would be suitable for patients when they or their doctors were not happy with the idea of randomisation, and when no suitable trial exists. Review of these registries would help guide future trial development. However, we would envisage that the registries would run in parallel with the randomised controlled trials, within the major project.

We agree that it is essential to ensure that the data entered is accurate. We accept, as Beghi states, that enthusiasm alone may not be sufficient to ensure this. We think that his recommendations have a great deal of merit, and we would enthusiastically support the proposal that the ILAE establish an ad-hoc commission to oversee the project. Perhaps neurologists will need to be credentialed in some way; our initial proposal was that doctors would need to be members of the ILAE before they could recruit patients, but some other form of credentialing might also be required. Perhaps the recruiting doctors should have to satisfy their local ILAE committee that they have the appropriate expertise to undertake this form of research. Perhaps there should be different levels of access; for example, general paediatricians with an interest in epilepsy may be able to recruit patients to a study of childhood absence epilepsy, but only registered paediatric neurologists might be able to recruit children with (say) Ohtahara syndrome or Dravet syndrome. If one wanted to perform a study on a highly specified group, then there may be a diagnostic test that needs to be met (e.g. confirmation of a ring chromosome 20). The details need to be considered carefully, but we remain optimistic that these problems can be overcome.

Asano raises the possibility that patients themselves enter data via the internet regarding their outcomes. This is something that we have considered, but it is not an approach that we have adopted for the pilot study we are currently undertaking in New Zealand. However, we can forsee that this approach may be appropriate for some patient groups.

Fisher has expressed concern that patient accrual might be slow, since participation will be a labour of love. This may turn out to be correct, but we have been delighted with the enthusiasm of the New Zealand neurologists and paediatric neurologists to the invitation to participate in the pilot study we are conducting. More than one third of the country’s neurologists have expressed a willingness to participate. We need to see whether this enthusiasm is maintained, and how much coercion is required to obtain the follow-up data. However, we remain enthusiastic regarding this proposal, and once again invite those who are interested in participating to contact us, or the ILAE, or both.

Peter Bergin Richard Frith

References

Marson, A. Al-Kharusi, A. Alwaidh, A. *et al*. 2007. 'The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial'. *Lancet*, 2007; 369: 1000-1015.