PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Study Protocol: Australasian registry of Severe Cutaneous Adverse Reactions (AUS-SCAR)
AUTHORS	James, Fiona; Goh, Michelle S Y; Mouhtouris, Effie; Vogrin, Sara; Chua, Kyra; Holmes, NE; Awad, Andrew; Copaescu, Ana-Maria; De Luca, Joseph; Zubrinich, Celia; Gin, Douglas; Cleland, H; Douglas, Abby; Kern, Johannes; Katelaris, Constance; Thien, Francis; Barnes, Sara; Yun, James; Tong, Winnie; Smith, William; Carr, Andrew; Anderson, Tara; Legg, Amy; Bourke, Jack; Mackay, Laura; Aung, Ar Kar; Phillips, Elizabeth; Trubiano, Jason

VERSION 1 – REVIEW

REVIEWER	Ramsey, Allison C Rochester Regional Health, Allergy & Immunology
REVIEW RETURNED	09-Nov-2021

GENERAL COMMENTS	This will be an exceedingly helpful registry to further characterize these rare drug reactions. This is an exciting undertaking. The authors' research plan is well thought out and thorough. I only have a few minor comments: 1. I understand how the accrual number was reached (500). Can the authors provide estimates of numbers of patient for each condition? Eg, DRESS, SJS/TEN, DILI, AGEP etc? 2. For the SJS patients - if a viral trigger is suspected, will these patients still be included? 3. For the primary outcome measure - how will the authors address if multiple drugs are potentially implicated and one etiologic agent cannot be confirmed? 4. Will all consented patients be referred to undergo further allergy/immunology evaluation or will this be at the discretion of the treating team?

REVIEWER	Nwadiugwu, Martin University of Stirling, Health
REVIEW RETURNED	28-Nov-2021

GENERAL COMMENTS	Thank you for your contributions to helping document SCAR in Australasia and to provide a useful registry. I have included some comments below. Are there previous studies that have examined the clinical presentation, drug causality, genomic predictors, potential diagnostic

approaches, treatment, and long-term outcomes of SCAR? And what is the rationale of limiting the focus to Australia and New Zealand? If the aim is to setup a national SCAR registry in Australasia, will this be part of the scope of this study?

What is the age bracket of adults and adolescent that would be recruited for the prospective study? The manuscript says >12yr old, but does the study envision documenting differences in SCAR in the young vs old?

The characteristics of participants being recruited is not clear? Apart from suspected SCAR, are patients expected to have underlying conditions/comorbidities and if yes, what are plans to mitigate this bias in the analysis?

What is the duration of the prospective study?

What is the duration of the retrospective study?

Will ethnicity and race be considered in the recruitment campaign?

Would the study have a control since the plan is to examine the clinical presentation, drug causality, genomic predictors, potential diagnostic approaches, treatments, and long-term outcomes of SCAR?

How would the authors mitigate bias in recruitment, sample processing etcetera?
Is this a prospective or retrospective study or both? If both, what is the rationale and how will the results interact with each other to reach the evidence?

Is there a common sample that would be collected for all participants? While Blood, blister fluid and skin biopsy sampling is optional and subject to patient consent and site capacity and DNA can be extracted from any of them, it could make sense if same tissue sample were collected and analyzed.

It may be necessary to state the rationale for the selected culprit drug identification method as recent articles have suggested a lack of consensus on common preferred method.

How would limitations due to race and ethnicity be mitigated to ensure results are truly representative?

What are the conditions that may necessitate extended recruitment after the project have begun? Why are these other phenotypes (AIN, DILI, FDE) not included from the start and how would the results be interpreted along with SJS, DRESS, TEN and AGEP?

Would REDCAP be the database for AUS-SCAR?

Will GWAS, RNA-seq and virologic assessment be performed on all specimen if its determined that difference in genetic and viral variants are needed?

Are participants expected to be on a recommended drug during the 12 months patient follow-up?

How will participants/patients be contacted? What is the recruitment

	strategy?

REVIEWER	Janković, Slobodan University of Kragujevac
REVIEW RETURNED	30-Nov-2021

GENERAL COMMENTS	This is detailed protocol about establishing Register for serious cutaneous adverse drug reactions in Australia. The Register will be of prime importance and significance for both research and healthcare in the area of managing serious cutaneous ADRs. It will be basis for establishing evidence-based diagnostics and treatment of these serious disorders that are currently underdiagnosed and undertreated. Methodology of the future Register is appropriate, and the authors are well aware of both strong and weak sides of the project. The project seems flexible and sustainable, since organizations that will take care of the Register in the future is well defined. Feasibility of the Register is also high, since it does not require much investments besides what is already used within the framework of services covered by health insurance. I do not see any major caveat of the project, and I suggest acceptance of the protocol for publication.

REVIEWER	Fahey, Tom Royal College of Surgeons in Ireland, Department of General Practice
REVIEW RETURNED	01-Dec-2021

GENERAL COMMENTS	Thank you for asking me to review this paper. It describes the setting up of a national registry for Severe Cutaneous Adverse Reactions (SCAR) in Australia. My main comment is that the paper is really a description of the process of setting up the registry. It is not really a protocol and has no results or discussion. For this reason, it is hard to judge why the authors are trying to get this paper published in a peer review journal. The context is given as to why this paper should appear in a peer review journal is hard to judge. For example, does this registry differ to other similar registries that they cite in Europe and Korea? In terms outcomes chosen and the type of testing proposed, what is the novelty of their registry in terms of potential drug exposure and outcomes chosen? What is the added value of their registry compared with other, similar national registries? In summary, it would be important for the authors of the paper to outline their rationale in relation to the publication of their registry description in a peer review journal. If they do wish to get it published a more critical discussion about the nature of the data collected in their (Australian) registry, how and why it differs from other national registries and the added value of the Australian registry in terms of SCARs nationally and internationally.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Dr Alison C Ramsey, Rochester Regional Health

Response to Reviewer 1:
1. The following phenotypic breakdown has been calculated from pilot data for 59 participants recruited across 12 sites: DRESS (58%), SJS (20.3%), SJS/TEN (10.2%), TEN (10.2%), AGEP (6.8%), GBFDE (1.7%). No pilot data is available for DILI as cases are not currently included in the registry. Although some cases are yet to be externally validated, we don't expect major deviation between these estimates and those of the final cohort.
2. SJS patients with a suspected viral trigger will still be included if they meet the requirements for internal and external case validation.
3. The primary outcome measure will be addressed using the most likely implicated drug, as determined through internal and external validation. All implicated drugs will be recorded by site investigators for each case and considered in the decision. Cases which are considered to have been caused by multiple drugs or for which drug causality cannot be agreed upon will not contribute to primary outcome analysis but may contribute to secondary outcome analysis.
4. Referral for further allergy/immunology evaluation will be at the discretion of the treating team however this will be one of the long-term outcomes assessed, as well as any allergy testing results.

Reviewer 2: Dr. Martin Nwadiugwu, University of Stirling

Response to Reviewer 2:
1. Increased attention has been directed towards SCAR research in the past 15 years with a number of papers published describing clinical presentation, known genomic predictors, potential diagnostic approaches and treatments for SCAR. However, research is hindered by the low incidence of SCAR and diagnostic approaches for culprit drugs and treatment options remain scarce and are utilised inconsistently. National or regional registries such as KoSCAR and RegiSCAR have provided valuable summary data at the population level; AUS-SCAR seeks to do this for the first time in Australasia. AUS-SCAR is an unfunded, investigator-led registry and cohort study led by an Australian team: the study will be limited to Australia and New Zealand for practical, financial and logistical reasons. There have been discussions with investigators working in the Pacific Islands with the intention of expanding recruitment to this region if feasible.
2. Adults are expected to comprise the majority of the cohort as many of the participating sites do not treat the paediatric population. However, some do and are able to recruit participants 12 years or over. Analyses may be performed to investigate SCAR in children of feasible.
3. The inclusion criteria are outlined on page 4 of the protocol: as a registry, AUS-SCAR's focus is to capture as many SCAR cases as possible. The criteria serve to screen out differential diagnoses and each case is subject to further validation by the Steering Committee. Clinical data including patient comorbidities are collected for every case and may be accounted for, depending on the analysis performed.
4. The study is planned to continue until accrual has reached n = 500; the expected duration is 5 years from commencement.
5. There is no retrospective aspect of the study.
6. Demographic and clinical data is collected for all participants: this includes self-reported ethnicity.
7. The recruitment of healthy controls is not proposed as part of the study but control samples will be used where appropriate (e.g. diagnostic laboratory assays).
8. AUS-SCAR is a prospective study. The authors acknowledge that a limitation of the study may be selection bias for participants with less severe disease due to the prioritisation of end of life care by the treating team. The authors also acknowledge the logistical challenges of sample collection which may also lead to selection bias (i.e. samples primarily collected from adults with less severe disease). The limitations section has been reworded to make this clearer.
9. Saliva is collected from all participants for the purpose of DNA extraction, excluding those who have died prior to consent. The authors believe a requirement for tissue sampling is unnecessary and would compromise recruitment.
10. AUS-SCAR is an observational study which in part seeks to explore currently available methods of identifying culprit drug. The lack of consensus provides the impetus for this exploration.
11. AUS-SCAR has sought participating sites across Australia and New Zealand in order to sample a representative cross-section of the population. The authors acknowledge there is likely to be selection bias however, due to the fact that most sites are located in metropolitan areas and there may be logistical difficulties in recruiting patients who require an interpreter to consent. The limitations section has been reworded to include mention of selection bias for metropolitan patients.

12. The Steering Committee would be required to approve extended recruitment, with consensus from >50% of the site principal investigators. AIN, DILI and FDE are not currently considered to be included in the SCAR group however this may change.

13. REDCap is used for data collection.

14. The protocol allows for GWAS, RNA-sequencing and virologic sequencing if feasible.

15. Participants are not necessarily expected to be taking any medications in the 12 months post-SCAR.

16. Participants will be recruited in person during their inpatient stay or outpatient appointment by study investigators or their medical treatment decisionmaker will be contacted by phone or in person to request consent.

Reviewer 3: Prof. Slobodan Janković, University of Kragujevac

Response to Reviewer 3: Thank you for your comments.

Reviewer 4: Prof. Tom Fahey, Royal College of Surgeons in Ireland

Response to Reviewer 4:

1. The paper submitted is a protocol which describes the study design, methodology and intended objectives of a registry and observational cohort study; a protocol does not include a results or discussion section as it is created before the analysis stage. BMJ Open accept study protocols for publication to help prevent unnecessary duplication of work, encourage collaboration, increase transparency and provide exposure to research activity that is not widely publicised. The authors agree with the importance of these aims and are grateful for the opportunity to publish this protocol. Although the AUS-SCAR study has formal ethics approval, BMJ Open still require independent peer review for protocols.

This registry and cohort study differs to predecessors in three key areas: 1) the study population is unique, encompassing the specific cultural and ethnic diversity of Australia and New Zealand, 2) prescribing practices, treatment options and guidelines in Australasia differ to those internationally and 3) the prospective biobanking component for immunological investigation and novel diagnostics has not been attempted at this scale nationally or internationally.

The unique study population is relevant due to the known association of numerous HLA variants with drug hypersensitivity. The HLA gene is highly polymorphic and allele frequencies differ across ethnic groups. HLA variation and its association with SCAR has not been well-described at the population level in Australia or New Zealand. Prescribing practices differ internationally and may influence the proportion of most likely implicated drugs seen here. SCAR management and treatment options are inconsistent not only at an international level, but also nationally and even between health services; collecting statistics on currently utilised treatments and associated long-term outcomes is valuable. Biobanking will allow researchers to further investigate the immunological mechanisms of SCAR and methods of assigning drug causality – two key aspects of SCAR research for which there is much to build upon.

An original research paper will be submitted for publication once accrual has reached 100 participants and there are sufficient results to publish.

VERSION 2 – REVIEW

REVIEWER	Nwadiugwu, Martin University of Stirling, Health
REVIEW RETURNED	22-Feb-2022

GENERAL COMMENTS	Author(s) addressed reviewer concerns

REVIEWER	Fahey, Tom Royal College of Surgeons in Ireland, Department of General Practice
REVIEW RETURNED	28-Feb-2022

GENERAL COMMENTS	No further comments