Rationale for Research

Sudden unexpected death in young adults (aged 20-45) with epilepsy is 27 times more common than sudden death in control populations[1].The pooled estimate from meta-analysis suggests there are 1.2 cases of sudden unexpected death in epilepsy (SUDEP) per 1000 people with epilepsy (PWE) per year[1-3]. The risk varies, depending on the severity of the epilepsy; in people with drug-resistant epilepsy the risk maybe as high as 1:200[1]. However, people who have experienced relatively few seizures can also die from SUDEP. The rate of SUDEP is thought to be highest in young adults, but SUDEP may be under-reported in older populations and in children[4]. SUDEP is second only to stroke as the leading neurological cause of total years of potential life lost[3].

The incidence of SUDEP in New Zealand is not established. However, if the incidence in New Zealand is similar to other countries, we would anticipate that approximately 40 people with epilepsy will die from SUDEP annually in New Zealand.

We have recently conducted a retrospective study of SUDEP in New Zealand. Coroners' reports of possible cases of SUDEP in New Zealand from 2007-2016 (n=190) were obtained and post-mortem and toxicology results were reviewed. We determined that 125 of the 190 cases were definite SUDEP, 41 were definite SUDEP-plus, three were probable SUDEP, and 21 were not SUDEP. Cases were aged 1.5 - 67 years, with 63% aged 15 - 45 (mean 37 years). Sixty-one percent were male. The majority of deaths (87%) occurred at home, with 74% found dead in their bed or bedroom. Antiepileptic drug (AED) use was detected in 63% of cases, with a single AED detected in 41%, two AEDs in 19%, and three AEDs in 2%. The number of cases per year varied from 11 to 26,and even the 26 cases identified in 2013 is likely an underestimate. (*Data not yet published*)

Thurman *et al* determined that if a child develops epilepsy before age one, and the epilepsy does not remit, then the lifetime risk of SUDEP by age 70 is 8.0 %; if the onset of epilepsy is at age 15 years, the corresponding lifetime risk of SUDEP by age 70 is 7.2%; and if the onset of epilepsy is at age 30 years, the corresponding lifetime risk of SUDEP by age 70 if the epilepsy does not remit is 4.6%[3].

The causes of SUDEP remain unknown[1 2]. Previous case control studies suggest that the most important risk factor is on-going tonic clonic seizures[2 5-7]. Other reported risk factors include being male[5 6], having nocturnal seizures[5 7 8], having on-going seizures[2], onset of epilepsy before age 16[5], disease duration of 15 or more years[5], intellectual disability[9], structural brain abnormalities[9], and the presence of an epileptic encephalopathy[10]. SUDEP rates may be increased in people with lower socio-economic status[1], those with psychiatric conditions[4], and possibly in patients who are non-compliant with treatment[2]. However, case control studies have not shown consistent findings, and many of these factors have not been conclusively established as being associated with an increased risk of SUDEP[1 2].

Some studies have found an increased risk from particular anti-epilepsy drugs (AEDs)[5 6]. However, once allowances are made for seizure severity, individual AEDs do not appear to be associated with SUDEP risk[5].

Two case control studies have found evidence that nocturnal supervision (checks at night or with a listening device) reduces the risk of SUDEP[6]. The study by Langan et al - the largest case-control study published to date - found that supervision at night (defined as the presence in the bedroom of another individual of normal intelligence aged at least 10 years old) was associated with an odds ratio (OR) of SUDEP of 0.4 (0.2 - 0.8), while regular checks throughout the night or the use of a listening device was associated with an OR of SUDEP of 0.1 (0.0 - 0.3). However, actual numbers were low, with 42 controls compared with 11 SUDEP cases using a listening device or having regular checks throughout the night.

More recently, a case-control study of people living in two residential care facilities identified 60 SUDEP cases who were compared with 198 controls[7]. People who died of SUDEP were more likely to have nocturnal convulsive seizures (77% of cases vs 33% of controls, $p < 0.001$). Although there was no significant difference in nocturnal supervision among cases and controls, there was a difference between centres: 2.21 / 1,000 patient-years (95% CI 1.49–3.27) vs 6.12 / 1,000 patient-years (95% CI 4.40–8.52). The authors noted that there were different institution-wide policies between the two centres, and that the centre with the lower grade of supervision had the higher incidence of SUDEP; they concluded that this was the most likely explanation for the difference in SUDEP rates; they speculated that they did not detect a difference between cases and controls because cases were matched to controls from the same site.

Special pillows designed to prevent suffocation are now being promoted to reduce the risk of SUDEP[11], but the evidence to support their use does not yet exist. Similarly, seizure detection devices are being promoted as a means of reducing the risk of SUDEP, but once again, evidence of their efficacy is currently lacking.

Most previous case-control studies have involved fewer than 100 SUDEP cases, though Langan's study included 150 SUDEP cases[6]. All these studies have included SUDEP cases that were identified retrospectively and controls have not been well matched. None of them have randomly selected controls from a well-defined cohort from which all subjects had a similar chance of experiencing the episode of interest (ie SUDEP.)

Diagnosis of SUDEP is often not straightforward. Sveinsson *et al* noted that only 62 of the 99 SUDEP cases (63%) they identified were actually correctly identified on death certificates[4]. SUDEP is not a diagnosis used by coroners in many parts of the world. Some patients who die in one of their first seizures may not be known to have epilepsy. Even when a patient does have epilepsy, it can be difficult to determine for an individual patient whether they have died from SUDEP or a cardiac arrhythmia. Cases initially described as SUDEP in New Zealand and elsewhere have subsequently been found to be due to primary arrhythmic syndromes such as long QT syndrome and CPVT (catecholaminergic polymorphic ventricular tachycardia)[12-14]. In New Zealand, one third of families ultimately diagnosed as long QT syndrome initially presented with the first family member misdiagnosed as epilepsy[13].

Serotonin dysfunction might increase the risk of SUDEP[1]. Serotonergic neurons stimulate breathing; they respond to hypercapnia and cause arousal from sleep. Sleep apnoea is associated with a disturbance of serotonergic neurons[15], while smoking influences serotonergic pathways[16]. DBA/2 mice have seizures followed by respiratory arrest, and pre-treatment with a selective serotonin reuptake inhibitor (SSRI) prevents death in this animal model[17]. SSRIs may have the potential to reduce SUDEP risk[1].

There is a need for a well-designed, large, case-control study of SUDEP in which cases are identified prospectively, with cases and controls identified from the same cohort. There is a particular need to confirm or refute the finding that nocturnal supervision reduces the risk of SUDEP, as this has major implications for how families and institutions care for people with epilepsy. We propose such a study using the EpiNet database.

EpiNet project

EpiNet comprises an international database established to clarify the optimal management of epilepsy (www.epinet.co.nz)[18]. The EpiNet database is stored on servers on Auckland's North Shore. Access to EpiNet is password protected, and personal data are encrypted. Records can be pseudonymised, so that no personal identifying data are transmitted. EpiNet allows accredited investigators to enrol patients in multicentre prospective observational studies, and simple, pragmatic randomised controlled trials[19 20].

There are registries in EpiNet for patients who have had a first seizure, or who start a first AED. Patients have been entered into the EpiNet database from over 20 countries. As of 24/10/2018, there were over 11,900 people with epilepsy (or possible epilepsy) who had records in EpiNet, with 4,900 patients from New Zealand.

EpiNet has received considerable support and funding from within New Zealand. Dr Bergin has held a Health Research Council (HRC) Clinical Fellowship to develop the project since 2014. He was awarded an HRC project grant in 2014 to undertake a study of status epilepticus in Auckland using EpiNet[21 22]. Most recently, in July 2018, he received a grant from the Neurological Foundation of New Zealand to develop a new form in EpiNet to collect data on SUDEP.

We plan to use EpiNet, which has proven utility in undertaking multicentre studies in epilepsy[23 24], to perform a case-control study of SUDEP. We wish to determine specifically whether the following are important risk factors for SUDEP: sleeping alone; having nocturnal supervision or nocturnal monitoring; use of drugs acting on serotonergic pathways. We are interested in these factors in particular, since they can be altered relatively easily. We will also consider epilepsy variables, anti-epilepsy medications and socio-economic factors.

Research Design and Methods

Aims:

To identify factors that are associated with an increased or decreased risk of SUDEP: specifically, we wish to determine whether the following factors are associated with SUDEP risk.

- epilepsy variables;
- sleeping arrangements;
- nocturnal monitoring or supervision;
- drug treatment, specifically AEDs, SSRI drugs;
- co-morbidities;
- socio-economic factors (including: years of education, employment status);
- family history of sudden death.

Methods:

We will conduct an international, multicentre, prospective, case-control study of SUDEP, recruiting participants over four years. Data regarding cases and controls will be recorded in the EpiNet database. Investigators and collaborators will include neurologists and epileptologists who are already participating in the EpiNet project and others who have not yet had involvement with EpiNet; they will be based at centres in New Zealand and Australia, Europe, North and South America, and Asia. Cases will be people who die from definite or probable SUDEP after the start date of this study. Controls will be people with epilepsy from the same cohort of each case. Information will be collected by review of patients' notes and telephone interviews.

Cohort definition:

Each centre will define a cohort from which cases and controls will be prospectively identified. The cohort will comprise all people with epilepsy who are local residents (to exclude patients referred from out of area for tertiary or quaternary assessments) and who have been seen at the centre since a specific time; the start date will be no earlier than 01/01/2015 for any centre. The database may either be established within EpiNet, or it may already exist outside of EpiNet. Only SUDEP cases that occur after the start date of this study - likely to be late 2019 - will be included. Control subjects will be identified from the same cohort. The cohorts will be dynamic; we will include patients with a current diagnosis of epilepsy, and will enrol new people with epilepsy into the cohorts who are seen during the conduct of the study so that they can enter the study as either cases or controls during follow-up.

Epilepsy will defined according to the ILAE 2014 definition[25]; it will be possible, therefore, to include patients who have had only a single seizure, if they meet the other criteria required by this definition. For each case and control, the investigator must have a level of certainty of at least 80% that they actually do have epilepsy. (A question regarding the level of certainty is included in the overview form of the EpiNet record.)

Case Selection:

Cases will be recruited over four years. Cases will be people with epilepsy who have died from definite or probable SUDEP after the start of the study, and provided we learn of the death within six months.

We will use the modified criteria for diagnosis of SUDEP proposed by Devinsky et al in early 2018[26]

Definitions of SUDEP

- **Definite SUDEP:**
  Sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death in an individual with epilepsy with or without evidence of a terminal seizure and excluding documented status epilepticus (seizure duration ≥ 30 min or seizures without recovery in between), in which investigation and post-mortem examination, including toxicology, do not reveal a cause of death other than epilepsy.
- **Definite SUDEP Plus other Comorbidity:**
  Satisfies definition of “Definite SUDEP”, but a concomitant condition other than epilepsy is also identified before or after death, and if the death may have been due to the combined / synergistic effects of both conditions, and if autopsy or direct observations / recordings of terminal event did

Robert Scragg 4/11/18 22:24
Commenta [1]: These variables need to be simple so that they can be used by all countries involved with the study.
Could include:
1. Years of education
2. Currently employed (Yes, No)
3. Occupation (more difficult to code)
4. Area of residence (part of NZDep in NZ, but probably not available for all participating countries.

We could enquire from our collaborators which they can easily collect.

user 24/10/18 20:13
Commenta [2]: Is this date reasonable? We need a date to ensure:
1) we are not selecting for people at low risk of SUDEP (ie the SUDEP cases have already died, and the survivors are left.)
2) we want people with active epilepsy who still live in the catchment area

user 4/11/18 22:17
Commenta [3]: Is this sensible? I think we need to have a time limit to ensure we can get accurate information from the relatives, and so that there is not too great a difference re questions asked of controls. I had previously suggested 3 months, but colleagues have suggested extending to 6 months

not prove the concomitant condition to be the cause of death. Differs from cases in which there is another condition that could independently cause death (i.e, Possible SUDEP).

- **Probable SUDEP:**
  Same as “Definite SUDEP” but without autopsy. The victim should have died unexpectedly while in a reasonable state of health, during normal activities, and in benign circumstances, without a history of another potentially fatal disease. Also includes cases with limited autopsy (ie, restriction of organs examined) or extensively decomposed body that limits forensic examination.
- **Probable SUDEP Plus other Comorbidity:**
  Same as “Probable SUDEP” but with a history of a potentially synergistic, but not a competing, cause of death.
- **Possible SUDEP**:
  The sudden death of an epilepsy patient in which there is a competing cause of death based on evidence from death scene and circumstances, medical history, or autopsy findings, or the confidence in the epilepsy diagnosis or the severity or presence of recent seizures is moderate or low.
- **Resuscitated SUDEP:**
  A patient with epilepsy who survives resuscitation for >1 hr after a cardio-respiratory arrest that is not due to another disorder (eg, cardiac) identified after investigation.
- **Not SUDEP:**
  A clear cause of death is known or evidence of epilepsy is uncertain.
- **Unclassified:**
  Incomplete information available; not possible to classify

We will include in the study patients who are diagnosed with:

- Definite SUDEP:
- Definite SUDEP Plus other Comorbidity
- Probable SUDEP:
- Probable SUDEP Plus other Comorbidity:
- Resuscitated SUDEP if the patient died within 24 hours of the initial collapse

In New Zealand, we will arrange for coroners and forensic and coronial pathologists to notify the research team of all people with epilepsy who die unexpectedly. We will also ask Epilepsy New Zealand field workers, general practitioners, physicians and paediatricians to notify us when they hear of someone with epilepsy who has died. Finally, we will review Ministry of Health national administrative datasets to identify patients who have SUDEP reported as their cause of death, or epilepsy listed as a contributing factor to their death; this will comprise our final check to ensure that we have not missed anyone who died from SUDEP; however, if we learn of a patient's death more than six months after death we will not include them in this study.

Co-investigators from other centres will adopt similar approaches to ensure that the majority of people who die from SUDEP are considered for this study;

All cases will be reviewed by two members of the steering committee to ensure that they meet the entry criteria; if there is disagreement, a third member of the steering committee will adjudicate. Investigators will send a de-identified summary of the circumstances of death, including the post mortem report, police report and coroner's report, if available; these will be scanned and sent electronically to the review committee.

Control subjects:

Controls will be people with epilepsy who will be individually-matched by age (±2 years), sex, centre, and enrolled in the cohort at the time of death of the case (with four controls for each case). Controls will not be matched for other variables, such as duration of epilepsy, type of epilepsy, aetiology or seizure type, as any variable that is used for matching cannot then be identified as a risk factor. For each case, four controls will be randomly selected from all patients in the same cohort who meet the above matching criteria, as cases enter the study (incidence-density sampling). When an investigator

user 24/10/18 19:23
Commenta [4]: Do we include patients in this category? I suggest we do if the patient then dies within 24 hr.

user 4/11/18 22:18
Commenta [5]: How is this going to be determined? I suggest each case reviewed by 2 members of central committee and if disagreement a 3rd adjudicates; do we need to spell this out?

Robert Scragg 2/11/18 10:44
Commenta [6]: I agree it is a good idea to have some form of quality control such as a central review. If initial reviews suggest the quality is OK for a specific centre, then it would only need to be done on a sample of cases going forwards.

user 4/11/18 22:26
Commenta [7]: Is this practical?

Robert Scragg 4/11/18 22:19
Commenta [8]: The term incidence-density sampling refers to the method of recruiting controls (at the same time as cases).
Random sampling of 4 controls from all eligible patients for a case could be done locally by each centre using software such as Winpepi or OpenEpi. We would best require that each centre provides evidence of its random selection by keeping some record of the random number generator each time it is used.

becomes aware of a SUDEP case, they will identify all people with epilepsy who are in their cohort who are the same sex as the case and within two years of the age. These cases will be numbered. A publically available random number generator will be used (eg Winpepi or OpenEpi) to generate ten possible controls; the first four subjects who are living within the centre's catchment area (i.e local residents) will be chosen as controls, and attempts will be made to contact them. If any of these people cannot be contacted, or they do not agree to act as controls, the next person on the list will be selected. Each centre will send a record of the random number generation to the EpiNet administrator each time the random number generation is used to identify controls; this is to provide confirmation that the controls are randomly selected. Details will be recorded regarding each patient for whom contact is attempted.

Data for this study will be recorded in a special registry within the EpiNet database. Patients may already have records in EpiNet, but this is not essential. If investigators already have a comprehensive, searchable database, then this database can be used to identify control subjects. If patients do not already have an EpiNet record, then they will have one created when they are identified as a case or control subject for this study.

Centres Included:

We will conduct the study in approximately ..x.. centres with the ability to contact patients who are selected as controls; many of these centres have 1000 patients or more in their epilepsy cohorts. Neurologists who already participate in the EpiNet project, and colleagues and associates of the named co-investigators, have been invited to collaborate. Centres from which investigators and collaborators have been identified are listed below.

Four New Zealand centres with suitable cohorts have so far been identified (Auckland, Wellington, Christchurch, Dunedin), which together provide epilepsy services for over half of New Zealand's population; we anticipate enrolling 10 -12 SUDEP cases per year in New Zealand. (We expect to identify more cases of SUDEP as a result of the screening that we will be undertaking; however, we may not learn of all the cases in the three month time window, and others will not be included in any New Zealand investigator's cohort.)

Data Collection:

When SUDEP cases are identified, research staff will write to their relatives, and matched controls, describing the study. The letter will include a participant information sheet (approved by the appropriate ethics committee). A trained nurse or research assistant will subsequently ring, and after getting consent, administer a structured questionnaire. Information will be collected about behaviour in the immediate period before death. Relatives will be asked about the deceased's sleeping arrangements for the night immediately prior to death, and whether this was different from the typical sleep arrangements.

Controls will be asked questions relating to a specific nominated night's sleep. A night will be randomly chosen between one and two weeks prior to the interview. Information will be collected about usual behaviour patterns during the fortnight before the nominated date and time for controls.

We expect a high response rate amongst control subjects because of the seriousness of this issue.

The following information will be recorded in the EpiNet database for SUDEP cases and controls.

- Demographic data:
  - Age, gender, ethnicity.
- Socio-economic factors;
  - years of education,
  - employment,
  - income brackets
- Epilepsy factors:
  - type of epilepsy and / or epilepsy syndrome;
  - aetiology;
  - when the epilepsy commenced, and its duration;
  - the seizure type(s) and seizure frequency over the previous year; specifically, whether the patient experienced tonic clonic seizures;
  - frequency of nocturnal seizures;
  - time passed since the most recent seizure of each type, and specifically tonic clonic seizures;

Robert Scragg 17/10/18 19:34
Commenta [9]: We need to list all participating centres, with expected number of cases so that reviewers will be reassured we will recruit enough. This was a point raised by the reviewers of the EOI, so we must address it.

Robert Scragg 21/10/18 15:12
Commenta [10]: We will need to include the participant information sheet in the initial letter sent to relatives and controls. Then it is OK to call and get consent over the phone – as they will have had the letter for 2-3 days (or more) and had time to think about participation. The Ethics committees will not approve cold-calling.

Robert Scragg 4/11/18 22:20
Commenta [11]: We should aim to get specific information for a nominated sleep. The pattern for the last sleep may have been different to usual practice for the case.

- Sleeping arrangements (these questions will be asked of cases for the last sleep, and the usual sleep behaviour over the previous two weeks; for controls, they will be asked regarding a nominated night's sleep - chosen at random between one and two nights prior to the interview, and for the usual sleep behaviour over the previous two weeks):
    - whether the patient slept alone;
    - whether any nocturnal supervision was in place, and if so, the nature of the supervision;
    - whether any monitoring device was being used to identify if the patient had a seizure;
    - whether the patient used a seizure-detection device, and if so, the nature of the device;
    - whether the patient used a special anti-suffocation pillow;
- Treatment for epilepsy:
    - was the patient under regular follow-up with a specialist or primary care physician;
    - the AEDs the patient had received in the week before death or interview;
    - whether the patient took the medication as prescribed (based on serum drug levels, drug dispensing records, and relatives' reports);
    - whether AED levels had been measured in the past year; (post mortem levels will be recorded for cases, if these were measured by the pathologist.)
    - whether treated with surgery or vagal nerve stimulation;
- Co-morbidities
    - other co-morbidities- including smoking history or a history of sleep apnoea;
    - history of mental health and / or psychiatric disorders;
    - treatment with other drugs-in particular, SSRI drugs;
    - alcohol and other recreational drug use; regular use and then use during the 24 hours prior to death, or nominated date for controls; (post mortem levels will be recorded for cases, if these were measured by the pathologist.)
- Investigations:
    - whether patient had a structural lesion on MRI
    - the result of EEG
    - the result of routine ECG.
- if female, whether the patient was pregnant;
- whether any first degree relatives have died suddenly;
- who provided the information;
    - spouse / partner; parent; child; sibling; friend; other

For SUDEP cases:

- the circumstances of death;
    - at home; at work / school / other educational institute; residential care / hospital; other
- whether the death was witnessed;
- whether death occurred while the patient was sleeping, and if so, whether the patient was sleeping alone; whether this was the patient's usual sleep arrangement;
- whether the patient had a seizure witnessed at the time of death, and if so,
    - the nature of the seizure, or, if no seizure was witnessed,
    - whether there was supportive evidence to suggest the patient had a seizure;
- the position in which the patient was found.
- whether resuscitation was attempted.
- whether an autopsy was performed
- the coroner's assessment of cause of death.

Information regarding the nature of the epilepsy and seizures will be entered by neurologists; other data will be entered by research assistants and nurses.

Sample size calculations:

200 cases and 800 controls will detect an odds ratio of 1.7 over a control exposure range of 20% to 70%, with 80% power and 95% confidence level (2-sided). If the estimated risk of SUDEP is 1/1000 per patients per year, then we will need 200 000 patient-years of follow up. For this reason, it is not practical to undertake this study in New Zealand alone. The cohorts we define will be enriched, as they will have a high incidence of patients with drug resistant epilepsy; the risk of SUDEP in this

user 8/10/18 15:00
Commenta [12]: is there a recognised questionnaire for assessing compliance?

Robert Scragg 4/11/18 22:20
Commenta [13]: Likely to be hard to get accurate information on this, as relatives could hide such information if they thought it to be socially undesirable.
Could ask questions about regular use of alcohol and recreational drugs, including binge drinking, without directly linking it to the last sleep.

patient group may be as high as 1 in 200[1]; the number of PWE we need to follow for four years will therefore probably be between10 000 and 50 000.

Data analysis:

Data cleaning will be performed by a member of Prof Scragg's department prior to analysis. Odds ratios will be calculated using the Mantel-Haenszel method and conditional logistic regression to control for covariates.

Robert Scragg 4/11/18 22:22
Commenta [14]: Changed to conditional logistic regression to run with matching at the individual level.

Funding:

Funding is being sought to:

i) adapt the EpiNet records to collect the information specific to this SUDEP study for cases and controls;
ii) payment of salaries for New Zealand research staff and an administrator;
iii) payment of $NZ3000 dollars to each investigator/collaborator for each case (with associated controls) for whom data is successfully collected;
iv) payment to national coordinators for costs associated with the co-ordination of this study at a national level: obtaining ethics and regulatory approval, coordination with individual centres and co-investigators; these costs would be up to a maximum of $? / centre;
v) data management and cleaning

Modifications to EpiNet

We are already in the process of developing a form to collect data regarding SUDEP, having obtained a small project grant from the Neurological Foundation in May to do this. However, following consultation with colleagues from around the world, and in particular from participants in the North American SUDEP study, we are adding further questions to the SUDEP form; this will allow meaningful combination of the datasets for SUDEP cases in the future. (Note that the North American study is not collecting data from controls.) In addition, we will develop a modified version of the form for subjects chosen as controls for the study.

Robert Scragg 17/10/18 21:39
Commenta [15]: Add reference for this study so that it is clear it is not part of this study (ie. a north American arm).

Because this study is being conducted from many centres around the world, some of which already have their own epilepsy databases, we are planning to use SNOMED terms to record data within EpiNet as much as possible. In particular, we will use these terms to record information relating to co-morbidities and drugs. This will provide a standardised approach to collecting the data in the forms and sorting the data in the data-extract. At the same time, we will re-organise the aetiology form so that it, too, uses SNOMED forms; this should allow easier mapping to EpiNet from other centres' databases.

The SUDEP registry and case-control study we are proposing will not be a stand-alone database; instead the SUDEP study is part of the larger EpiNet project; some of the patients included in the SUDEP study will already have records in the First Seizure registry and the First AED registry; some of them may also have records in the AED withdrawal registry. EpiNet has been designed to allow investigators to enter data about a person's epilepsy in the most efficient manner possible. We do not want people to have to enter the same data more than once. We therefore need to integrate the SUDEP form with the other forms that already exist within EpiNet

Research Impact

1) Benefits:

We aim to improve understanding of the pathological basis of SUDEP. It is crucial to identify factors associated with an increased risk of SUDEP if we are to reduce this risk and prevent avoidable deaths. We will focus on factors that could be altered relatively easily. The example set by New Zealand's landmark case-control study in sudden infant death syndrome (SIDS) is notable[27 28]. This research, involving co-Investigator Prof Scragg, resulted in a dramatic reduction in SIDS in New Zealand. The researchers identified that the risk of death was associated with sleeping prone, and advising parents of this simple fact had a dramatic impact on reducing death rates. SUDEP probably now kills more New Zealanders than SIDS. Like SIDS, SUDEP typically occurs while the individual is

asleep. If we find an association with sleeping arrangements –sleeping alone, being monitored overnight, or use of anti-suffocation pillows - then it should be relatively easy to reduce the incidence of SUDEP via public health campaigns. If we find an association with sleep apnoea or smoking, these health problems can be addressed. If we confirm the increased risk with tonic clonic seizures, this information will be shared with PWE, their families, physicians and epilepsy support workers, and health care administrators so that PWE receive more effective treatment for this seizure type; this may entail more frequent clinic reviews, closer monitoring of AED use, and enhanced efforts to improve compliance. These relatively simple changes in management would contribute to cost-effective economically sustainable solutions to reduce the risk of SUDEP. If an association is found with use of SSRI drugs, this may lead to a randomised controlled trial of SSRI drugs in people at high risk of SUDEP. The New Zealand-led EpiNet project could be used for multinational pragmatic randomised controlled trials of this nature.

2) Activities to maximise benefits:

Although SUDEP places PWE at far higher risk of death than the general population, and kills more New Zealanders than fires, public awareness is low. This research will enhance knowledge about this problem. We will publish our findings in high-impact journals and present the results at national and international meetings. The research team has a strong track record in publishing outputs in the field of epilepsy and SUDEP[1-3 5 6 8 26 29-35], including the largest case control study of SUDEP[6] and an influential meta-analysis of SUDEP[5]. Prof Scragg's experience with translating research findings to public awareness will ensure we disseminate via the right channels for maximum impact. The research team includes members with backgrounds in medical education and prominent roles in the International League against epilepsy (ILAE). We will inform GP practices, ILAE chapters, EpiNet collaborators, epilepsy support groups (Epilepsy New Zealand and other chapters of the International Bureau for Epilepsy), and also the NZ Ministry of Health who would be likely to run a media campaign to notify the public of any important findings.

Responsiveness to Māori

Epilepsy is more common in people from lower socio-economic groups, and there is evidence that SUDEP is also more common in these groups[1]. There is no information at present regarding the incidence of SUDEP in Maori. However, because Maori have a higher incidence of other illnesses associated with social deprivation, it is likely that SUDEP is more common in Maori; this study will help determine if this is the case. There is scant knowledge regarding epilepsy and Maori in general, and the EpiNet studies we are conducting are helping to generate information to improve this knowledge base. We would like to get a Maori health worker involved with the research team to conduct interviews with the whanau of Maori who die from SUDEP; as well as helping with this particular study, this will hopefully help grow capacity in Maori health research.

Previous studies on the use of the EpiNet platform were developed after consultation with Whaea Mata Forbes (Ngāti Tama, Ngāti Mutunga), previously Māori Health Consultant for Auckland DHB. Dr Bergin has continued this relationship with Dr Helen Wihongi, the Director of Maori Health research for the Northern DHBs, to ensure the proposed research meets requirements of the Treaty of Waitangi and Tikanga Best Practice, and that the study is supported by Māori. Lines of communication between the Research advisor Māori and the research team will remain open, and issues relating to Māori will be discussed and if necessary include the Chief Advisor Tikanga for Waitemata and Auckland DHBs.

Expertise and Track Record of the Research Team

Robert Scragg 17/10/18 21:47
Commenta [16]: This section needs to be expanded.

Dr Peter Bergin is the medical director of the Auckland Hospital Epilepsy Surgery Programme. He is past president of the New Zealand Chapter of the ILAE, and the current President of Epilepsy New Zealand. He established the EpiNet project and is chairman of the EpiNet steering group. He was awarded a Clinical Fellowship by the Health Research Council in 2014 to develop the EpiNet project. (0.1 FTE)

Prof Robert Scragg is an epidemiologist with substantial experience in conducting case control studies. He was the lead epidemiologist on the New Zealand Cot Death Study that resulted in halving the mortality rate in New Zealand[27 28]. Other case control studies he has carried out include neural tube defects[36], gallstone disease[37-39], asthma deaths[40], cerebrovascular disease[41], coronary heart disease[42-46], Paget's disease[47], pertussis[48] and giardiasis[49-51]. These studies were earlier in his career,

as his recent studies have been either cross-sectional studies or randomised controlled trials. He will advise on the design and conduct of the study, oversee the data management and cleaning, carry out the data analyses, and contribute to writing scientific reports. (0.1 FTE)

Dr Ian Rosemergy is clinical lead for neurology and head of the epilepsy group at Wellington hospital. He is on the committee of the NZLAE and was previous secretary. (0.05 FTE)

Dr Debbie Mason is a neurologist in Christchurch and current President of the Neurological Association of NZ. (0.05 FTE)

Prof Ettore Beghi (Milan) is an experienced epilepsy epidemiologist who is on the EpiNet steering committee, co-chair of the Epidemiology Panel of the European Academy of Neurology, and previous co-chair of the Epidemiology Commission of the ILAE; he helped develop the ICD-11 classification of epilepsy. He represents the Italian Epilepsy Chapter members who will participate in the project. (0.03 FTE)

Prof Dale C Hesdorffer (New York) is an experienced epilepsy epidemiologist who has written extensively on SUDEP[1 5 7 26 29-32], including the public health burden. She has co-authored recommendations for the investigation and certification of death in people with epilepsy. She has written a manuscript on a case-control study of risk factors for SUDEP across four sites, and considered whether antiepileptic drugs or generalized tonic-clonic seizure frequency increases SUDEP risk. With Philippe Ryvlin, she considered the long-term surveillance of SUDEP in drug-resistant epilepsy patients with the suggestion that SUDEP risk decreases in those with VNS therapy. She is interested in SUDEP in people with low socioeconomic factors. (0.03 FTE).

Dr Yvonne Langan (Dublin) is a Clinical Neurophysiologist at St James's Hospital, Dublin and Senior Lecturer at Trinity College, Dublin. She trained in neurology and clinical neurophysiology in UK and Ireland. She has a particular interest in epilepsy mortality and was first author on the largest case control study of SUDEP reported to date[5 6 8 30]. (0.03 FTE)

Prof Phil Smith (Cardiff) is a neurologist with a special interest in epilepsy. He is the past president of the Association of British Neurologists (2015–17) and was President of the UK Chapter of the International League Against Epilepsy (2008–11). He co-edits Practical Neurology and has a busy commitment to training as Sub-Dean for Assessments, and Associate Medical Director for Quality for the Royal College of Physicians. (0.03 FTE)

Prof Mark Richardson (London) is on the EpiNet steering group. He is a clinical epileptologist and Head of Division of Neuroscience at King's College London, Director of King's Health Partners Neurosciences, and was a member of the Scientific Advisory Committee of Epilepsy Research UK for 10 yr. (0.03 FTE)

Prof Hannah Cock (London) is Professor of Epilepsy & Medical Education, Institute of Medical & Biomedical Education, member of ILAE (global) Epilepsy Education Task force. (0.03 FTE)

Dr Rhys Thomas (Newcastle, UK) is a consultant neurologist with interest in mortality in epilepsy (0.03)

Ass Prof Wendyl D'Souza (Melbourne) is on the EpiNet steering committee, head of epilepsy services at St Vincent's hospital, and has an academic appointment at the University of Melbourne. He has expertise in neurology, epilepsy, epidemiology, public health and a wide spectrum of brain wave interpretation including circadian, prolonged invasive and provoked recordings. He divides his time equally as a clinical leader as head of epilepsy services, with 17 years experience, in a world-leading clinical epilepsy programme. He leads a neuro-epidemiology and health services research team at the University of Melbourne. (0.03 FTE)

Dr Elizabeth Donner (Toronto), is the Director of the Comprehensive Epilepsy Program at the Hospital for Sick Children and an Associate Professor in the Faculty of Medicine at University of Toronto. She holds peer-reviewed funding to examine the risk factors for sudden death in epilepsy and the efficacy of dietary therapies for drug-resistant epilepsy. Most recently, her research has demonstrated that the rates of sudden unexpected death in children with epilepsy are equal to the rates of sudden unexpected death in adults with epilepsy. (0.03 FTE)

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