PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

Title (Provisional)

RESILIENCE (Retrospective Linkage study of Autoimmune Encephalitis): protocol for an Australian retrospective cohort study of outcomes in autoimmune encephalitis using data linkage techniques.

Authors

Halliday, Amy Jean; Lambert, Katrina; Bundell, Christine; McLean-Tooke, Andrew; Gillis, David; Prain, Kerri M; Bryson, Greg; Gillinder, Lisa; Brown, David; Ramanathan, Sudarshini; Dale, Russell; Brilot, Fabienne; Jordan, Nerissa; Lawn, Nicholas; Lai, Alan; Boyd, James; Epilepsy Centres Consortium, Australian Adult Comprehensive; Camacho, Ximena; D'Souza, Wendyl

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VERSION 1 - REVIEW

Reviewer	**1**
Name	**Le Maréchal , Marion**
Affiliation	**Hôpital Albert Michallon**
Date	**17-May-2024**
COI	**I don't have any competing interests**

Thank you for giving me the opportunity to review the protocol for the RESILIENCE study, an Australian retrospective cohort study of outcomes in autoimmune encephalitis using data linkage techniques.

Your study project plans on using data linkage techniques to establish a 10-year population cohort of autoimmune encephalitis. This method is very powerfull and will provide high quality data.

COMMENTS

INTRODUCTION

- p. 6, Research questions : the primary objective isn't clear. If it's the first of the research questions, then it must be clearly identified. The other research questions will be in a "secondary objectives" paragraph.

METHOD AND ANALYSIS

- p. 6, line 24 : on top of giving the reference number 16, please add in the text that it's the paper from Graus et al, so the reader doesn't have to check within the reference section

- Reference cohort paragraph : please give the definition for definite and probable encephalitis. Provide explanation of why possible encephalitis were excluded from the included patients

- Primary outcomes section : none of the outcomes have been clearly defined : what is called relapse ? Is it a clinical definition ? Biological ? On imaging ? How long after diagnosis or treatment is it consider as a relapse ?

For seizure : is it only clinical seizure, or abnormal EEG data fitting with possible seizures ?

Cognitive impairment has not been defined. What test will be acceptable to decide for a cognitive impairment ? Will there be a cut-off for each test ? Or a comparison with existing cohort of general population having those tests ?

Educational attainment has not been described. What difference will be considered as an attainment between the child and the rest of the children ?

What is considered as a delayed diagnosis ? How long after the diagnosis of AE the tumour diagnosis is considered delayed ? What is the diagnosis time for the tumour ? Imaging ? Pathophysiology exam ? Oncology physician first meeting ?

OTHER COMMENTS

- There is no section with inclusion and exclusion criteria

- You didn't provide any section about the number of patients to be included regarding the main hypothesis

In total, this study will provide with very interesting results, but the study pro

Reviewer	2
Name	**Piccini, Cristian**
Affiliation Medicine	**Universidade Federal do Rio Grande do Sul, Faculty of**
Date	**16-Jun-2024**
COI	**No competing interests**

Halliday et al. present the protocol of an observational study that aims to produce a retrospective cohort of Australian patients with a presumed diagnosis of autoimmune encephalitis over a ten-year period, using data linkage techniques. From this cohort, the authors aim to assess the incidence, prevalence, mortality and prognosis of AE in Australia, as well as immunotherapeutic and non-immunotherapeutic prognostic factors, neoplasm

associated with AE at the onset of the disease, and what occult tumors are diagnosed in subsequent years.

Overall, the protocol is well written. I would recommend it for publication after some minor adjustments, with a view to increasing transparency and reducing the risk of bias:

ABSTRACT:

1) Research questions are presented as "primary outcomes". I would advise standardizing the primary outcomes in the abstract section with the primary outcomes that are subsequently reported in the "Methods and Analysis" section of the manuscript (ie., "relapse rate, frequency of the development of epilepsy and its severity, cognitive disability, educational attainment, timing of tumor diagnosis, and death").

METHODS AND ANALYSIS:

2) The authors mention that "Operational definitions used to estimate primary and secondary outcomes and covariates will be derived from published algorithms where available, or developed with input from study collaborators, and validated using the Reference Cohort where possible".

It is highly desirable that such definitions are provided in the protocol, including measurement time points for all outcomes.

3) There is mention of secondary outcomes throughout the manuscript, but few details are provided. All outcomes must be explicit, including when and how they will be measured. I would suggest including a "Secondary outcomes" subsection in the "Methods and analysis" section.

4) "Linked patient data will be stored, cleaned and analyzed using Stata, R and Python in the SURE provided by the Sax Institute, Australia."

Please, pre-specify which software (and package) will be used for each analysis.

5) "For each outcome, statistical analysis will be conducted on samples with complete data, and some missing data on variables will be imputed depending on the nature of missingness."

I suggest explaining how, and in which situations, this imputation will be conducted. Will missing data be imputed as an event? As no event? According to an observed risk?. More details should be provided.

Naturally, these suggestions increase the likelihood that post hoc decisions may be necessary. These must be duly justified and their impacts on the results and conclusions of the study analyzed.

VERSION 1 - AUTHOR RESPONSE

Reviewer #1:

INTRODUCTION
1. p.6, Research questions: the primary objective isn't clear. If it's the first of the research questions, then it must be clearly identified. The other research questions will be in a "secondary objectives" paragraph.
Thank you for this comment, a similar comment was made by the second reviewer. We have changed the 'Research questions' section to describe only the primary study aims, as follows:

> "The primary aim of the RESILIENCE study is to describe the prognosis of AE in Australia and prognostic factors associated with disease outcomes. The primary outcomes of interest are relapse rate, prevalence and control of epilepsy, cognitive disability, poor educational attainment, delayed tumour diagnosis and mortality."

A 'Secondary outcomes' section has been added as suggested, describing the remaining intended analyses, as follows:

> "In addition to the primary aims and outcomes described above, we will undertake a number of secondary analyses. We will describe the epidemiology of AE in Australia including its prevalence, annual incidence and demographic features. Further aspects of disease prognosis will be described including movement disorders, mood disorders and psychotic illness, which will be estimated using prescriptions data. In patients who develop AE-associated epilepsy, we will examine seizure control and factors associated with seizure control, including epilepsy surgery. In patients accessing disability services, we will describe the domains of disability reported to the disability dataset. We will describe the disability support services utilised by these patients, their carer arrangements, income sources and labour force status. In the paediatric subgroup we will also examine childhood development, as reported to the Australian Early Development Census."

METHOD AND ANALYSIS
- p. 6, line 24: on top of giving the reference number 16, please add in the text that it's the paper from Graus et al, so the reader doesn't have to check within the reference section
Thank you for this suggestion, this sentence has been changed to "The Reference Cohort consists of 145 individuals meeting Graus et al. (2016) consensus diagnostic criteria for AE[16]" as suggested.

- Reference cohort paragraph: please give the definition for definite and probable encephalitis. Provide explanation of why possible encephalitis were excluded from the included patients
Thank you for these queries. The definitions of definite and probable AE have been added to the text, and the explanation for excluding patients with 'possible encephalitis' has been added, as follows:

> "Patients were included if they met consensus diagnostic criteria for definite or probable AE after a review of the medical record, and symptom onset occurred between January 2008 and December 2019. Definite AE includes patients with encephalitis-associated antibodies, a suggestive clinical presentation (subacute short-term memory loss, altered mental status or psychiatric symptoms), and at least one line of evidence for brain inflammation (new focal neurology, new seizures, CSF pleocytosis, or MRI features suggestive of encephalitis). Probable AE includes antibody-negative cases with a suggestive clinical syndrome and multiple lines of evidence for brain inflammation, with reasonable exclusion of other causes. Graus et al. (2016) also define a category of 'possible AE', describing patients with a suggestive clinical syndrome, at least one line

of evidence for brain inflammation and reasonable exclusion of other causes. Possible AE is intended as a prompt to investigate further for AE with antibodies and additional tests for brain inflammation, rather than a definitive diagnosis, and thus patients meeting criteria for possible AE were not included in the Reference Cohort."

- Primary outcomes section: none of the outcomes have been clearly defined:
What is called relapse? Is it a clinical definition? Biological? On imaging? How long after diagnosis or treatment is it consider as a relapse?
For seizure: is it only clinical seizure, or abnormal EEG data fitting with possible seizures?
Cognitive impairment has not been defined. What test will be acceptable to decide for a cognitive impairment? Will there be a cut-off for each test? Or a comparison with existing cohort of general population having those tests?
Educational attainment has not been described. What difference will be considered as an attainment between the child and the rest of the children?
What is considered as a delayed diagnosis? How long after the diagnosis of AE the tumour diagnosis is considered delayed? What is the diagnosis time for the tumour? Imaging? Pathophysiology exam? Oncology physician first meeting?
Thank you for these queries, reviewer #2 also sought precise definitions of the primary outcomes. As this is a data linkage study, we do not have access to clinical data such as results of laboratory, EEG, imaging or cognitive test results, and outcomes are 'operationally defined' using data accessible in linked datasets. These operational definitions have now been provided in Appendix 2 in the revised manuscript.

Within the main text, we have also provided further details regarding delayed tumour diagnosis as follows:
> "We will describe the incidence and types of tumours diagnosed more than 90 days after the onset of AE, using diagnoses and dates from the National Cancer Registry and hospital discharge diagnosis codes."

and regarding the definition of cognitive disability, as follows:
> "We will estimate the 2- and 5-year prevalence of cognitive disability in this cohort using Australia's national disability services dataset, with cognitive disability defined as the need for assistance in the domain of "learning, applying knowledge and general tasks and demands"."

OTHER COMMENTS
- There is no section with inclusion and exclusion criteria
The main study cohort will be selected using an 'operational definition'. This operational definition will consist of a list of criteria that must be met for the patient to be included in the cohort, each stipulating data elements that must be present or absent, rather than a set of clinical inclusion and exclusion criteria typically obtained from patient assessment or medical records review in clinical studies. This explanation has been added to this section of the methods, as follows in italics:
> "Using the Reference and Mimicker Cohorts, we will develop and validate an operational case definition of AE, this being an algorithm to accurately identify patients with AE using coding elements available from linked administrative datasets. *The algorithm will be a list of criteria, each being a data element or combination of elements that must be present (or absent if so stipulated) for an individual to be included in the study cohort, thus functioning as a set of inclusion and exclusion criteria.*"

This definition will be developed as part of the project, as described in the section "Methods and Analysis, Operational case definition", and thus this operational definition cannot be prospectively published with these methods.

- You didn't provide any section about the number of patients to be included regarding the main hypothesis
Thank you for this query. The estimated cohort sizes were described in the "Study cohorts" section: "The Reference Cohort consists of 145 individuals meeting consensus diagnostic criteria…" and "The size of the Operationally Defined Cohort is estimated to be approximately 5000 individuals". However, as you state, the sample sizes are usually expected in the data analysis section when discussing analysis of the primary outcomes. Reference to these cohort sizes has now been made in the 'Data analysis' section describing use of these cohorts in statistical analyses, as well as at the start of the 'Estimation of covariates and outcomes' subsection, as follows:

> "Primary outcomes will be determined using the Operationally Defined Cohort (n≈5000). Some prognostic factors and secondary outcomes will be determined using the Reference Cohort, for covariates not accessible through linked datasets such as inpatient first-line immunotherapy treatment (n=145)."

Reviewer: 2

ABSTRACT:
1) Research questions are presented as "primary outcomes". I would advise standardizing the primary outcomes in the abstract section with the primary outcomes that are subsequently reported in the "Methods and Analysis" section of the manuscript (ie., "relapse rate, frequency of the development of epilepsy and its severity, cognitive disability, educational attainment, timing of tumor diagnosis, and death").
Thank you for this comment, the list of primary outcomes has been amended in the abstract to "relapse rate, prevalence and control of epilepsy, cognitive disability, poor educational attainment, delayed tumour diagnosis and mortality", as suggested.

METHODS AND ANALYSIS:
2) The authors mention that "Operational definitions used to estimate primary and secondary outcomes and covariates will be derived from published algorithms where available, or developed with input from study collaborators, and validated using the Reference Cohort where possible".
It is highly desirable that such definitions are provided in the protocol, including measurement time points for all outcomes.
Thank you for this comment. An appendix of operational definitions has been provided at the end of the revised manuscript, and reference made to the appendix within the manuscript.

3) There is mention of secondary outcomes throughout the manuscript, but few details are provided. All outcomes must be explicit, including when and how they will be measured. I would suggest including a "Secondary outcomes" subsection in the "Methods and analysis" section.
Thank you for this comment. A 'secondary outcomes' section has been added to the "Methods and analysis" section, as suggested, describing the secondary analyses, as follows:

"In addition to the primary aims and outcomes described above, we will undertake a number of secondary analyses. We will describe the epidemiology of AE in Australia including its prevalence, annual incidence and demographic features. Further aspects of disease prognosis will be described including movement disorders, mood disorders and psychotic illness, which will be estimated using prescriptions data. In patients who develop AE-associated epilepsy, we will examine seizure control and factors associated with seizure control, including epilepsy surgery. In patients accessing disability services, we will describe the domains of disability reported to the disability dataset. We will describe the disability support services utilised by these patients, their carer arrangements, income sources and labour force status. In the paediatric subgroup we will also examine childhood development, as reported to the Australian Early Development Census."

4) "Linked patient data will be stored, cleaned and analyzed using Stata, R and Python in the SURE provided by the Sax Institute, Australia."
Please, pre-specify which software (and package) will be used for each analysis.
We appreciate the reviewer's suggestion to specify the software and packages to be used for each analysis. However, we believe the flexibility of using the specified software (Stata, R, and Python) allows us to adapt our analysis methods to best suit the data as it evolves. While we have preliminary plans for analysis, the specific software and packages may need to be adjusted based on the data characteristics and emerging needs, the availability of new packages at the time of analysis, or shift in the biostatistical literature towards alternative statistical methods. We will of course ensure to report the final methodologies, including the software and packages used, when presenting and publishing results in future publications.

5) "For each outcome, statistical analysis will be conducted on samples with complete data, and some missing data on variables will be imputed depending on the nature of missingness."
I suggest explaining how, and in which situations, this imputation will be conducted. Will missing data be imputed as an event? As no event? According to an observed risk?. More details should be provided.
Thank you for your suggestion to clarify the imputation process for missing data. As you will be aware, we can classify the nature of the missing data into three categories: Missing Completely at Random (MCAR), Missing at Random (MAR), and Missing Not at Random (MNAR). Various imputation methods will be used to handle missing data depending on the nature of, and to allow us to account for uncertainty related to, the degree and type of missingness. For MCAR variables and variables where MAR is reasonable to assume, we will use Multiple Imputation with Denoising Autoencoders using Python (MIADASpy) and R (rMIDAS) to compute missing values which preserve relationships within the observed data. For MNAR data (data that may depend on unobserved outcomes) we will conduct sensitivity analyses to assess how different assumptions about the missing data might affect our results.In all cases, we will clearly document the proportion of missing data for each variable and provide detailed justification for our chosen imputation approach.

This has now been explained in the "Data analysis" section of the manuscript, as follows:
"For each outcome, initial statistical analysis will be conducted on samples with complete data. Proportion and assumptions missing values for each variable in the complete data set will be described and we will then employ various imputation methods to address missing data, utilizing Multiple Imputation with Denoising Autoencoders in Python (MIADASpy) and R (rMIDAS) for Missing Completely at

Random (MCAR) and Missing at Random (MAR) variables, while conducting sensitivity analyses for Missing Not at Random (MNAR) data to evaluate the impact of various assumptions on our results."

Naturally, these suggestions increase the likelihood that post hoc decisions may be necessary. These must be duly justified and their impacts on the results and conclusions of the study analyzed.

Thank you for noting this. This limitation has been added to the first paragraph of "Primary outcomes" and to the data analysis section, as follows:

> "Operational definitions have been provided in Appendix 2. These operational definitions may be modified if development and validation using the Reference Cohort demonstrates better performance of an alternative operational definition or there is interim publication of other validated definitions. This will be justified and discussed when presenting the results in publication."

VERSION 2 - REVIEW

Reviewer	**2**
Name	**Piccini, Cristian**
Affiliation Medicine	**Universidade Federal do Rio Grande do Sul, Faculty of**
Date	**27-Oct-2024**
COI	

Thank you for the opportunity to review this protocol. The concerns raised have been appropriately addressed by the authors, and relevant changes were made. The manuscript is now suitable for publication.