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Validation of the Seizure-Related Impact Assessment Scale (SERIAS): a study protocol

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ABSTRACT

Introduction This study aims to validate the Seizure-Related Impact Assessment Scale (SERIAS). This novel patient-reported outcome measure (PROM) compares the 'trade-off' between seizures and treatment-related adverse effects, and measures epilepsy disability qualitatively and quantitively. It fills an important gap in PROMs for epilepsy clinical trials and practice.

Methods and analysis Adults with epileptologist-confirmed epilepsy from two Australian Epilepsy Centres are being recruited. People with functional seizures, or who are unable to self-complete English-language validated instruments are excluded. Participants providing informed consent are invited to complete questionnaires at baseline, 3 and 6 months later. SERIAS includes five questions that ask about the number of days per month that seizures or treatment-related adverse effects partially or fully impact work/home/school and family/social/non-work activities, as well as a visual analogue scale regarding epilepsy-related disability. SERIAS is completed alongside seven internationally validated instruments measuring treatment-related adverse effects, mood disorders and quality of life. Target recruitment is n=100, ensuring>50 people complete all questionnaires at all timepoints. Comprehensive psychometric analysis will be performed. Convergent validity will be investigated using bivariate correlations with relevant measures. Reliability will be investigated using Cronbach's alpha, McDonald's omega and test–retest correlation coefficients. SERIAS will be a novel PROM for epilepsy clinical trials and practice.

Ethics and dissemination Multisite ethics approval was granted by the Alfred Health Ethics Committee (HREC 17/23). Results of this study will be disseminated through publication in peer-reviewed journals and presentations at scientific conferences.

Trial registration number ACTRN12623000599673.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Multisite, prospective, longitudinal validation of a self-report epilepsy disability scale that balances seizure and seizure-related disability against treatment-related disability.
⇒ Validation cohort will include a broad range of people living with epilepsy in terms of age, sex, duration and type of epilepsy, seizure frequency, antiseizure medication regimen and exposure to dietary, neurointerventional (eg, vagus nerve stimulation) and resective epilepsy surgery treatments.
⇒ Study participants are being recruited from two national Comprehensive Epilepsy Centres; results may not be generalisable to all people living with epilepsy.
⇒ Loss to follow-up at 3 and 6 month timepoints may limit generalisability of study outcomes across all people living with epilepsy.
⇒ It is beyond the scope of this study to validate Seizure-Related Impact Assessment Scale (SERIAS) for people who are age <18 years at time of enrolment, and for people who cannot self-complete English-language versions of validated international instruments.

INTRODUCTION

Epilepsy is a common chronic neurological condition, affecting approximately 45.9 million people worldwide.[1] It is characterised by an enduring tendency towards epileptic seizures,[2 3] which drive much of the burden associated with epilepsy. This burden may include seizure-related accidents (eg, motor vehicle crashes), injuries (eg, fractures, burns and head injuries) and death (eg, drowning); a debilitating postictal ('after seizure') phase that affects work and home life through factors such as exhaustion and musculoskeletal pain; and 'seizure worry', where people experience substantial anxiety over the unpredictable nature of seizures and may deliberately curtail their activities because of this. Running parallel to seizure burden is treatment-related adverse effects. Antiseizure medications control seizures for approximately two-thirds of people with epilepsy,[4] but are associated with dose-related adverse effects including tiredness, psychiatric symptoms (eg, mood changes) and physical symptoms (eg, dizziness).[5] Non-pharmaceutical interventions may also exert substantial adverse effects. Vagus nerve stimulation (VNS) may cause hoarseness of voice, cough

and throat discomfort.[6] Ketogenic diet therapy may cause unintentional weight loss, diarrhoea or constipation and headache.[7] Resective epilepsy surgery may cause cognitive decline, personality or behaviour change, speech difficulties and weakness or poor balance.[8] In summary, seizures and treatment-related adverse effects may contribute substantially to the burden of epilepsy.

Self-reported burden of disease is increasingly recognised as an important outcome in clinical research and practice.[9] In epilepsy, there are many widely accepted international validated patient-reported outcome measures (PROMs) that are used to capture these data. For example, health-related quality of life (HRQoL) may be measured through generic (eg, EQ5D)[10] or epilepsy-specific instruments (eg, Quality of Life in Epilepsy Inventory, QoLIE-31 and QoLIE-89),[11] seizure severity through the Liverpool Seizure Severity Scale[12] and Seizure Severity Questionnaire,[13] epilepsy-related disability through the Global Assessment of Disability related directly to Seizures[14] and antiseizure medication adverse effects through the Liverpool Adverse Events Profile (LAEP).[15] However, these instruments have several important limitations. First, the majority of these instruments focus on capturing aspects of the seizure itself, such as degree of impaired awareness, but not seizure frequency. The sporadic nature of seizures means patients' epilepsy-related burden may fluctuate substantially over time. There is a need for a PROM instrument that asks after the severity of the seizure symptoms as well as the frequency of the seizures. Seizure-Related Impact Assessment Scale (SERIAS) is able to disambiguate a severe disability that is less frequent, from a milder disability that is common, and also how much of that disability is resulting from seizures versus from the treatment of seizures. Second, modifications to treatment regimens may improve seizure control, but these may come at the expense of substantial adverse effects. A treatment that reduces seizures by half, but causes substantial sleepiness every day may not ultimately prove to be of benefit. There is a need for a PROM that directly compares seizure-related disability against treatment-related disability, which longitudinally may demonstrate the 'trade off' between seizure control and modifying treatment regimens. Finally, SERIAS focuses on disability rather than quality of life. Disability and HRQoL are related but separate concepts. Disability may be defined as the degree to which a person is limited in carrying out activities of daily living due to disease-related impairment.[16] Examples of epilepsy-related impairment include hemisensory change and impaired awareness, and epilepsy-related disability may include missing a work meeting or a family function. Impairment and disability contribute to HRQoL, which is a broad measure that also includes a person's social functioning, perceived health status and well-being.[17]

A similar migraine-specific PROM, the Migraine Disability Assessment Scale (MIDAS), is the most implemented condition-specific PROM used in new neurological drug approvals in Europe.[18] MIDAS is a five-question instrument that measures disability by asking after migraine-related 'lost time' from school or work, household work or chores and family/social/leisure activities. It is widely utilised in clinical migraine research and practice.

In this prospective, multicentre study, we aim to create and validate the Seizure-Related Impact Assessment Scale (SERIAS) to address these critical gaps in epilepsy PROMs.

METHODS AND ANALYSIS

Aims

1. To assess the convergent and divergent validity of the SERIAS with relevant and established measures
2. To assess the psychometric reliability of the SERIAS and estimate the measurement error associated with derived scores.
3. To assess stability of the SERIAS over a short test–retest interval.

Study design

This is a multisite, prospective, unblinded cohort study that aims to validate the ability of the novel self-report SERIAS instrument to sensitively measure changes in epilepsy-related disability over time, based on seizure-related and treatment-related adverse effects. Participants will complete the SERIAS, alongside internationally validated generic and epilepsy-specific instruments, at baseline, and 3 and 6 months later. Clinicians will update clinicodemographic details, for example, epilepsy type, seizure frequency and antiseizure medication regimen, at each time point. The full list of clinicodemographic data points is contained in online supplemental appendix 1. Researchers aim to collect data at all time points from a total of 50 patients, who will be recruited over a 12 month period. The study is being conducted at two major Australian Comprehensive Epilepsy Centres, The Alfred and The Royal Melbourne Hospital. This is an investigator-initiated study, receiving funding from LivaNova USA. Multisite ethics approval was granted by the Alfred Health Ethics Committee (HREC 17/23). The study commenced recruitment at Alfred Health on 10 March 2023, and is anticipated to be completed by December 2024.

SERIAS creation

Two versions of SERIAS will be validated in this study; the 'original', and the 'traffic light' version. Both ask patients to indicate the impact of seizures/seizure-related effects and treatment side effects qualitatively and quantitatively, but are presented in different formats to ascertain if one is significantly preferred by participants. The original version focuses on the types of activities that may be affected (work, study and social activities), while the traffic light version focuses on the degree of disability experienced (green, yellow and red). They have been informed by feedback from a person with lived experience of epilepsy, connected to the research team through Monash

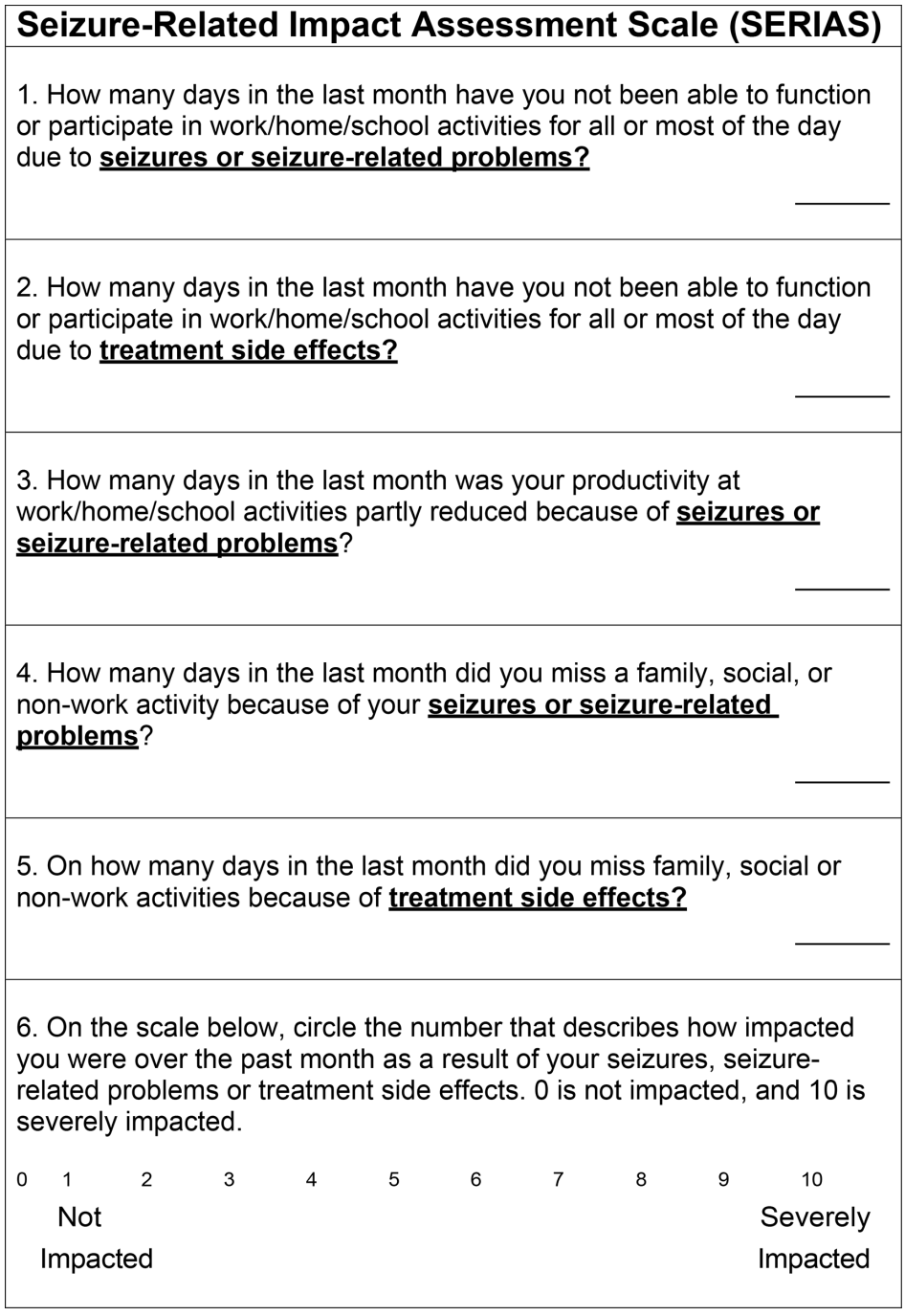

Figure 1 Seizure-Related Impact Assessment Scale (SERIAS), original version.

University School of Translational Medicine's Community and Researcher Engagement (CaRE) programme.[19] Although SERIAS measures epilepsy-related disability, the use of the word 'disability' in the instrument was felt to be stigmatising, and so was replaced with the word 'impact' to improve user acceptability. The original and traffic light versions of the SERIAS are presented in figures 1 and 2, respectively.

In further detail, the original SERIAS instrument was created by JF. It is adapted from the Migraine Disability Assessment test (MIDAS), a validated instrument that is widely used to capture the qualitative and quantitative burden of migraine headache.[20] The original SERIAS is a 6-point self-report questionnaire. The first five questions ask patients to self-report the impact of seizure-related and treatment-related disability that they have experienced in the last month, ranging from partially impacted through to fully impacted with regard to work/home/school activities and family/social/non-work activities, as well as on how many days that month the impact was experienced. The total score is computed as the number of days impacted summed across activity domains. The sixth question is a visual analogue scale, which asks patients to circle a number between 0 (no impact) and 10 (severe impact) to indicate how impacted they have been in the

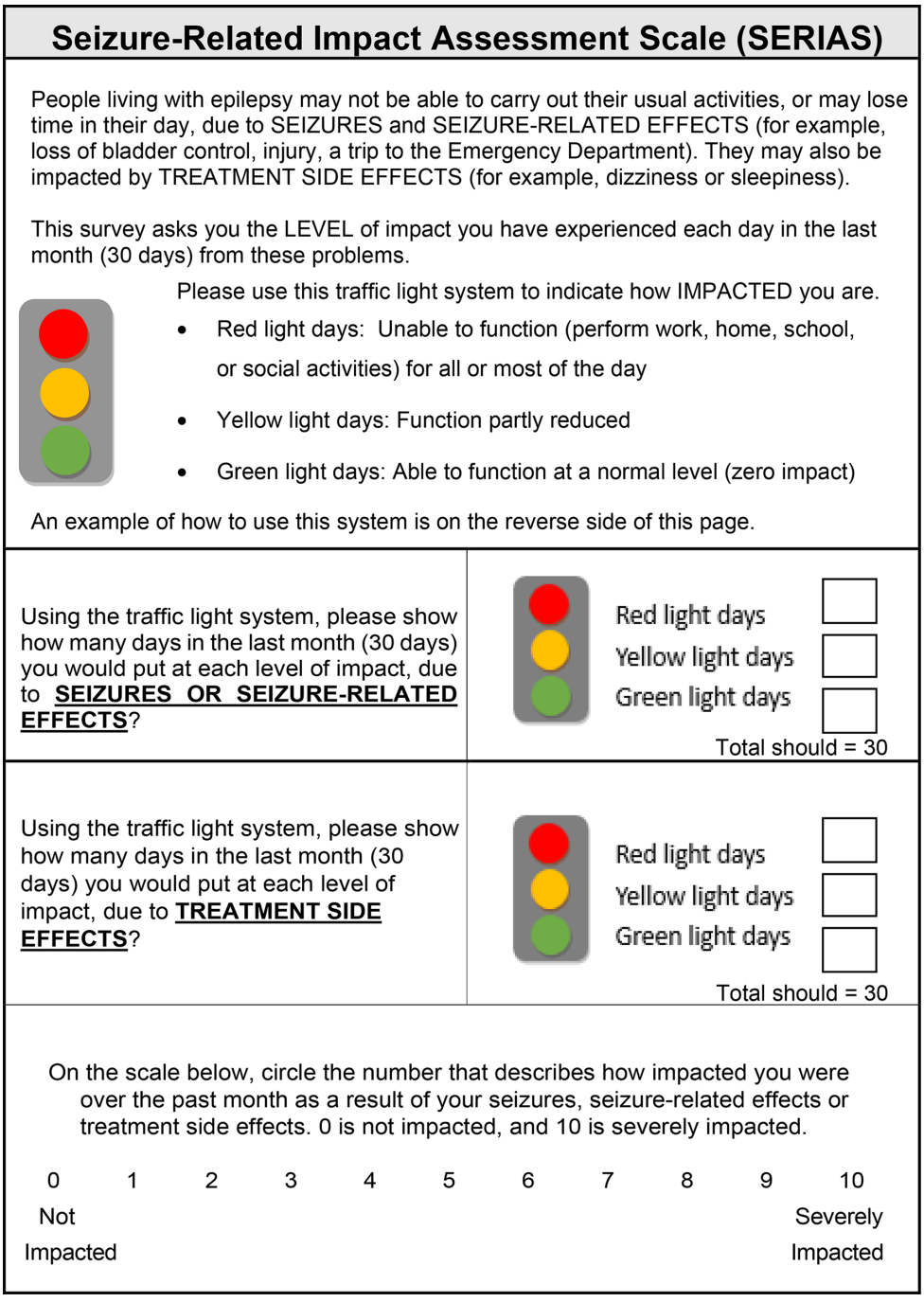

Figure 2 Seizure-Related Impact Assessment Scale (SERIAS), traffic-light version.
Example 1: Person A had 3 seizures in the past month. 2 seizures were convulsions. They had to go home from work, and slept the rest of the day. 1 seizure was a focal seizure. They recovered after 10 minutes and continued working afterwards. This would be equivalent to 2 red light days, 1 yellow light day, and 27 green light days for the SEIZURES and SEIZURE RELATED-EFFECTS section.
Example 2: Person B has been seizure free for 5 years. They always feel quite tired, and because of this, they work part-time. Two weeks into this month, their doctor advised them to reduce their antiseizure medication dose. They feel much better on the lower dose and return to working full-time. This would be equivalent to 15 yellow light days and 15 green light days this month for the TREATMENT SIDE EFFECTS section.

past month due to seizures, seizure-related problems or treatment-related adverse effects.

The traffic light SERIAS was created by the core investigator team: EF, AC, PK, CM and JAF. This is a different approach to measuring seizure, seizure-related and treatment-related impairment both quantitatively and qualitatively. It contains three questions. The first two questions ask patients to state the number of days in the last month that their function has been affected by either seizures or treatment-related adverse effects, by numbering the amount of red (unable to function), yellow (partly reduced function) or green (able to function normally) days, for a total of 30 days. The total score is computed as the total number of 'red light'

days multiplied by two and added to the total number of 'yellow light' days. The third question is a visual analogue scale, and is the same as the sixth question in the original version of the SERIAS.

After completing both versions of SERIAS, participants are asked to nominate their preferred questionnaire, and explain why that is so, and are then invited to complete the remaining instruments (please see below).

Recruitment procedures

This study involves recruitment of participants from The Alfred and The Royal Melbourne Hospital during inpatient and outpatient epilepsy encounters. This includes outpatient visits and elective video EEG monitoring admissions. The study involves participants completing both versions of the SERIAS at baseline, 3 and 6 month timepoints. In order to determine whether change in epilepsy-related variables (such as seizure frequency) are associated with change in SERIAS scores, we will also ask participants to complete other study measures at the same three timepoints. These measures are the LAEP,[15] Somatic Symptom Scale (SSS-8),[21] Work and Social Adjustment Scale (WSAS),[22] QOLIE-31,[11] Neurological Disorders Depression Inventory for Epilepsy (NDDI-E),[23] Generalised Anxiety Disorder (GAD-7)[24] and EQ5D.[10] To ensure all treatment-related adverse effects are accounted for, researchers have also custom-built short questionnaires to enquire after common VNS, ketogenic diet and postepilepsy surgery adverse effects for participants who have undertaken these interventions. Eligible participants are approached by researchers during their inpatient or outpatient hospital visit and the study is explained. Verbal and written informed consent is also obtained to approach the participants 3 and 6 months following their baseline assessment to complete the battery of instruments once more. These questionnaires are administered via a secure online Research Electronic Data Capture (REDCap) platform. Paper-based questionnaires are available for those who prefer this option. At the 3 and 6 month follow-up timepoints, participants are also asked: 'Overall, compared to the last time you did these questionnaires, do you think the level of epilepsy-related impact (driven by seizures and the treatment used for seizures) has: (1) meaningfully changed for the better, (2) changed for the worst, (3) stayed the same, or (4) unsure. Please pick one option'. This will assist in correlating changes in SERIAS with changes in disability, over time.

In addition to these self-report instruments, researchers prospectively collect key clinicodemographic data to characterise the cohort. This includes age, sex, epilepsy and seizure type(s) and frequency, antiseizure medication type and doses and presence of active depression and anxiety. At 3 and 6 months follow-up, researchers prospectively update these data points as needed, including any changes in VNS settings or ketogenic diet for eligible participants.

Test–retest reliability subgroup

Two weeks prior to their scheduled hospital visit, 30 consecutive participants will be contacted by study investigators, consented to the study and emailed a secure REDCap link to SERIAS, NDDIE, GAD7 and 'What date was your last seizure?' These participants then complete the full battery of instruments during their hospital episode (elective inpatient admission or outpatient clinic appointment), in line with the main study group.

Data collection

Data for this study are being collected primarily via the REDCap platform. Participants are emailed a secure link to the electronic version of the questionnaires hosted on the hospital-based REDCap, held on the hospital-based firewall and password protected server. They can complete these questionnaires via their mobile phone, tablet (eg, iPad) or computer. The Epilepsy Unit at each hospital also has iPads that may be used for research purposes. If they are available at the time of recruitment, they are offered to participants who may wish to use a tablet over their mobile phone for completing the questionnaires. Paper-based questionnaires are made available for people who would prefer to respond via this method. The paper-based responses are then entered into the participant's corresponding REDCap record by a member of the study team. Deidentifiable participant data will be securely and electronically transmitted from each participating hospital site to a Monash University REDCap at the completion of participant recruitment. Monash University researchers will analyse these data for the study outcomes.

Eligibility

Inclusion criteria

People aged 18 years and over with confirmed diagnosis of epilepsy, who provide informed consent and are able to read and comprehend the study questionnaire.

Exclusion criteria

People aged less than 18 at time of study; those with psychogenic non-epileptic seizures; those with a coexisting intellectual disability that would preclude them from comprehending and completing questionnaires; those with limited English reading proficiency that would preclude them from comprehending and completing questionnaires; those in catatonic/floridly psychotic /postictal state at time of intended questionnaire administration.

Concomitant anxiety, depression and personality disorders are NOT exclusion criteria. Given that these are highly prevalent disorders in people with epilepsy, it is important to include and adjust for these to ensure SERIAS is validated in a cohort that is generalisable to as many people living with epilepsy as possible.

Participant safety and withdrawal

It is possible, although not expected, that the nature of some questions may cause concern or distress to some

participants. These will be addressed in the first instance by the clinician who sees the participant after the survey is completed. If required, referrals for neuropsychology and neuropsychiatry services within The Alfred and The Royal Melbourne Hospital will be made, and the participant's referring general practitioner will be notified with their consent.

Statistical methods

As described above, the first aim will be to assess the convergent and divergent validity of the SERIAS with relevant and established measures, including the QOLIE, NDDI-E, GAD-7 and seizure frequency. Initially, simple bivariate correlation coefficients between the original SERIAS, traffic light SERIAS and other relevant instruments will be computed. We expect that correlations between both of the SERIAS and these measures will fall between medium and large effect sizes, so we have computed power analysis based on Pearson's r of 0.4. A priori power analysis indicates that 46 participants are required to achieve 80% with a 5% critical alpha (two-tailed). We will therefore aim to recruit a minimum of 100 participants to allow for missing data and dropout. These analyses will be repeated separately for each timepoint (baseline, 3 month and 6 month). If the sample size permits, general linear mixed models will be computed to investigate these relationships using the entire data set with multiple observations per participant (with a random intercept specified for each participant).

The second aim will be to assess the psychometric reliability of the SERIAS and estimate the measurement error associated with derived scores. Psychometric reliability will be computed in the form of Cronbach's alpha and McDonald's omega coefficients. Specific power analysis is not indicated for these coefficients, as formal null hypothesis significance testing is not conventionally performed. CIs, however, will be computed for these coefficients to understand how much uncertainty there is in the estimation.

The third aim will be to assess stability of the SERIAS over a short test–retest interval. Test–retest reliability will be examined using bivariate correlation coefficients between prebaseline and baseline timepoints. Based on a lower bound acceptable test–retest reliability of 0.6, power analysis indicates that 19 participants would be required to achieve 80% power with an alpha level of 5% (two-tailed). Nevertheless, we will aim to recruit a minimum of 30 participants to the test–retest group in order to accommodate for missing data and to benefit from central limit theorem sampling distribution implications.

Sample size estimation and justification

We aim to recruit a minimum of 100 consecutive participants for this study. Of these participants, a minimum 30 participants will also complete a limited battery of instruments (SERIAS, NDDIE and GAD7) 2 weeks prior to their scheduled hospital visit as part of a test–retest component. The main analysis will consider only participants who do not undergo major neurosurgical intervention in the subsequent 6 months following completion of baseline questionnaires. Supplementary analysis will include all enrolled participants, regardless of whether or not they underwent surgical intervention in the follow-up period.

Primary outcome

Compare SERIAS to a validated epilepsy-specific QoL instrument, the QoLIE-89 and/or QoLIE-31, for measuring QoL.

Secondary outcomes

1. Compare SERIAS to WSAS for measuring impact on functioning.
2. Compare SERIAS to a validated epilepsy-specific depression instrument, the NDDI-E, for measuring depressive symptoms.
3. Compare SERIAS to a validated generic anxiety instrument, GAD-7, for measuring anxiety symptoms.
4. Compare SERIAS to a validated generic QoL instrument, the EQ5D-5L, for measuring QoL.
5. Compare SERIAS to a validated somatic symptom scale, the SSS-8, for measuring somatic symptom burden.
6. Compare SERIAS to a validated epilepsy-specific antiseizure medication adverse effect instrument, the LAEP, for measuring impact of antiseizure medication-related adverse effects. In addition, for eligible participants, researchers will ask after common and important adverse effects from VNS, ketogenic diet and epilepsy surgery, measured by a Likert scale, to capture adverse effects from these adjunct epilepsy treatments.

Data security and handling, confidentiality and security

Electronic records are kept on the REDCap database, hosted on a password and firewall protected system. Only authorised users are granted access to the database. These users are given individual usernames and passwords to track usage and allow audit trails to be conducted. Records will be kept for a minimum of 7 years before hard-end deletion. Paper-based participant information and consent forms (PICFs) and questionnaires are stored in a locked filing cabinet in a locked office, in a restricted area only accessible with an organisational ID swipe badge. Only authorised personnel have access to these documents. Hard copy documents will be kept for a minimum of 7 years, in line with Australian privacy law.

REDCap

Study data at all sites are collected and managed using the REDCap electronic data capture tool hosted and managed by each individual site's institutions; DATA and Analytics Services at Alfred Health, Business Intelligence Unit at The Royal Melbourne Hospital and Monash University.[25 26] 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.

Patient and public involvement

Community engagement was directly sought for the design, conduct and recruitment of this study. We aim to engage with patient-advocacy organisations including the Epilepsy Foundation (Australia and USA), Epilepsy Action Australia, and Brain Foundation to disseminate our findings.

ETHICS AND DISSEMINATION

The study has been granted multisite ethics approval by the Alfred Health Ethics Committee (HREC 17/23) for all sites. Governance has been granted by the Offices for Research at the individual study sites. Any amendments to the protocol will be approved by the HREC prior to implementation. These changes will also be updated on ANZCTR.

Results of this study will be disseminated through publication in peer-reviewed journals and presentations at scientific conferences.

Availability of SERIAS

SERIAS is copyrighted to the Epilepsy Study Consortium, which was founded and is directed by senior author JAF. The Consortium is a group of scientific investigators dedicated to the development of new therapies in epilepsy to improve patient care. As with many validated instruments, SERIAS will be made available free of charge for investigator-initiated research on application by suitably qualified investigators, and for a fee for commercial studies.

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.

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Contributors EF, lead investigator: devised study concept, drafted protocol, secured funding, built study REDCaps, prospective collection of clinicodemographic data. AC, senior research coordinator: contributed to revision of the protocol, assisted with securing funding, secured ethics and governance approvals, assisted with testing and finalising study REDCaps, prospective enrolment of participants, data management. CE, consumer advocate and person with lived experience: informed the content, wording and formatting of the SERIAS instruments, and provided feedback on study recruitment strategies. J-PN, principal investigator at The Royal Melbourne Hospital site: contributed to revision of the protocol, assisted with securing funding, assisted with governance approval, overseeing study at The Royal Melbourne Hospital. GR, senior neuropsychologist: contributed to revision of the protocol, including intellectual input regarding study design and instruments. TW-B, senior neuropsychiatrist: contributed to revision of the protocol, prospective assessment of patients for anxiety and depression. TJOB, Head of Alfred Brain Programme: contributed to revision of the protocol. PK, principal investigator at The Alfred site: contributed to revision of the protocol, assisted with securing funding, overseeing study at The Alfred. CM, senior neuropsychologist and biostatistician: devised study concept, drafted protocol (including study methodology, statistical analysis plan and power calculation sections), assisted with securing funding. JAF, senior investigator: created original SERIAS, devised study concept, drafted protocol and assisted with securing funding.

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

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