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Foster, E;Chen, Z;Vaughan, DN;Tailby, C;Carney, PW;D'Souza, W;Au Yong, HM;Nicolo, JP;Pellinen, J;Carrillo de Albornoz, S;Liew, D;O'Brien, TJ;Kwan, P;Ademi, Z

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STUDY PROTOCOLS

Prospective multisite cohort study of patient-reported outcomes in adults with new-onset seizures

Emma Foster[1,2,3] | **Zhibin Chen**[1,4,5] | **David N. Vaughan**[6,7] | **Christopher Tailby**[6,7] | **Patrick W. Carney**[6,8] | **Wendyl D'Souza**[9] | **Hue Mun Au Yong**[1,2,3] | **John-Paul Nicolo**[1,2,3] | **Jacob Pellinen**[10] | **Sara Carrillo de Albornoz**[11] | **Danny Liew**[5] | **Terence J. O'Brien**[1,2,3,4] | **Patrick Kwan**[1,2,3,4,5] | **Zanfina Ademi**[5]

[1]Department of Neuroscience, Central Clinical School, Monash University, Melbourne, Victoria, Australia

[2]Department of Neurology, The Royal Melbourne Hospital, Parkville, Victoria, Australia

[3]Department of Neurology, Alfred Health, Melbourne, Victoria, Australia

[4]Department of Medicine, The University of Melbourne, Parkville, Victoria, Australia

[5]School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia

[6]Florey Institute of Neuroscience and Mental Health, Melbourne, Victoria, Australia

[7]Department of Neurology, Austin Health, Heidelberg, Victoria, Australia

[8]Eastern Health Clinical School, Monash University Faculty of Medicine, Nursing, and Health Sciences, Clayton, Victoria, Australia

[9]Department of Medicine, St Vincent's Hospital Melbourne, University of Melbourne, Fitzroy, Victoria, Australia

[10]Department of Neurology, University of Colorado School of Medicine, Aurora, Colorado, USA

[11]Centre for Health Economics, Monash Business School, Monash University, Caulfield East, Victoria, Australia

Correspondence
Dr Emma Foster, Central Clinical School, Monash University, 99 Commercial Road, Melbourne, Vic. 3000, Australia.
Email: emma.foster@monash.edu

A/Prof Zanfina Ademi, School of Public Health and Preventive Medicine, Monash University, 553 St Kilda Road, Melbourne, Vic. 3000, Australia.
Email: zanfina.ademi@monash.edu

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Abstract

Objective: New-onset seizures affect up to 10% of people over their lifetime, however, their health economic impact has not been well-studied. This prospective multicenter study will collect patient-reported outcome measures (PROMs) from adults with new-onset seizures seen in six Seizure Clinics across Melbourne, Australia and The University of Colorado, USA.

Methods: Approximately 450 eligible patients will be enrolled in the study at or following their initial attendance to Seizure Clinics at the study hospitals. Inclusion criteria for the study group are those with new-onset acute symptomatic seizures, new-onset unprovoked seizures, and new-onset epilepsy. Inclusion criteria for the three comparator groups are those with noncardiac syncope, those with psychogenic nonepileptic seizures, as well as published PROMs data from the Australian general population. Exclusion criteria are those aged less than 18 years, those with a preexisting epilepsy diagnosis, and those with intellectual disabilities or other impairments which would preclude them from

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comprehending and completing the questionnaires. Patients will complete eight online questionnaires regarding the effect that their seizures (or seizure mimics) have had on various aspects of their life. These questionnaires will be readministered at 6 and 12 months. Patients with new-diagnosis epilepsy will also be asked to share the reasons why they have accepted or declined antiseizure medications.
Analysis: Primary outcome measures will be quality of life, work productivity, informal care needs, and mood, at baseline compared to 6 and 12 months later for those with new-onset seizures and comparing these outcomes to those in the three comparator groups. Secondary outcomes include mapping of QoLIE-31 to the EQ-5D-5L in epilepsy, modelling indirect costs of new-onset seizures, and exploring why patients may or may not wish to take antiseizure medications.
Significance: These data will form an evidence-base for future studies that examine the effectiveness of various healthcare interventions for new-onset seizure patients.
Ethics and dissemination: This study is approved by the Alfred Health Human Research Ethics Committee (SERP: 52 538, Alfred HREC: 307/19), the Austin Health Human Research Ethics Committee (HREC/59148/Austin-2019), and the Colorado Multiple Institutional Review Board (COMIRB) (COMIRB #20-3028).
ANZCTR trial registration number: ACTRN12621000908831.

KEYWORDS
mood disorders, patient-reported outcomes, quality of life, seizures, work productivity

1 | INTRODUCTION

The health and economic burden of epilepsy is profound. The 2016 Global Burden of Disease Study estimated that worldwide, 182.6 per 100,000 disability-adjusted life years (DALYs) were due to epilepsy,[1] and epilepsy-related DALYs have increased by 30%[2] between 1990 and 2010. Far less is known about the social and economic consequences of new-onset seizures, which affect up to 10% of people over their lifetimes.[3] New-onset seizures impose a significant burden not only on our healthcare system but also through productivity losses, out of pocket costs, new or increased informal care needs, and disease-related anxiety and depression.[4]

Direct medical costs of epilepsy have been well studied, but there is a paucity of evidence for new-onset seizures. Direct medical costs for new-onset seizures include ambulance transfers to hospital, emergency department care, hospital ward admissions, investigations including neuroimaging and electroencephalograms (EEGs), outpatient visits, and antiseizure medications. The assessment of direct medical costs for patients newly diagnosed with epilepsy provides an important snapshot of patient

Strengths of this study

- Multisite, prospective, longitudinal assessment of patient-reported outcome measures for adult patients attending a Seizure Clinic following new-onset seizures.
- Comprehensive assessment of the impact that new-onset seizures has on quality of life, work, informal care needs, mood, and out of pocket costs, as well as understanding treatment decisions from a patient's perspective.

Limitations of this study

- Study participants will be recruited from tertiary hospital Seizure Clinics; results may not be generalizable to all those with new-onset seizures.
- Loss to follow up at 6- and 12-month timepoints may limit generalizability of study outcomes across all those attending Seizure Clinics

costs during the early period of intensive consultation and investigation typically required for new-onset seizure work-up. A multicenter observational Italian study[5] reported "new referral" costs averaged $US4473 per patient per year, compared to an "old referral" cohort with established epilepsy diagnoses that had costs averaging $US845 per patient per year. Importantly, two-thirds of these "new" costs related to hospitalization. Similar patterns were observed in a prospective Russian study,[6] with direct medical costs due to newly diagnosed epilepsy outweighing direct medical costs of established and well-controlled epilepsy, at €782 and €646 per person, respectively. These studies do not, however, capture the out of pocket costs to patients, which can impose a substantial personal impact. Even in countries with universal healthcare, financial gaps exist for many services (eg, ambulance transfers, outpatient testing, medications) that are not fully covered by public and private health insurances. These costs may impose a substantial burden to patients and their families and become a barrier to accessing necessary healthcare. Further research is needed to measure and quantify direct medical costs and out of pocket costs of new-onset seizures, and to identify factors that influence decisions to workup new-onset seizures in the in- or outpatient setting.

Indirect costs of new-onset seizures are not well reported. The main sources of indirect costs are likely to be due to reduced work productivity and increased informal care needs. Reduced work productivity may be due to sick leave (absenteeism), reduced work capacity while at work (presenteeism), and early retirement. Employment for new-onset seizure patients may be affected by limitations to potentially dangerous activities, such as operating heavy machinery or driving, and these restrictions may be in place for at least 6-12 months.[7] If alternative work duties are not readily available, individuals with new-onset seizures may need to retrain, change careers, or face unemployment or early retirement. A large UK-study reported that almost 5% of people who have experienced a single seizure or newly diagnosed epilepsy had to change jobs within 12 months because of their seizure(s).[8] Informal care needs of individuals with new-onset seizures are likely underrecognized and underreported and may impose a considerable burden on families and carers. This may include driving patients to medical appointments, school and work, and temporarily assuming potentially dangerous household duties, such as bathing infants or kitchen duties.[4] The indirect costs of new-onset seizures are understudied, and the true burden, including absenteeism, presenteeism, early retirement, and change in informal care needs may be substantially greater than previously estimated.

Patients' view of their health and quality of life is an underreported but an important outcome of new-onset seizures, and assessable through patient reported outcome measures (PROMS). PROMS is an overarching term encompassing measures of general- and health-related quality of life (HRQoL), disease symptoms, and level of function. HRQoL may be measured by generic health state utility instruments such as the 5-level EuroQoL Group's 5-dimension instrument (EQ-5D-5L), which assesses five HRQoL domains comprising mobility, pain/discomfort, usual activities, self-care, and anxiety/depression. Patients rate these domains at five levels, for example "no problems," "slight problems," "moderate problems," "severe problems," and "extreme problems." HrQOL may also be measured by disease-specific validated scales such as the quality of life in epilepsy inventory (QoLIE-31). Several generic screening instruments have been validated for assessing anxiety and depressive symptoms, such as the Hospital Anxiety and Depression Scale (HADS). Some literature already exists on the neuropsychological effect of new-onset seizures, particularly in regard to anxiety and depression. In a study of patients with single seizures, 17% were moderately to extremely fearful of having a recurrent seizure, and 38% stated that 12 months after the event, the seizure still had a moderate to extreme impact on their quality of life.[9] It is important to note that psychiatric comorbidities occur at increased frequency in patients with unprovoked new-onset seizures. These psychiatric comorbidities and cognitive problems may even precede seizure occurrence.[10] A study found that patients with unprovoked new-onset seizures had higher prevalence of depression (33%) compared to controls, and many had depression and anxiety present at the time of their index seizure.[11] There is a strong association between new-onset seizures and depression, suggesting common disease pathways.[12] Prompt recognition and treatment of psychiatric morbidity in new-onset seizure patients may help reduce the effect this event has on emotional well-being and quality of life, and relevant PROMS questionnaires may be helpful for expediting diagnosis and management.

Finally, a proportion of patients with new-onset seizures will meet epilepsy diagnostic criteria.[13] Establishing seizure control is a central goal of epilepsy management, and up to two-thirds of patients attain seizure-freedom with antiseizure medications.[14] However, a recent study from Western Australia found that 11.6% of a cohort of new-onset epilepsy patients remained untreated at follow-up.[15] Reasons for this "treatment gap" included the patients being unconvinced of their epilepsy diagnosis or need for treatment. The existence of a treatment gap in a high-income country with readily accessible universal healthcare is concerning. This is an important area requiring further exploration of patients' perspectives as to why they may or may not wish to take antiseizure medications.

There are many ways in which new-onset seizures cost patients, caregivers, and society. These include direct

medical costs and out of pocket costs, through health care utilization; indirect costs, through loss of ability to perform paid and unpaid work; and impact on quality of life and mood disorders, as assessed through PROMS. New-onset seizures are common and important neurological events, and further research is needed to better quantify their health and economic impact in our society. These data will form an important evidence base for assessing effectiveness of healthcare interventions in the first seizure management paradigm.

2 | METHODS AND ANALYSIS

2.1 | Aims

1. To measure the impact of new-onset seizures on people's quality of life, work productivity, informal care needs, out of pocket costs, and anxiety and depressive symptoms through validated questionnaires. These outcomes will be measured at the time of the initial Seizure Clinic appointment, and at 6- and 12-month intervals following this appointment.
2. To compare these new-onset seizure outcomes to outcomes for those with seizure mimics, specifically, noncardiac syncope and psychogenic nonepileptic seizures, as well as to the Australian general population.
3. To explore the factors that influence clinician and patient decision-making regarding initiation of antiseizure medication therapy for those with new-diagnosis epilepsy.

2.2 | Study design

2.2.1 | Summary

This is a multisite, prospective cohort study with a comparison cohort to understand the effect of new-onset seizures on people's quality of life, work, informal care needs, mood, and out of pocket costs. Participants complete validated questionnaires at their initial Seizure Clinic appointment, and again at 6 and 12 months to assess patient reported outcomes over time. Up to 450 patients will be recruited over a 3-year period. The study will be conducted at five Seizure Clinics in Melbourne, Australia (Alfred Health, Austin Health, Eastern Health, The Royal Melbourne Hospital, and St Vincent's Hospital Melbourne) as well as at the University of Colorado School of Medicine, USA. This is an investigator-initiated study, with no external funding received from public, commercial, or not-for-profit sectors. Multisite ethics approval was granted by the Alfred Health Human Research Ethics Committee (HREC 307/19), Austin (HREC/59148/Austin-2019), and the Colorado Multiple Institutional Review Board (COMIRB) (COMIRB #20-3028). The trial is registered with ANZCTR (ACTRN12621000908831). The trial commenced recruitment at Alfred Health in April 2020, and is anticipated to continue until at least 2023, or the target number of patients are recruited, whichever comes first.

2.2.2 | Recruitment procedure

1. Eligible patients are identified by researchers prior to, during, or after the initial Seizure Clinic appointment based on review of referral letters and/or outcomes of the clinic appointment. The study is explained verbally to the patient, and verbal informed consent is obtained. For patients who provide verbal consent to participate in the study, written consent is then obtained via an online purpose-built e-consent form that is included with the electronic questionnaires emailed to patients.
2. Responses from the completed questionnaires are automatically uploaded onto a secure online digital platform.
3. Researchers also complete a separate questionnaire, linked to the patient's digital platform profile, that contains a minimum amount of clinical data (eg, seizure type, investigation results) that are necessary to complete data analysis in line with the study objectives. These data points represent standard clinical information that are collected routinely during medical consultations.
4. If patients provide written consent for future contact, they are automatically sent a link to their nominated email addresses at 6 and 12 months to complete the same surveys to longitudinally measure the impact of new-onset seizures.

2.2.3 | Eligibility

Inclusion criteria

Adults aged 18 or over, who attend one of the study sites' Seizure Clinics via telehealth, telephone, or in-person, following their new-onset seizures or seizure mimic events. Patients must be able to give informed consent. The study group consists of those with new-onset acute symptomatic seizures, new-onset unprovoked seizures, and new-onset epilepsy. The two "seizure mimic" comparator groups consist of those with noncardiac syncope and those with psychogenic nonepileptic seizures (PNES). These are both common alternate referrals to Seizure Clinics. These comparator groups will be analyzed separately, as although they both may manifest with transient episodes of loss of

consciousness or functional impairment, they have very different underlying mechanisms, prognoses, and treatment strategies, justifying separate analyses. In addition, we will compare quality of life and productivity data from these study and comparator groups against published quality of life and productivity data drawn from the Australian general population. These general population data will be stratified based on sex and 5-year age brackets and so offer a fairly tailored comparison for individuals within the seizure and seizure mimic groups.

Exclusion criteria

Patients less than 18 years of age, those with a preexisting epilepsy diagnosis, and those with intellectual disabilities or other impairments which would preclude them from comprehending and completing the questionnaires. In addition, if patients are prescribed antiseizure medication at time of enrolment in the study, researchers will clarify the condition it is intended to treat. Many antiseizure medications are prescribed for a range of other, often common, conditions. For example, topiramate is often prescribed for migraine, and valproate is often prescribed for bipolar disorder. Patients in the study or comparator groups will be excluded if they are prescribed antiseizure medication for a preexisting seizure disorder, or if the reason for the antiseizure medication is unclear.

2.2.4 | Participant safety, risk management, and withdrawal

This is an observational study and does not involve a new therapy or device. This study does not pose any safety issues to participants. Participants complete internationally validated questionnaires, which will take approximately 20-30 minutes. The questions regarding anxiety and depressive symptoms are few in number, and not of a personal or invasive nature, but they may raise issues for some patients. If this is the case, research clinicians will encourage patients to discuss their concerns, and if appropriate, refer to their general practitioner for community psychology, or one of the mental health services attached to that study site's hospital. Consent may be withdrawn at any time by patients via email or telephone call. This means that the patient's data will not be included in data analysis.

2.2.5 | Assessment of quality of life

Health-related quality of life will be assessed by generic (EQ-5D-5L) and disease-specific (Quality of Life in Epilepsy Inventory, QOLIE-31) questionnaires. The EQ-5D-5L is a simple, generic measure of five dimensions of HRQoL used in economic evaluation: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression plus overall self-rated health. The self-rated EQ-5D-5L provides a basis for deriving preference-based HRQoL and calculating quality-adjusted life years (QALYs), which are used to compare the benefits of different interventions in cost-utility analyses (CUA). A valuation algorithm for EQ-5D-5L is required to generate utility values for the estimation of QALYs. An Australian algorithm for the newly developed five-level version of the EQ-5D using a discrete choice experiment to estimate preference weight for the EQ-5D-5L will be used. The discrete choice experiment was implemented in an online Australian-representative sample and an algorithm provides a 0 to 1 scale to estimate QALYs.[16]

The QoLIE-31 questionnaire contains 31 items split into 7 sections that are specifically designed to evaluate the emotional well-being, social functioning, energy levels, cognitive functioning, seizure worry, medication effects, and overall quality of life in adult epilepsy patients. Each item and section will be scored according to the scoring manual.[17] An overall score ranges between 0, representing the worst possible quality of life, to 100, representing a perfect quality of life, and will be calculated as the weighted total of the seven sections' scores.

2.2.6 | Assessment of costs

Indirect costs arising from lost productivity due to new-onset seizure-related absence from work, or days of inactivity, will be included, using the Work Productivity Activity Impairment (WPAI) questionnaire. Data regarding informal care duties will be collected using a purpose-built questionnaire with up to three questions: "do you receive informal, unpaid care?," and if yes, "how many hours of informal, unpaid care per week do you receive?," and "how many of these hours per week are provided by persons under the age of retirement?"

2.2.7 | Assessment of factors influencing antiseizure medication prescription and adherence

Where applicable, a questionnaire regarding antiseizure medication therapy initiation will be completed by clinicians to provide clinical context, and a separate questionnaire regarding treatment adherence is completed by patients. At time of epilepsy diagnosis, antiseizure medication therapy initiation will be defined as (1) "immediately treated" if the treating clinician recommends treatment and the patient commences treatment; or (2) "untreated" if the clinician does not recommend treatment or the

patient declines to start treatment. For "untreated" new-onset epilepsy patients, clinicians will provide reasons for not prescribing therapy. Patients who are prescribed therapy will complete a questionnaire regarding the factors that have influenced their decisions to commence or decline therapy.

2.2.8 | Statistical methods

Central tendency of continuous variables will be measured using mean and standard deviation if approximately normally distributed or using median and interquartile range if otherwise. Categorical variables will be summarized using frequency count and proportion. Wilcoxon signed-rank test will be used to assess the differences in utilities between baseline and each subsequent follow-up timepoint. Two sample t-test will be used to assess the association between dichotomous and independent continuous variables if the continuous variable is approximately normal, otherwise Mann-Whitney U-test will be performed. Chi-square test will be used to explore the associations between categorical variables and Fisher's exact test will be performed in case of rare events.

Repeated measures analysis using generalized linear mixed models (GLMMs) with random effects for patients will be used to assess differences in the baseline, 6-, and 12-month timepoints (change in quality of life, work productivity, and informal care) and between groups of interest. Purposeful selection of covariates approach using p-value <0.2 as cut-off will be performed to include potential confounding factors in multivariable GLMMs. Using the same purposeful selection of covariates approach, multivariable generalized linear models will be used to explore and estimate the effects of factors associated with clinicians' and patients' decision-making regarding initiation of antiseizure medication therapy in patients with new-diagnosis epilepsy. Reasons for treatment initiation decision and treatment adherence outcomes will be descriptively summarized.

Statistical significance will be set at p-value <0.05. The Holm-Bonferroni method will be used to correct p-values in multiple comparisons where applicable. All statistical analyses will be performed using *Stata* (StataCorp) or *R* (R Core Team).

2.2.9 | Power and sample size

Researchers will recruit approximately five new-onset seizure patients each week through the study sites. There are approximately 45 clinic weeks a year (accounting for doctors' leave and public holidays), which will allow recruitment of approximately 225 patients / year, and 450 patients by 2 years. Allowing for a 10% loss to follow-up as reported in previous publications, it is estimated that there will be follow-up data on approximately 405 participants. In order to assess baseline differences in a wider sense, utilities at the 6-month timepoint and at time of initial Seizure Clinic consultation will be analyzed, as the situation at the initial timepoint may be influenced by the condition that has led to the seizure (eg, acute stroke, brain tumor, etc). The sample size will provide 80% power to detect an effect size of Cohen's d_z=0.14 for the difference between baseline and at follow-up timepoints. If differences between the groups are observed, interpretation of results will consider whether these are below or above minimally important difference criteria for the EQ-5D (reported effect size=0.37 for UK algorithm; minimal Cohen's d_z=0.185 between outcomes correlation r=−1)[18] and QOLIE-31 (reported effect size=0.72; minimal Cohen's d_z=0.36).[19] The sample size has 96% and >99% power to detect the minimal clinically important differences for EQ-5D and QOLIE-31, respectively. Occurrence of missing values in variables relevant for the calculation or multivariable adjustment of results will be assessed. If missing values occur in a relevant proportion of patients (>10% in any group or with dissimilar occurrence in both groups), missing value patterns and associations of study variables with missingness will be assessed. Assumptions on the missing data mechanisms will be made on this basis and suitable imputation methods will be applied to quality-of-life data and work productivity.

2.2.10 | Primary outcomes

1. Quality of life, as measured by EQ-5D and QoLIE-31 questionnaires, at time of initial Seizure Clinic appointment (primary timepoint), and at 6- and 12-month intervals following this appointment
2. Effect of new-onset seizures on work productivity, as measured by WPAI, at time of initial Seizure Clinic appointment (primary timepoint), and at 6- and 12-month intervals following this appointment
3. Effect of new-onset seizures on informal care needs, as measured by the Informal Care Needs questionnaire, at time of initial Seizure Clinic appointment (primary timepoint), and at 6- and 12-month intervals following this appointment

2.2.11 | Secondary outcomes

1. Indirect costs of new-onset seizures will be assessed in terms of economic impact, derived from effect

on productivity, via WPAI, at time of initial Seizure Clinic appointment, and at 6- and 12-month intervals following this appointment
2. Factors contributing to a "treatment gap," that is, delayed initiation of antiseizure medication for those with new diagnosis epilepsy, will be assessed via purpose-built clinician- and patient-respondent questionnaires
3. Effect of new-onset seizures on self-rated anxiety and depressive symptoms, via HADS, at time of initial Seizure Clinic appointment, and at 6- and 12-month intervals following this appointment
4. Out of pocket costs of new-onset seizure (eg, attending hospital, clinic appointments, medications) will be assessed via a custom-built questionnaire, at time of initial Seizure Clinic appointment, and at 6- and 12-month intervals following this appointment

2.2.12 | Data security and handling, confidentiality, and security

Electronic records are kept on the secure, firewall and password-protected digital platforms at the study sites at which patients are recruited. Only authorized users will be granted access to this platform, and users will have individual usernames and passwords to track usage. Records will be kept for a minimum of 7 years. At completion of the study, principal investigators at each site will provide de-identified data to the chief investigator for analysis.

REDCap

Study data at all sites except St Vincent's Hospital Melbourne are collected and managed using the REDCap (Research Electronic Data Capture) electronic data capture tool hosted and managed by each individual site's institutions.[20,21] REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources. Study data for The Alfred are collected and managed using REDCap electronic data capture tools hosted by DATA and Analytics Services at Alfred Health. Study data for Austin Health and The Florey Institute of Neuroscience and Mental Health are collected and managed using REDCap electronic data capture tools hosted at The University of Melbourne. Study data for Eastern Health are collected and managed using REDCap electronic data capture tools hosted at Eastern Health.[20,21] Study data for The Royal Melbourne Hospital are collected and managed using REDCap electronic data capture tools hosted by The Royal Melbourne Hospital Business Intelligence Unit.[21] Study data for the University of Colorado are collected and managed using an institutional REDCap electronic data capture tools supported by NIH/NCATS Colorado CTSA Grant Number UL1 TR002535. Its contents are the authors' sole responsibility and do not necessarily represent official NIH views.

KLETCH. St Vincent's Hospital Melbourne collects, stores, and manages data for this study via a purpose-built secure online platform KLETCH. KLETCH is equipped with industry standard data security measures. All data are encrypted with AES-256 standard at-rest and with TLS/SSL at-transit in a data center with PROTECTED status certified from The Australian Signals Directorate (AS) and is Health Insurance Portability and Accountability Act (HIPAA) compliant. Patient confidentiality is protected at all times by adherence to the Australian Privacy Principles established by the Privacy Act 1988 (Cth).

2.2.13 | Patient and public involvement

Community engagement was not directly sought for the design, conduct, or recruitment of this study. We aim to engage with patient-advocacy organizations including the Epilepsy Foundation (Australia and US), Epilepsy Action Australia, and Brain Foundation to disseminate our findings.

CONFLICT OF INTEREST

EF reports grants from NHMRC Medical Postgraduate Research Scholarship (#APP1150482), grants from Brain Foundation Grant, grants from AVANT Doctors In Training Scholarship, grants from The Royal Australasian College of Physicians Research Entry Scholarship, grants from the Monash University Bridging Fellowship outside the submitted work. ZC is supported by the National Health and Medical Research Council of Australia Early Career Fellowship (GNT1156444) and has received grants from the University of Melbourne Early Career Researcher Grant Scheme. His institution has received research funding from UCB Pharma, outside the submitted work. DV reports NHMRC Project Grant (#APP1157145) and grants from Brain Australia, outside the submitted work. CT reports NHMRC Program Grant (#APP1157145) and grants from Brain Australia, outside the submitted work. PWC reports no disclosures relating to this project. WDS's salary is part-funded by The University of Melbourne. He has received travel, investigator-initiated, scientific advisory board, and speaker honoraria from UCB Pharma Australia & Global; investigator-initiated, scientific advisory board, travel, and speaker honoraria from Eisai Australia &

Global; advisory board honoraria from Liva Nova and Tilray; educational grants from Novartis Pharmaceuticals, Pfizer Pharmaceuticals, and Sanofi-Synthelabo; educational, travel, and fellowship grants from GSK Neurology Australia, and honoraria from SciGen Pharmaceuticals. He has an equity interest in the device company EpiMinder. HMAY reports no disclosures relating to this project. JP reports intradepartmental grants from the University of Colorado Department of Neurology outside the submitted work. J-P-N reports no disclosures relating to this project. SCA reports no disclosures relating to this project. DL reports no disclosures relating to this project. ToB reports NHMRC Program Grant (#APP1091593), grants from UCB Pharma, grants from Eisai Pharma, grants and personal fees from Zynerba Pharmaceuticals, grants from Biogen, outside the submitted work. PK is supported by a Medical Research Future Fund Practitioner Fellowship (MRF1136427). His institution has received research grants from Biscayne Pharmaceuticals, Eisai, GW Pharmaceuticals, LivaNova, Novartis, UCB Pharma, and Zynerba outside the submitted work; and he has received consultancy/speaker fees from Eisai, LivaNova, and UCB Pharma outside the submitted work. ZA reports no disclosures relating to this project.

AUTHORS' CONTRIBUTIONS

Dr Foster and A/Prof Ademi devised the study concept. Dr Foster wrote the original draft of the protocol. Dr Chen wrote the statistical aspects of the analysis. Dr Foster, Dr Chen, Dr Vaughan, Dr Tailby, Dr Carney, Prof D'Souza, Dr Au Yong, Dr Nicolo, Dr Pellinen, Ms Carillo de Albornoz, Prof Liew, Prof O'Brien, Prof Kwan, and A/Prof Ademi contributed to revisions of the protocol.

ETHICAL APPROVAL

The study has been granted multisite ethics approval by the Alfred Hospital HREC (SERP: 52 538, Alfred HREC: 307/19), for all sites apart from the Austin Hospital and the University of Colorado. Data collection and analysis at Austin Health has been approved by the Austin Health HREC (HREC/59148/Austin-2019). Data collection and analysis at University of Colorado has been approved by the Colorado Multiple IRB (COMIRB #20-3028). Governance has been granted by the Offices for Research at the individual study sites. Results of this study will be disseminated through publication in peer-reviewed journals and presentations at scientific conferences. Any amendments to the protocol will be approved by the relevant HREC and IRB prior to implementation. These changes will also be updated on ANZCTR (trial number ACTRN12621000908831). We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

ORCID

Emma Foster https://orcid.org/0000-0001-8958-3844
Jacob Pellinen https://orcid.org/0000-0002-0747-7210
Patrick Kwan https://orcid.org/0000-0001-7310-276X

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