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Australasian registry of Severe Cutaneous Adverse Reactions (AUS-SCAR)

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Australasian registry of Severe Cutaneous Adverse Reactions (AUS-SCAR)

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Abstract

Introduction Severe cutaneous adverse reactions (SCAR) are a group of T cell-mediated hypersensitivities associated with significant morbidity, mortality and hospital costs[1]. Clinical phenotypes include Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP). In this Australasian, multi-centre, prospective registry, we plan to examine the clinical presentation, drug causality, genomic predictors, potential diagnostic approaches, treatments and long-term outcomes of SCAR in Australia and New Zealand.

Methods and analysis Adult and adolescent patients with SCAR including SJS, TEN, DRESS, AGEP and another T cell-mediated hypersensitivity, generalised bullous fixed drug eruption (GBFDE), will be prospectively recruited. A waiver of consent has been granted for some sites to retrospectively include cases which result in early mortality. DNA will be collected for all prospective cases. Blood, blister fluid and skin biopsy sampling is optional and subject to patient consent and site capacity. To develop culprit drug identification and prevention, genomic testing will be performed to confirm HLA type and ex vivo testing will be performed via IFN-γ release ELISpot assay using collected peripheral blood mononuclear cells (PBMCs). The long term outcomes of SCAR will be investigated with a 12-month quality of life survey and examination of prescribing and mortality data.

Ethics and dissemination This study was reviewed and approved by the Austin Health Human Research Ethics Committee (HREC/50791/Austin-19). Results will be published in peer-reviewed journals and presented at relevant conferences.

Registration Number: ACTRN12619000241134

Strengths and limitations of the study

- The strength of AUS-SCAR lies in its prospective design, allowing for the real-time collection of clinical data, standardised investigation and sampling for genomic evaluation and ex-vivo diagnostics
- A limitation of the sampling strategy is the large number of PBMCs required for successful ELISpot assay, complicated by the poor viability of cells from acute bleeds due to critical illness
- Many hospital-adjacent laboratories are also not set up to process PBMCs, blister fluid or skin specimens requiring same-day transport to specialised research labs
- Regarding recruitment, there will likely be some selection bias for less critically ill patients due to the challenges surrounding obtaining consent
- Finally, the registry is not designed to achieve complete case capture across the study period and recruiting the target sample size will be dependent on successful recognition of cases at each site

INTRODUCTION

SCAR are a group of T cell-mediated hypersensitivities – including Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP) (1). Other severe T cell-mediated hypersensitivities include diseases such as generalized bullous fixed drug eruption (GBFDE), drug-induced liver injury (DILI) and acute interstitial nephritis (AIN) (1, 2). SCAR can be associated with significant morbidity, hospital costs, increased demand for specialist testing and high mortality (3-6).

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Despite this, an understanding of the clinical, genomic and pharmacological predictors of each phenotype remains absent from current practice. Further, there is currently a lack of consistency among the recommendations in treatment guidelines for these severe reactions.

Causality assessment in SCAR is often complex as multiple drugs are frequently involved (3, 7-9). Whilst the use of skin testing (*in vivo)* has been increasingly employed, it is hampered by low sensitivity and concerns around safety (10-12). Progress has been made in understanding the underlying immune mechanisms and genetic predisposition of SCAR (13), providing strong support for the role of HLA typing in identifying specific drug-associated reactions (e.g. HLA*B:57-01 for abacavir hypersensitivity, HLA-B*58:01 for allopurinol hypersensitivity) (14, 15). Further association studies are required, however, to capitalise on this knowledge and previously provided roadmap. The use of novel *ex vivo* T-cell diagnostics to aid drug causality assessment, including lymphocyte transformation testing (LTT) and IFN-γ Enzyme Linked ImmunoSpot (ELISpot) Assay, has been utilized with some success in a research setting but their clinical utility is not yet established (12, 16-22).

The long-term outcomes of SCAR including quality of life, disease recurrence, inadvertent drug re-exposure and medication safety are not well-described. The development of a regional clinical and DNA registry of SCAR will allow investigators to (i) perform surveillance for new and emerging drug causality, (ii) develop causality and phenotypic prediction rules, (iii) understand best-practice treatment approaches, (iv) discover genomic predictors that prevent SCAR onset and (v) improve long-term outcomes and medication safety. The additional biospecimen component of the study will allow investigators to assess the utility of T-cell diagnostics in aiding drug causality. While national SCAR registries have been set up successfully in Europe (RegiSCAR) and Korea (KoSCAR) (23-24), AUS-SCAR will be the first registry of severe drug allergy in the Australasian region.

METHODS AND ANALYSIS

AUS-SCAR is an Australasian, multicentre, prospective registry of severe cutaneous adverse reactions in adults and adolescents > 12 years of age. Participating sites for recruitment include Austin Health, Alfred Health, Eastern Health, Peter MacCallum Cancer Centre, St Vincent's Hospital Melbourne, Monash Health, Royal Melbourne Hospital, Epworth Healthcare, Campbelltown Hospital, Nepean Hospital, St Vincent's Hospital Sydney, Fiona Stanley Hospital, Sir Charles Gairdner Hospital, Royal Brisbane and Women's Hospital, Queensland Children's Hospital, Royal Adelaide Hospital, Flinders Medical Centre, Royal Darwin Hospital, Launceston General Hospital and Auckland City Hospital. The Peter Doherty Institute for Infection and Immunity and Institute for Immunology and Infectious Diseases (IIID) are collaborating sites for sample analysis. Recruitment commenced in July 2019 and is planned to continue across all sites until accrual has reached $n = 500$.

Study Oversight
A 5-7 person steering committee will be formed following nominations from participating site principal investigators. Steering Committee members will meet regularly to discuss the direction of the project, assess requests from investigators and identify any potential risks or issues. The chair of the Steering Committee will be the Chief Investigator. A Steering Committee member can step down from this role at any time and nominations for a new member will be sought from participating site principal investigators. The Steering Committee should have at least one of the following at all times: infectious diseases physician, allergist/immunologist and dermatologist.

The clinical and DNA database and results of the study are the common property of AUS-SCAR investigators and cannot be utilised without the formal authorization of the Steering Committee. The

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3   release of results at conference proceedings, meetings and/or in publication are decided upon by the
4   Steering Committee of AUS-SCAR.
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7   **Project development**
8   Any principal investigator can propose a project utilizing AUS-SCAR data. This proposal will be
9   forwarded to all investigators for comment and the Steering Committee will provide (i) feedback to
10   the proposing investigator and (ii) approval/non-approval of the project.
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14   **Patient Involvement**
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16   Although they have not been involved in the study design, patients will be invited to assist with
17   identifying the best methods of disseminating results to patients and the public following publication.
18   Patients or consumer representatives may also be considered for inclusion in the Steering Committee.
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46   **Figure 1. Overview of AUS-SCAR study design**
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48   **Participants**
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51   Patients will be invited to participate in the registry if 1) they are admitted to or referred to a
52   participating site with a suspected SCAR, 2) two site investigators have agreed on inclusion, 3) SCAR
53   is confirmed by a site dermatologist or immunologist or is biopsy proven and 4) the SCAR phenotype
54   is consistent with disease-specific criteria and alternative diagnoses have been ruled out. Disease-
55   specific criteria for SJS/TEN includes the presence of widespread erythema with skin detachment and
56   more than 1 blister. For GBFDE, there must be multifocal, widespread, bullous-type fixed drug
57   eruption characterised by sharply defined bullae at site of recurrent drug administration. Criteria for
58   DRESS and AGEP are outlined in **Supplementary Tables 1** and **2**, respectively**.**
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At a later stage of the project, extended recruitment may include the following phenotypes, following approval by > 50% of principal investigators and the Project Steering Committee:

  a. **AIN** – Required hospitalization and biopsy proven with acute kidney injury (increase in serum creatinine by ≥ 0.3 mg/dl within 48 hours or increase in serum creatinine to ≥ 1.5 times baseline within 7 days or urine output < 0.5ml/kg/h for 6 hours) (25) with other common causes excluded. Non-biopsy proven cases with a single implicated drug, urinary and peripheral eosinophilia, acute kidney injury and resolution of renal disease post drug removal can be included.

  b. **DILI** – Required hospitalization and biopsy proven with ≥ 5x upper limit of normal (ULN) for ALT or ≥ 2 ULN for ALP, or ≥ 3 ULN for ALT with bilirubin ≥ 2 ULN (26). Non-biopsy proven cases with a single implicated drug, acute liver injury, autoimmune and other causes excluded and resolution of liver disease post drug removal can be included.

  c. **FDE** – Dermatologist confirmed, well-defined, circular, hyper-pigmented single or a few plaques that recur in fixed locations upon ingestion of drug (therefore requires 2 or more occurrences).

Biospecimen Collection and Analysis

Part 1. Clinical data and DNA collection

Following informed consent, baseline patient demographics, medical history and clinical data including histopathology and clinical photography will be collected from the patient and medical record and entered into a secure REDCap database. Consent may be obtained from the patient, parent/guardian or medical treatment decision-maker, as appropriate and subject to local or national law. A waiver of consent has been obtained for some participating institutions to collect clinical data retrospectively for patients that die prior to obtaining informed consent.

DNA will be collected for all patients enrolled prospectively: this will be extracted from saliva for patients who do not consent to additional sample collection or from whole blood or peripheral blood mononuclear cells (PBMCs) for patients who agree to additional blood collection. Genomic testing will be performed at the Institute for Immunology and Infectious Diseases (IIID), Murdoch University, Perth, Western Australia for HLA-A, HLA-B, HLA-C, DR/DQ/DP. Four-digit typing is performed on extracted DNA using the 454 FLX platform. Specific HLA loci are PCR-amplified using sample specific MID-tagged primers that amplify polymorphic exons from Class I (A, B, C Exons 2 and 3) and Class II (DQ, Exons 2 and 3; DRB and DPB1, Exon 1) MHC genes. Amplified DNA products from unique MID-tagged products (up to 48 MIDs) are then pooled in equimolar ratios and subjected to library preparation, quantitation and emulsion PCR suitable for entry into the 454 FLX sequencing pipeline. Clonally enriched beads are used for 454 Titanium chemistry based sequencing on the 454 FLX+ sequencer. Sequences are then separated by MID tags and alleles called using an in house accredited HLA allele caller software pipeline using the latest IMGT HLA allele database as the allele reference library. Further Genome Wide Association Studies (GWAS), RNA-seq and virologic assessment may be performed on stored DNA samples to determine if genetic and viral variants are associated with SCAR phenotype.

Part 2. Additional biospecimen collection

This part of the study is <u>optional for participating sites and for patients</u>. Samples will need to be stored at the participating site or at a collaborating AUS-SCAR site if there is capacity. Informed consent must

be obtained for all samples requested. The sampling schedule is outlined below and in **Supplementary Table 3.**

Blood

For adults, an initial blood sample of 100 - 150 ml will be taken following informed consent. A reduced blood volume of 20 – 50 ml is taken for patients under 18 years of age. A convalescent follow-up blood draw of the same volume will be taken at 12 months post-SCAR onset for consenting patients. Repeat blood draws may be requested at both time points if the full volume was unable to be collected or cell viability is poor, subject to ongoing patient consent.

Skin biopsy

A 3-4mm punch biopsy may be taken from an affected area at the acute stage and 12 months post-SCAR onset. For a subset of patients, repeat biopsies may be requested for comparison studies.

Blister fluid

For patients with blisters present, blister fluid of any volume may be collected into a heparinised tube for the extraction of PBMCs. For patients whose blisters reform, additional fluid collection may be requested.

Additional clinical samples

Additional clinical samples may be collected if considered to be of potential clinical relevance by the site investigator (eg. cerebrospinal fluid, lymph node aspirate).

Sample processing

Samples are to be processed and stored at participating sites (or a collaborating AUS-SCAR site on request from participating site) and cannot be used in AUS-SCAR studies without written approval from the participating site. The participating site can choose to utilize these samples for any research project they have additional local ethics approval for, without consent required from AUS-SCAR investigators. The Doherty Institute for Infection and Immunity or Institute for Immunology and Infectious Diseases are available for assistance with sample processing where possible.

Part 3. Patient follow up

A 12-month follow-up will be performed to collect data regarding (i) drug utilization, (ii) health outcomes and (iii) quality of life **(Supplementary Materials)**. Mortality/morbidity and prescribing data will be extracted from the medical record. For available patients a quality of life assessment will be performed using the previously validated and adapted Drug Hypersensitivity Quality of Life Questionnaire (DrHy-Q) (27). A telephone script is provided with the DrHy-Q in Supplementary Materials. The questionnaire may also be sent out via email. Prescribing and mortality data may be obtained from PBS following approval or the participant's GP where not available from the medical record or patient.

Study Aims

1. To develop a national registry of SCAR to ensure continuous surveillance of new and emerging causative drugs and improve pharmacovigilance

2. To describe the causality and epidemiology of SCAR in Australasia

3. To determine patient, drug and clinical factors that predict SCAR phenotypes and which treatments improve outcomes

4. To determine the treatments employed for SCAR in Australasia and describe patient outcomes

5. To determine pharmacogenomic and genomic associations in SCAR.

6. To examine the long term impacts of SCAR including restricted medication use and QOL impact

Primary outcome measures

- Proportions (n, %) of SCAR secondary to antibiotics or non-antibiotics
  - Proportions (n, %) for each drug class

Secondary outcome measures

- Proportion (n, %) of SCAR treated with a potentially disease-modifying therapy
  - Proportions (n, %) for each treatment type e.g. topical or systemic corticosteroids, intravenous immunoglobulin (IVIG), immunomodulators (e.g. rituximab), antivirals (e.g. ganciclovir)
  - For each treatment type: Length-of-stay (days), inpatient mortality, all-cause mortality (90-day, 12-months), disease recurrence
- Proportion (n, %) of SCAR referred for in vivo/ex vivo allergy testing
  - Proportions (n, %) of each testing modality – patch testing, intradermal testing, *ex vivo* (LTT, ELISpot, other)
  - Proportion (n, %) positive on skin testing
- For each SCAR phenotype: Proportion (n, %) associated with inpatient and 12-month mortality
- For each SCAR phenotype: Proportion (n, %) associated with relapse or drug re-exposure within 12 months
- Risk factors associated with development of each SCAR phenotype
  - Patient (host factors), drug (pharmacological class), clinical (disease factors)
- Risk factors associated with SCAR mortality
  - Patient (host factors), drug (pharmacological class), disease (phenotype)
- For each SCAR phenotype and implicated drug: Genomic associations within HLA class I and/or II
- Utility of *in vitro/ex vivo* diagnostics in assigning drug causality in SCAR
- The long-term sequelae of SCAR

Sample size

Due to the registry study design, a sample size calculation is not required. The projected recruitment number over a 5-year period is 500 (80 cases are estimated over 5 years at a single institution (3) - allowing for 35% minimum case capture at 20 sites, the extrapolated numbers are 560 over this period).

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Statistical analysis

Statistical analysis using StataTM (StataCorp, Texas) will be performed by study investigators with the assistance of a biostatistician as required. Categorical variables will be summarized using frequency and percentage and compared using a chi-square test or Fisher's exact test. Continuous variables will first be assessed for significant skew using a Shapiro-Wilk test. They will then be summarized using mean and standard deviation (SD) or median and inter-quartile range as appropriate and compared using a t-test or Wilcoxon signed-rank / Mann-Whitney U test. Multivariable logistic regression modelling will be utilized to examine secondary objectives related to variables/factors predicting specified outcomes.

ETHICS AND DISSEMINATION

This study was registered on the Australian New Zealand Clinical Trials Registry (ANZCTR) on 19th February 2019 (Trial ID ACTRN12619000241134) and received ethical approval from the Austin Health Human Research Ethics Committee (HREC Number HREC/50791/Austin-19) in May 2019.

An initial publication of pilot data is planned after the recruitment of 100 patients. Patient demographics, SCAR phenotype, implicated drugs, ELISpot and HLA results will be included. Principal investigators from each participating site will be included as authors. Authorship will be guided by the Project Steering Committee with reference to the International Committee of Medical Journal Editors guidelines.

Further results of this research project are planned to be published and/or presented in a variety of scientific forums and journals. The data presented will explore SCAR epidemiology in Australasia, drug causality, genomic predictors, diagnostic tools and potential treatments.

Authors' contributions

FJ is the first author and coordinator of the study. JAT is the senior author and guarantor, providing overarching responsibility for project governance. MSYG, EJP, AKA, JY, CHK, HC and DG all contributed to the initial design of the study and writing of the protocol. EM, FJ, SV, KC, NEH, AA, WT, JDL, CZ, AD, JK, FT, SB, WS, AC, TA, AL, JB and LM contributed to substantial revisions of the manuscript. All authors have read and approved the final manuscript.

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Competing interests

None to declare.

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Figure 1. Overview of AUS-SCAR study design

523x381mm (59 x 48 DPI)

SUPPLEMENTARY MATERIALS

Supplementary Table 1. SCAR phenotype-specific criteria for Drug reaction with eosinophilia and systemic symptoms (DRESS). RegiSCAR scoring system (8, 22). Inclusion of cases with drug reaction with eosinophilia and systemic symptoms (DRESS) requires a RegiSCAR score of ≥ 4 and hospitalisation.

RegiSCAR Item		Present		Absent
Fever ≥38.5°C (101.3°F)		0		-1
Enlarged lymph nodes (>1 cm size, at least two sites)		1		0
Eosinophilia: ≥700 or ≥10 percent (leucopenia)	≥1500 or ≥20 percent (leucopenia)	1	2	0
Atypical lymphocytes		1		0
Rash ≥50 percent of body surface area		1		0
Rash suggestive (≥2 of facial edema, purpura, infiltration, desquamation)		1		0
Skin biopsy suggesting alternative diagnosis		-1		0
Organ involvement: one	two or more	1	2	0
Disease duration >15 days		0		-2
Investigation for alternative cause (blood cultures, ANA, serology for Hepatitis viruses, mycoplasma, Chlamydia) ≥3 done and negative		1		0

Supplementary Table 2. SCAR phenotype-specific criteria for Acute generalized exanthematous pustulosis (AGEP). AGEP validation score, EuroSCAR group (23). Inclusion of cases with acute generalised exanthematous pustulosis (AGEP) requires an AGEP score of ≥ 5.

Morphology	Score

Pustules
    Typical*
    Compatible**
    Insufficient***
	+2
	+1
	0

Erythema
    Typical*
    Compatible**
    Insufficient***
	1

Distribution/patter
    Typical*
    Compatible**
    Insufficient***
	1

Post pustular desquamation
    Yes
     No/insufficient
	1

Course	
Mucosal involvement Yes No	-2 0
Acute onset (≤10 days) Yes No	0 -2
Resolution	

Yes	0
No	-4
Fever ≥ 38	
Yes	+1
No	0
PMN ≥ 7000/mm^3	
Yes	+1
No	0
Histology	
Other disease	-10
Not representative/no histology	0
Exocytosis of PMN	+1
Subcorneal and/or intraepidermal non-spongiform or NOS ¹2 pustule(s) with papillary oedema or subcorneal and/or intraepidermal spongiform or NOS pustule(s) without papillary oedema (NOS½not otherwise specified)	+2
Spongiform subcorneal and/or intraepidermal pustule(s) ¹3 with papillary edema	+3

Supplementary Table 3. Schedule of assessments during study period.

Schedule of Assessments			
Procedure	**Visit**	**Timeline**	**Volume**
Part 1: DNA	Acute admission / outpatient visit	Acute	Saliva sample or additional 9mls blood
Part 2: Blood draws	Acute or follow-up admission / outpatient visit	Acute / convalescent	≤150mls blood (adults) OR ≤50ml (aged 12 – 18 years)
Part 2: Skin sample	Acute admission / outpatient visit	Acute / convalescent	3-4mm punch biopsy
Part 2: Blister fluid	Acute admission	Acute	Any amount
Part 2: Other relevant fluid samples (eg. CSF, urine, LN aspirate)	Acute or follow-up admission / outpatient visit	Acute / convalescent	Any amount
Part 3: Patient survey	Follow-up phone call / electronic mail-out	12 months post SCAR onset (convalescent)	N/A

Drug Hypersensitivity Quality of Life Questionnaire (DrHy-Q)

To be performed at 12 months post onset of rash. Assessment should be performed over the phone by a study investigator or via an online tool (REDCap) if they prefer.

If the patient doesn't speak English:

1. Prior to calling all patients, extract the data from the medical record as outlined above. During the medical record review, check Emergency Department presentation notes medical record to determine whether an interpreter was needed during any episodes.
   a. If an interpreter was needed during the episode, the telephone interview should be undertaken with the assistance of an interpreter.
   b. If an interpreter was not used during hospital episodes, but a family member was involved with the patient's care due to a language barrier, contact this person to determine whether a suitable time can be set up to invite the patient to participate.
2. If a potential language barrier is not identified in the episode notes, telephone the patient as outlined below. If during the telephone call, it is apparent that an interpreter is needed, attempt to explain to the patient that you will organise an interpreter to assist with the conversation or ask to speak with an English-speaking family member.
3. If a family member or professional telephone interpreter assists with the interview, note this on the data collection form and the scanned medical record.

Verbal consent script for patients discharged from hospital identified from AUS-SCAR database.

"Hello could I please speak to (patient's full given name and surname)?

Hello, I am _____, a nurse or doctor at the _____ Hospital.

Before we proceed, can I please confirm your full name, your date of birth and address?

We are doing an audit to see how your health is following a recent episode of an adverse reaction you had to a medication and managed at _____ Hospital. If you agree to be involved, we will ask you some questions about yourself. Usually the interview takes about 10 minutes.

We initially obtained your consent to contact you for this survey and this will be your final involvement in the study.

If you would prefer we can email you a link to a safe online version of the questions for you to answer in your own time.

If patient is not home:

"Is there a time that I could call back to speak with (patient's name)?

If the patient is busy:

"Is there another time that I could call back that would be convenient?

Questions:

1. "Would you consider yourself allergic to any drugs?"
   a. **If Yes** – "Could you please list them?"
2. "Did you have any allergy testing performed after your discharge from hospital"?
   a. **If Yes** – "Do you know the results?"
3. "Did you receive a medical alert letter or card on discharge from the hospital"?
   a. **If Yes** – "What is listed on this?"
4. "Have you had any recurrent rashes to drugs since discharge from hospital"?
   a. **If Yes** – "Could you please list the drugs and describe the reactions"

Phenotype-specific questions

Page **3** of **4**

5. **If antibiotic associated SCAR** - "Have you received any antibiotics since the antibiotic allergy testing was performed?" (if antibiotic associated SCAR)
   a. **If Yes** – "Could you tell me which antibiotics, what they were given for and if you had any reactions?"
   b. **If Yes** – **"**Would you be happy with us contacting your general practitioner for these details?"
6. **If SJS or TEN** - "Do you have any ongoing issues with your eyes or vision?"
7. **If SJS or TEN** - "Do you have any ongoing issues of scarring or contractures?"
8. **If DRESS** – "Do you have any autoimmune problems since / after your reaction such as thyroid disease or diabetes"
   a. **If Yes** – "Diabetes" (Y/N), "Thyroid disease" (Y/N), "Lupus" (Y/N), "Other" (Y/N)

Drug Hypersensitivity Quality of Life Questionnaire (DrHy-Q) – as per previously published protocol (24) – Answer True or False

1. I would like an allergy doctor's opinion before taking drugs prescribed by other doctors
2. I feel different from others
3. Even a little discomfort is a problem for me
4. Since I am unable to take drugs every illness limits me more than other people
5. My allergy problems interfere with my sexual life
6. My family and partner are aware of my allergy problem
7. I am afraid of being administered a drug during an emergency to which I am allergic
8. For each infection I would be confident that there is a drug that I can take safely
9. I feel anxious due to my allergy reaction
10. I worry every time I take a drug different from ones that cause my allergic reactions
11. The idea of taking a medicine makes me feel anxious
12. My family doctor is aware of my adverse drug reaction
13. Experiencing an adverse reaction to drugs affects my life
14. I feel anguished due to my problem of allergy reaction
15. I am afraid I could not deal with the pain
16. I've given up leisure activities (sport, vacations, trips) because of my problem
17. I'm in a bad mood due to my problem of allergy reaction

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2,3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7,11-12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-8
Bias	9	Describe any efforts to address potential sources of bias	2
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA

Discussion

Key results	18	Summarise key results with reference to study objectives	NA
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	NA
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	NA
Generalisability	21	Discuss the generalisability (external validity) of the study results	NA

Other information

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	8

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Study Protocol: Australasian registry of Severe Cutaneous Adverse Reactions (AUS-SCAR)

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Manuscripts

Study Protocol: Australasian registry of Severe Cutaneous Adverse Reactions (AUS-SCAR)

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Protocol Version: 8

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Abstract

Introduction Severe cutaneous adverse reactions (SCAR) are a group of T cell-mediated hypersensitivities associated with significant morbidity, mortality and hospital costs[1]. Clinical phenotypes include Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug

reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP). In this Australasian, multi-centre, prospective registry, we plan to examine the clinical presentation, drug causality, genomic predictors, potential diagnostic approaches, treatments and long-term outcomes of SCAR in Australia and New Zealand.

Methods and analysis Adult and adolescent patients with SCAR including SJS, TEN, DRESS, AGEP and another T cell-mediated hypersensitivity, generalised bullous fixed drug eruption (GBFDE), will be prospectively recruited. A waiver of consent has been granted for some sites to retrospectively include cases which result in early mortality. DNA will be collected for all prospective cases. Blood, blister fluid and skin biopsy sampling is optional and subject to patient consent and site capacity. To develop culprit drug identification and prevention, genomic testing will be performed to confirm HLA type and ex vivo testing will be performed via IFN-γ release ELISpot assay using collected peripheral blood mononuclear cells (PBMCs). The long term outcomes of SCAR will be investigated with a 12-month quality of life survey and examination of prescribing and mortality data.

Ethics and dissemination This study was reviewed and approved by the Austin Health Human Research Ethics Committee (HREC/50791/Austin-19). Results will be published in peer-reviewed journals and presented at relevant conferences.

Registration Number: ACTRN12619000241134

Strengths and limitations of the study

- The strength of AUS-SCAR lies in its prospective design, allowing for the real-time collection of clinical data, standardised investigation and sampling for genomic evaluation and ex-vivo diagnostics.
- There will likely be selection bias favouring the recruitment of adults, less critically ill patients, patients living in metropolitan areas where the majority of study sites are located and patients whose first language is English.
- A limitation of the sampling strategy is the large blood volume required due to the number of PBMCs required for successful ELISpot assay, complicated by the often poor viability of cells from acute bleeds due to critical illness. Many hospital-adjacent laboratories are also not set up to process PBMCs, blister fluid or skin specimens requiring same-day transport to specialised research labs.
- Selection bias is also likely to affect the sampling strategy as treating teams may be less willing to overburden children and critically ill patients.
- Finally, the registry is not designed to achieve complete case capture across the study period and recruiting the target sample size will be dependent on successful recognition of cases at each site.

INTRODUCTION

SCAR are a group of T cell-mediated hypersensitivities – including Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP) (1). Other severe T cell-mediated hypersensitivities include diseases such as generalized bullous fixed drug eruption (GBFDE), drug-induced liver injury (DILI) and acute interstitial nephritis (AIN) (1, 2). SCAR can be associated with significant morbidity, hospital costs, increased demand for specialist testing and high mortality (3-6).

Despite this, an understanding of the clinical, genomic and pharmacological predictors of each phenotype remains absent from current practice. Further, there is currently a lack of consistency among the recommendations in treatment guidelines for these severe reactions.

Causality assessment in SCAR is often complex as multiple drugs are frequently involved (3, 7-9). Whilst the use of skin testing (*in vivo*) has been increasingly employed, it is hampered by low sensitivity and concerns around safety (10-12). Progress has been made in understanding the underlying immune mechanisms and genetic predisposition of SCAR (13), providing strong support for the role of HLA typing in identifying specific drug-associated reactions (e.g. HLA-B*57:01 for abacavir hypersensitivity, HLA-B*58:01 for allopurinol hypersensitivity) (14, 15). Further association studies are required, however, to capitalise on this knowledge and previously provided roadmap. The use of novel *ex vivo* T-cell diagnostics to aid drug causality assessment, including lymphocyte transformation testing (LTT) and IFN-γ Enzyme Linked ImmunoSpot (ELISpot) Assay, has been utilized with some success in a research setting but their clinical utility is not yet established (12, 16-22).

The long-term outcomes of SCAR including quality of life, disease recurrence, inadvertent drug re-exposure and medication safety are not well-described. The development of a regional clinical and DNA registry of SCAR will allow investigators to (i) perform surveillance for new and emerging drug causality, (ii) develop causality and phenotypic prediction rules, (iii) understand best-practice treatment approaches, (iv) discover genomic predictors that prevent SCAR onset and (v) improve long-term outcomes and medication safety. The additional biospecimen component of the study will allow investigators to assess the utility of T-cell diagnostics in aiding drug causality. While national SCAR registries have been set up successfully in Europe (RegiSCAR) and Korea (KoSCAR) (23-24), AUS-SCAR will be the first registry of severe drug allergy in the Australasian region.

METHODS AND ANALYSIS

AUS-SCAR is an Australasian, multicentre, prospective registry of severe cutaneous adverse reactions in adults and adolescents > 12 years of age. Participating sites for recruitment include Austin Health, Alfred Health, Eastern Health, Peter MacCallum Cancer Centre, St Vincent's Hospital Melbourne, Monash Health, Royal Melbourne Hospital, Epworth Healthcare, Campbelltown Hospital, Nepean Hospital, St Vincent's Hospital Sydney, Fiona Stanley Hospital, Sir Charles Gairdner Hospital, Royal Brisbane and Women's Hospital, Queensland Children's Hospital, Royal Adelaide Hospital, Flinders Medical Centre, Royal Darwin Hospital, Launceston General Hospital and Auckland City Hospital. The Peter Doherty Institute for Infection and Immunity and Institute for Immunology and Infectious Diseases (IIID) are collaborating sites for sample analysis. Recruitment commenced in July 2019 and is planned to continue across all sites until accrual has reached $n = 500$.

Study Oversight
A 5-7 person steering committee will be formed following nominations from participating site principal investigators. Steering Committee members will meet regularly to discuss the direction of the project, assess requests from investigators and identify any potential risks or issues. The chair of the Steering Committee will be the Chief Investigator. A Steering Committee member can step down from this role at any time and nominations for a new member will be sought from participating site principal investigators. The Steering Committee should have at least one of the following at all times: infectious diseases physician, allergist/immunologist and dermatologist.

The clinical and DNA database and results of the study are the common property of AUS-SCAR investigators and cannot be utilised without the formal authorization of the Steering Committee. The

release of results at conference proceedings, meetings and/or in publication are decided upon by the Steering Committee of AUS-SCAR.

Project development

Any principal investigator can propose a project utilizing AUS-SCAR data. This proposal will be forwarded to all investigators for comment and the Steering Committee will provide (i) feedback to the proposing investigator and (ii) approval/non-approval of the project.

Patient Involvement

Although they have not been involved in the study design, patients will be invited to assist with identifying the best methods of disseminating results to patients and the public following publication. Patients or consumer representatives may also be considered for inclusion in the Steering Committee.

Figure 1. Overview of AUS-SCAR study design (adapted from Eldridge et al., 2010)[28]

Participants

Patients will be invited to participate in the registry if 1) they are admitted to or referred to a participating site with a suspected SCAR, 2) two site investigators have agreed on inclusion, 3) SCAR is confirmed by a site dermatologist or immunologist or is biopsy proven and 4) the SCAR phenotype is consistent with disease-specific criteria and alternative diagnoses have been ruled out. Disease-specific criteria for SJS/TEN includes the presence of widespread erythema with skin detachment and more than 1 blister. For GBFDE, there must be multifocal, widespread, bullous-type fixed drug eruption characterised by sharply defined bullae at site of recurrent drug administration. Criteria for DRESS and AGEP are outlined in **Supplementary Tables 1** and **2**, respectively**.** The study design and biospecimen sampling schedule are outlined in **Figure 1.**

At a later stage of the project, extended recruitment may include the following phenotypes, following approval by > 50% of principal investigators and the Project Steering Committee:

    a. **AIN** – Required hospitalization and biopsy proven with acute kidney injury (increase in serum creatinine by $\geq$ 0.3 mg/dl within 48 hours or increase in serum creatinine to $\geq$ 1.5 times baseline within 7 days or urine output < 0.5ml/kg/h for 6 hours) (25) with other common causes excluded. Non-biopsy proven cases with a single implicated drug, urinary and peripheral eosinophilia, acute kidney injury and resolution of renal disease post drug removal can be included.

    b. **DILI** – Required hospitalization and biopsy proven with $\geq$ 5x upper limit of normal (ULN) for ALT or $\geq$ 2 ULN for ALP, or $\geq$ 3 ULN for ALT with bilirubin $\geq$ 2 ULN (26). Non-biopsy proven cases with a single implicated drug, acute liver injury, autoimmune and other causes excluded and resolution of liver disease post drug removal can be included.

    c. **FDE** – Dermatologist confirmed, well-defined, circular, hyper-pigmented single or a few plaques that recur in fixed locations upon ingestion of drug (therefore requires 2 or more occurrences).

Biospecimen Collection and Analysis

Part 1. Clinical data and DNA collection

Following informed consent, baseline patient demographics, medical history and clinical data including histopathology and clinical photography will be collected from the patient and medical record and entered into a secure REDCap database. Consent may be obtained from the patient, parent/guardian or medical treatment decision-maker, as appropriate and subject to local or national law. A waiver of consent has been obtained for some participating institutions to collect clinical data retrospectively for patients that die prior to obtaining informed consent.

DNA will be collected for all patients enrolled prospectively: this will be extracted from saliva for patients who do not consent to additional sample collection or from whole blood or peripheral blood mononuclear cells (PBMCs) for patients who agree to additional blood collection. Genomic testing will be performed at the Institute for Immunology and Infectious Diseases (IIID), Murdoch University, Perth, Western Australia for HLA-A, HLA-B, HLA-C, DR/DQ/DP. Four-digit typing is performed on extracted DNA using the 454 FLX platform. Specific HLA loci are PCR-amplified using sample specific MID-tagged primers that amplify polymorphic exons from Class I (A, B, C Exons 2 and 3) and Class II (DQ, Exons 2 and 3; DRB and DPB1, Exon 1) MHC genes. Amplified DNA products from unique MID-tagged products (up to 48 MIDs) are then pooled in equimolar ratios and subjected to library preparation, quantitation and emulsion PCR suitable for entry into the 454 FLX sequencing pipeline. Clonally enriched beads are used for 454 Titanium chemistry based sequencing on the 454 FLX+ sequencer. Sequences are then separated by MID tags and alleles called using an in house accredited HLA allele caller software pipeline using the latest IMGT HLA allele database as the allele reference library. Further Genome Wide Association Studies (GWAS), RNA-seq and virologic assessment may be performed on stored DNA samples to determine if genetic and viral variants are associated with SCAR phenotype.

Part 2. Additional biospecimen collection

This part of the study is underlined optional for participating sites and for patients. Samples will need to be stored at the participating site or at a collaborating AUS-SCAR site if there is capacity. Informed consent must be obtained for all samples requested. The sampling schedule is outlined below and in **Supplementary Table 3.**

Blood

For adults, an initial blood sample of 100 - 150 ml will be taken following informed consent. A reduced blood volume of 20 – 50 ml is taken for patients under 18 years of age. A convalescent follow-up blood draw of the same volume will be taken at 12 months post-SCAR onset for consenting patients. Repeat blood draws may be requested at both time points if the full volume was unable to be collected or cell viability is poor, subject to ongoing patient consent.

Skin biopsy

A 3-4mm punch biopsy may be taken from an affected area at the acute stage and 12 months post-SCAR onset. For a subset of patients, repeat biopsies may be requested for comparison studies.

Blister fluid

For patients with blisters present, blister fluid of any volume may be collected into a heparinised tube for the extraction of PBMCs. For patients whose blisters reform, additional fluid collection may be requested.

Additional clinical samples

Additional clinical samples may be collected if considered to be of potential clinical relevance by the site investigator (e.g. cerebrospinal fluid, lymph node aspirate).

Sample processing

Samples are to be processed and stored at participating sites (or a collaborating AUS-SCAR site on request from participating site) and cannot be used in AUS-SCAR studies without written approval from the participating site. The participating site can choose to utilize these samples for any research project they have additional local ethics approval for, without consent required from AUS-SCAR investigators. The Doherty Institute for Infection and Immunity or Institute for Immunology and Infectious Diseases are available for assistance with sample processing where possible.

Part 3. Patient follow up

A 12-month follow-up will be performed to collect data regarding (i) drug utilization, (ii) health outcomes and (iii) quality of life **(Supplementary Materials)**. Mortality/morbidity and prescribing data will be extracted from the medical record. For available patients a quality of life assessment will be performed using the previously validated and adapted Drug Hypersensitivity Quality of Life Questionnaire (DrHy-Q) (27). A telephone script is provided with the DrHy-Q in Supplementary Materials. The questionnaire may also be sent out via email. Prescribing and mortality data may be obtained from PBS following approval or the participant's GP where not available from the medical record or patient.

Study Aims

1. To develop a national registry of SCAR to ensure continuous surveillance of new and emerging causative drugs and improve pharmacovigilance
2. To describe the causality and epidemiology of SCAR in Australasia
3. To determine patient, drug and clinical factors that predict SCAR phenotypes and which treatments improve outcomes
4. To determine the treatments employed for SCAR in Australasia and describe patient outcomes
5. To determine pharmacogenomic and genomic associations in SCAR.
6. To examine the long term impacts of SCAR including restricted medication use and QOL impact

Primary outcome measures

- Proportion (n, %) of SCAR secondary to antibiotics or non-antibiotics
  - Proportion (n, %) for each drug class

Secondary outcome measures

- Proportion (n, %) of SCAR treated with a potentially disease-modifying therapy

- o Proportion (n, %) for each treatment type e.g. topical or systemic corticosteroids, intravenous immunoglobulin (IVIG), immunomodulators (e.g. rituximab), antivirals (e.g. ganciclovir)
  - o For each treatment type: Length-of-stay (days), inpatient mortality, all-cause mortality (90-day, 12-months), disease recurrence
- Proportion (n, %) of SCAR referred for in vivo/ex vivo allergy testing
  - o Proportion (n, %) of each testing modality – patch testing, intradermal testing, *ex vivo* (LTT, ELISpot, other)
  - o Proportion (n, %) positive on skin testing
- For each SCAR phenotype: Proportion (n, %) associated with inpatient and 12-month mortality
- For each SCAR phenotype: Proportion (n, %) associated with relapse or drug re-exposure within 12 months
- Risk factors associated with development of each SCAR phenotype
  - o Patient (host factors), drug (pharmacological class), clinical (disease factors)
- Risk factors associated with SCAR mortality
  - o Patient (host factors), drug (pharmacological class), disease (phenotype)
- For each SCAR phenotype and implicated drug: Genomic associations within HLA class I and/or II
- Utility of *in vitro/ex vivo* diagnostics in assigning drug causality in SCAR
- The long-term sequelae of SCAR

Sample size

Due to the registry study design, a sample size calculation is not required. The projected recruitment number over a 5-year period is 500 (80 cases are estimated over 5 years at a single institution (3) - allowing for 35% minimum case capture at 20 sites, the extrapolated numbers are 560 over this period).

Statistical analysis

Statistical analysis using Stata (StataCorp, Texas) will be performed by study investigators with the assistance of a biostatistician as required. Categorical variables will be summarized using frequency and percentage and compared using a chi-square test or Fisher's exact test. Continuous variables will first be assessed for significant skew using a Shapiro-Wilk test. They will then be summarized using mean and standard deviation (SD) or median and inter-quartile range as appropriate and compared using a t-test or Wilcoxon signed-rank / Mann-Whitney U test. Multivariable logistic regression modelling will be utilized to examine secondary objectives related to variables/factors predicting specified outcomes.

ETHICS AND DISSEMINATION

This study was registered on the Australian New Zealand Clinical Trials Registry (ANZCTR) on 19th February 2019 (Trial ID ACTRN12619000241134) and received ethical approval from the Austin Health Human Research Ethics Committee (HREC Number HREC/50791/Austin-19) in May 2019.

An initial publication of pilot data is planned after the recruitment of 100 patients. Patient demographics, SCAR phenotype, implicated drugs, ELISpot and HLA results will be included. Principal investigators

Page **7** of **10**

from each participating site will be included as authors. Authorship will be guided by the Project Steering Committee with reference to the International Committee of Medical Journal Editors guidelines.

Further results of this research project are planned to be published and/or presented in a variety of scientific forums and journals. The data presented will explore SCAR epidemiology in Australasia, drug causality, genomic predictors, diagnostic tools and potential treatments.

Authors' contributions

FJ is the Project Manager and Corresponding Author, responsible for providing central operational oversight of the study. JT, EJP, JY, MSYG, WT, CZ, DG and CK contributed to the initial design of the study and drafting of the protocol. FJ, MSYG, EM, SV, KC, NEH, AA, AMC, JFD, CZ, DG, HC, AD, JK, CK, FT, SB, JY, WT, WS, AC, TA, AL, JB, LM, AKA, EJP and JT contributed to pilot data acquisition informing the study design and substantial revision of the manuscript. JAT is the Coordinating Principal Investigator, providing overall responsibility for the study. All authors have read and approved the final manuscript.

Funding statement

Competing interests

None to declare.

Word count: 2675

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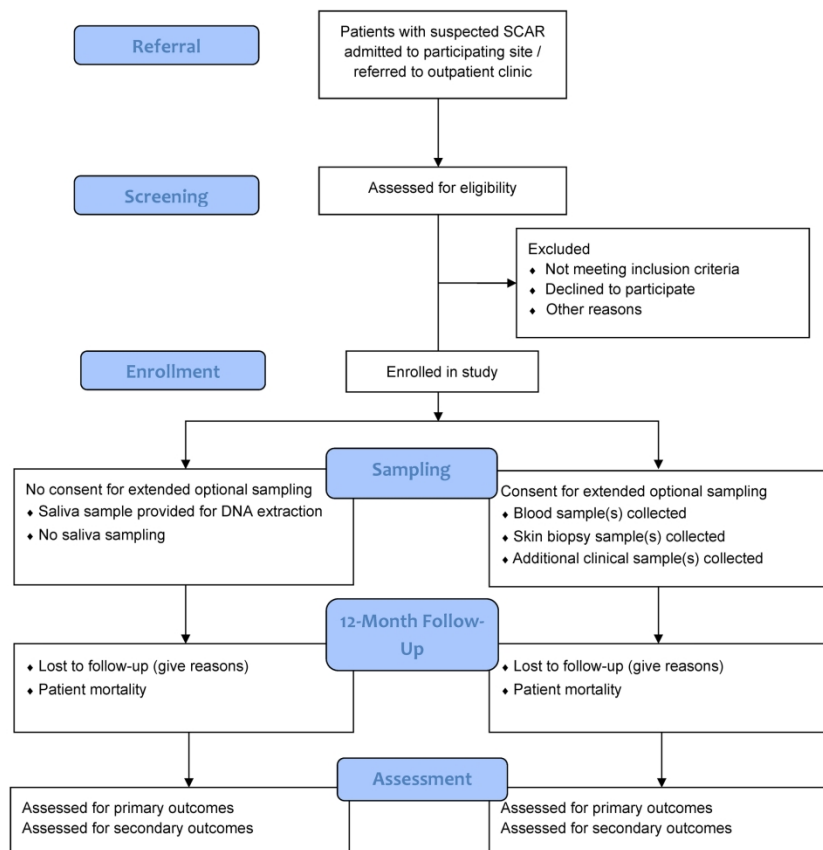
Figure 1. Overview of AUS-SCAR study design (adapted from Eldridge et al., 2010)28

215x279mm (300 x 300 DPI)

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SUPPLEMENTARY MATERIALS

Supplementary Table 1. SCAR phenotype-specific criteria for Drug reaction with eosinophilia and systemic symptoms (DRESS). RegiSCAR scoring system (8, 22). Inclusion of cases with drug reaction with eosinophilia and systemic symptoms (DRESS) requires a RegiSCAR score of ≥ 4 and hospitalisation.

RegiSCAR Item		Present		Absent
Fever ≥38.5°C (101.3°F)		0		-1
Enlarged lymph nodes (>1 cm size, at least two sites)		1		0
Eosinophilia: ≥700 or ≥10 percent (leucopenia)	≥1500 or ≥20 percent (leucopenia)	1	2	0
Atypical lymphocytes		1		0
Rash ≥50 percent of body surface area		1		0
Rash suggestive (≥2 of facial edema, purpura, infiltration, desquamation)		1		0
Skin biopsy suggesting alternative diagnosis		-1		0
Organ involvement: one	two or more	1	2	0
Disease duration >15 days		0		-2
Investigation for alternative cause (blood cultures, ANA, serology for Hepatitis viruses, mycoplasma, Chlamydia) ≥3 done and negative		1		0

Supplementary Table 2. SCAR phenotype-specific criteria for Acute generalized exanthematous pustulosis (AGEP). AGEP validation score, EuroSCAR group (23). Inclusion of cases with acute generalised exanthematous pustulosis (AGEP) requires an AGEP score of ≥ 5.

Morphology	Score

Pustules
    Typical*
    Compatible**
    Insufficient***
	+2
	+1
	0

Erythema
    Typical*
    Compatible**
    Insufficient***
	1

Distribution/patter
    Typical*
    Compatible**
    Insufficient***
	1

Post pustular desquamation
    Yes
     No/insufficient
	1

Course	
Mucosal involvement Yes No	-2 0
Acute onset (≤10 days) Yes No	0 -2
Resolution	

Yes	0
No	-4
Fever ≥ 38	
Yes	+1
No	0
PMN ≥ 7000/mm³	
Yes	+1
No	0
Histology	
Other disease	-10
Not representative/no histology	0
Exocytosis of PMN	+1
Subcorneal and/or intraepidermal non-spongiform or NOS ¹2 pustule(s) with papillary oedema or subcorneal and/or intraepidermal spongiform or NOS pustule(s) without papillary oedema (NOS½not otherwise specified)	+2
Spongiform subcorneal and/or intraepidermal pustule(s) ¹3 with papillary edema	+3

Supplementary Table 3. Schedule of assessments during study period.

Schedule of Assessments			
Procedure	**Visit**	**Timeline**	**Volume**
Part 1: DNA	Acute admission / outpatient visit	Acute	Saliva sample or additional 9mls blood
Part 2: Blood draws	Acute or follow-up admission / outpatient visit	Acute / convalescent	≤150mls blood (adults) OR ≤50ml (aged 12 – 18 years)
Part 2: Skin sample	Acute admission / outpatient visit	Acute / convalescent	3-4mm punch biopsy
Part 2: Blister fluid	Acute admission	Acute	Any amount
Part 2: Other relevant fluid samples (eg. CSF, urine, LN aspirate)	Acute or follow-up admission / outpatient visit	Acute / convalescent	Any amount
Part 3: Patient survey	Follow-up phone call / electronic mail-out	12 months post SCAR onset (convalescent)	N/A

Drug Hypersensitivity Quality of Life Questionnaire (DrHy-Q)

To be performed at 12 months post onset of rash. Assessment should be performed over the phone by a study investigator or via an online tool (REDCap) if they prefer.

If the patient doesn't speak English:

Page **2** of **4**

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2
3   1. Prior to calling all patients, extract the data from the medical record as outlined above. During
4   the medical record review, check Emergency Department presentation notes medical record
5   to determine whether an interpreter was needed during any episodes.
6   a. If an interpreter was needed during the episode, the telephone interview should be
7   undertaken with the assistance of an interpreter.
8   b. If an interpreter was not used during hospital episodes, but a family member was
9   involved with the patient's care due to a language barrier, contact this person to
10   determine whether a suitable time can be set up to invite the patient to participate.
11   2. If a potential language barrier is not identified in the episode notes, telephone the patient as
12   outlined below. If during the telephone call, it is apparent that an interpreter is needed,
13   attempt to explain to the patient that you will organise an interpreter to assist with the
14   conversation or ask to speak with an English-speaking family member.
15   3. If a family member or professional telephone interpreter assists with the interview, note this
16   on the data collection form and the scanned medical record.
17
18
19
20   *Verbal consent script for patients discharged from hospital identified from AUS-SCAR database.*
21
22   "Hello could I please speak to (patient's full given name and surname)?
23
24   Hello, I am _____, a nurse or doctor at the _____ Hospital.
25
26   Before we proceed, can I please confirm your full name, your date of birth and address?
27
28   We are doing an audit to see how your health is following a recent episode of an adverse reaction you
29   had to a medication and managed at _____ Hospital. If you agree to be involved, we will ask you
30   some questions about yourself. Usually the interview takes about 10 minutes.
31
32   We initially obtained your consent to contact you for this survey and this will be your final
33   involvement in the study.
34
35   If you would prefer we can email you a link to a safe online version of the questions for you to answer
36   in your own time.
37
38   If patient is not home:
39
40   "Is there a time that I could call back to speak with (patient's name)?
41
42   If the patient is busy:
43
44   "Is there another time that I could call back that would be convenient?
45
46   **Questions:**
47
48   1. "Would you consider yourself allergic to any drugs?"
49   a. **If Yes** – "Could you please list them?"
50   2. "Did you have any allergy testing performed after your discharge from hospital"?
51   a. **If Yes** – "Do you know the results?"
52   3. "Did you receive a medical alert letter or card on discharge from the hospital"?
53   a. **If Yes** – "What is listed on this?"
54   4. "Have you had any recurrent rashes to drugs since discharge from hospital"?
55   a. **If Yes** – "Could you please list the drugs and describe the reactions"
56
57
58
59   **Phenotype-specific questions**
60

5. **If antibiotic associated SCAR** - "Have you received any antibiotics since the antibiotic allergy testing was performed?" (if antibiotic associated SCAR)
   a. **If Yes** – "Could you tell me which antibiotics, what they were given for and if you had any reactions?"
   b. **If Yes** – **"**Would you be happy with us contacting your general practitioner for these details?"
6. **If SJS or TEN** - "Do you have any ongoing issues with your eyes or vision?"
7. **If SJS or TEN** - "Do you have any ongoing issues of scarring or contractures?"
8. **If DRESS** – "Do you have any autoimmune problems since / after your reaction such as thyroid disease or diabetes"
   a. **If Yes** – "Diabetes" (Y/N), "Thyroid disease" (Y/N), "Lupus" (Y/N), "Other" (Y/N)

Drug Hypersensitivity Quality of Life Questionnaire (DrHy-Q) – as per previously published protocol (24) – Answer True or False

1. I would like an allergy doctor's opinion before taking drugs prescribed by other doctors
2. I feel different from others
3. Even a little discomfort is a problem for me
4. Since I am unable to take drugs every illness limits me more than other people
5. My allergy problems interfere with my sexual life
6. My family and partner are aware of my allergy problem
7. I am afraid of being administered a drug during an emergency to which I am allergic
8. For each infection I would be confident that there is a drug that I can take safely
9. I feel anxious due to my allergy reaction
10. I worry every time I take a drug different from ones that cause my allergic reactions
11. The idea of taking a medicine makes me feel anxious
12. My family doctor is aware of my adverse drug reaction
13. Experiencing an adverse reaction to drugs affects my life
14. I feel anguished due to my problem of allergy reaction
15. I am afraid I could not deal with the pain
16. I've given up leisure activities (sport, vacations, trips) because of my problem
17. I'm in a bad mood due to my problem of allergy reaction

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2,3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7,11-12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-8
Bias	9	Describe any efforts to address potential sources of bias	2
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA

Discussion

Key results	18	Summarise key results with reference to study objectives	NA
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	NA
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	NA
Generalisability	21	Discuss the generalisability (external validity) of the study results	NA

Other information

| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 8 |

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Study Protocol: Australasian registry of Severe Cutaneous Adverse Reactions (AUS-SCAR)

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Manuscript ID	bmjopen-2021-055906.R2
Article Type:	Protocol
Date Submitted by the Author:	29-Jun-2022
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	Phillips, Elizabeth; Murdoch University, Institute for Immunology and Infectious Diseases; Vanderbilt University Medical Center, Department of Infectious Diseases Trubiano, Jason ; Austin Health, Centre for Antibiotic Allergy & Research, Infectious Diseases; Peter MacCallum Cancer Centre, National Centre for Infections in Cancer
Primary Subject Heading:	Immunology (including allergy)
Secondary Subject Heading:	Epidemiology
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Manuscripts

Study Protocol: Australasian registry of Severe Cutaneous Adverse Reactions (AUS-SCAR)

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Abstract

Introduction Severe cutaneous adverse reactions (SCAR) are a group of T cell-mediated hypersensitivities associated with significant morbidity, mortality and hospital costs[1]. Clinical phenotypes include Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug

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reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP). In this Australasian, multi-centre, prospective registry, we plan to examine the clinical presentation, drug causality, genomic predictors, potential diagnostic approaches, treatments and long-term outcomes of SCAR in Australia and New Zealand.

Methods and analysis Adult and adolescent patients with SCAR including SJS, TEN, DRESS, AGEP and another T cell-mediated hypersensitivity, generalised bullous fixed drug eruption (GBFDE), will be prospectively recruited. A waiver of consent has been granted for some sites to retrospectively include cases which result in early mortality. DNA will be collected for all prospective cases. Blood, blister fluid and skin biopsy sampling is optional and subject to patient consent and site capacity. To develop culprit drug identification and prevention, genomic testing will be performed to confirm HLA type and ex vivo testing will be performed via IFN-γ release ELISpot assay using collected peripheral blood mononuclear cells (PBMCs). The long term outcomes of SCAR will be investigated with a 12-month quality of life survey and examination of prescribing and mortality data.

Ethics and dissemination This study was reviewed and approved by the Austin Health Human Research Ethics Committee (HREC/50791/Austin-19). Results will be published in peer-reviewed journals and presented at relevant conferences.

Registration Number: ACTRN12619000241134

Strengths and limitations of the study

- The strength of AUS-SCAR lies in its prospective design, allowing for the real-time collection of clinical data, standardised investigation and sampling for genomic evaluation and ex-vivo diagnostics.
- There will likely be selection bias favouring the recruitment of adults, less critically ill patients, patients living in metropolitan areas where the majority of study sites are located and patients whose first language is English.
- A limitation of the sampling strategy is the large blood volume required due to the number of PBMCs required for successful ELISpot assay, complicated by the often poor viability of cells from acute bleeds due to critical illness. Many hospital-adjacent laboratories are also not set up to process PBMCs, blister fluid or skin specimens requiring same-day transport to specialised research labs.
- Selection bias is also likely to affect the sampling strategy as treating teams may be less willing to overburden children and critically ill patients.
- Finally, the registry is not designed to achieve complete case capture across the study period and recruiting the target sample size will be dependent on successful recognition of cases at each site.

INTRODUCTION

SCAR are a group of T cell-mediated hypersensitivities – including Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP) (1). Other severe T cell-mediated hypersensitivities include diseases such as generalized bullous fixed drug eruption (GBFDE), drug-induced liver injury (DILI) and acute interstitial nephritis (AIN) (1, 2). SCAR can be associated with significant morbidity, hospital costs, increased demand for specialist testing and high mortality (3-6).

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Despite this, an understanding of the clinical, genomic and pharmacological predictors of each phenotype remains absent from current practice. Further, there is currently a lack of consistency among the recommendations in treatment guidelines for these severe reactions.

Causality assessment in SCAR is often complex as multiple drugs are frequently involved (3, 7-9). Whilst the use of skin testing (*in vivo)* has been increasingly employed, it is hampered by low sensitivity and concerns around safety (10-12). Progress has been made in understanding the underlying immune mechanisms and genetic predisposition of SCAR (13), providing strong support for the role of HLA typing in identifying specific drug-associated reactions (e.g. HLA-B*57:01 for abacavir hypersensitivity, HLA-B*58:01 for allopurinol hypersensitivity) (14, 15). Further association studies are required, however, to capitalise on this knowledge and previously provided roadmap. The use of novel *ex vivo* T-cell diagnostics to aid drug causality assessment, including lymphocyte transformation testing (LTT) and IFN-γ Enzyme Linked ImmunoSpot (ELISpot) Assay, has been utilized with some success in a research setting but their clinical utility is not yet established (12, 16-22).

The long-term outcomes of SCAR including quality of life, disease recurrence, inadvertent drug re-exposure and medication safety are not well-described. The development of a regional clinical and DNA registry of SCAR will allow investigators to (i) perform surveillance for new and emerging drug causality, (ii) develop causality and phenotypic prediction rules, (iii) understand best-practice treatment approaches, (iv) discover genomic predictors that prevent SCAR onset and (v) improve long-term outcomes and medication safety. The additional biospecimen component of the study will allow investigators to assess the utility of T-cell diagnostics in aiding drug causality. While national SCAR registries have been set up successfully in Europe (RegiSCAR) and Korea (KoSCAR) (23-24), AUS-SCAR will be the first registry of severe drug allergy in the Australasian region.

METHODS AND ANALYSIS

AUS-SCAR is an Australasian, multicentre, prospective registry of severe cutaneous adverse reactions in adults and adolescents > 12 years of age. Participating sites for recruitment include Austin Health, Alfred Health, Eastern Health, Peter MacCallum Cancer Centre, St Vincent's Hospital Melbourne, Monash Health, Royal Melbourne Hospital, Epworth Healthcare, Campbelltown Hospital, Nepean Hospital, St Vincent's Hospital Sydney, Fiona Stanley Hospital, Sir Charles Gairdner Hospital, Royal Brisbane and Women's Hospital, Queensland Children's Hospital, Royal Adelaide Hospital, Flinders Medical Centre, Royal Darwin Hospital, Launceston General Hospital and Auckland City Hospital. The Peter Doherty Institute for Infection and Immunity and Institute for Immunology and Infectious Diseases (IIID) are collaborating sites for sample analysis. Recruitment commenced in July 2019 and is planned to continue across all sites until accrual has reached $n = 500$.

Study Oversight
A 5-7 person steering committee will be formed following nominations from participating site principal investigators. Steering Committee members will meet regularly to discuss the direction of the project, assess requests from investigators and identify any potential risks or issues. The chair of the Steering Committee will be the Chief Investigator. A Steering Committee member can step down from this role at any time and nominations for a new member will be sought from participating site principal investigators. The Steering Committee should have at least one of the following at all times: infectious diseases physician, allergist/immunologist and dermatologist.

The clinical and DNA database and results of the study are the common property of AUS-SCAR investigators and cannot be utilised without the formal authorization of the Steering Committee. The

release of results at conference proceedings, meetings and/or in publication are decided upon by the Steering Committee of AUS-SCAR.

Project development

Any principal investigator can propose a project utilizing AUS-SCAR data. This proposal will be forwarded to all investigators for comment and the Steering Committee will provide (i) feedback to the proposing investigator and (ii) approval/non-approval of the project.

Patient Involvement

Although they have not been involved in the study design, patients will be invited to assist with identifying the best methods of disseminating results to patients and the public following publication. Patients or consumer representatives may also be considered for inclusion in the Steering Committee.

Figure 1. Overview of AUS-SCAR study design (adapted from Eldridge et al., 2010)

Participants

Patients will be invited to participate in the registry if 1) they are admitted to or referred to a participating site with a suspected SCAR, 2) two site investigators have agreed on inclusion, 3) SCAR is confirmed by a site dermatologist or immunologist or is biopsy proven and 4) the SCAR phenotype is consistent with disease-specific criteria and alternative diagnoses have been ruled out. Disease-specific criteria for SJS/TEN includes the presence of widespread erythema with skin detachment and more than 1 blister; patients with a suspected viral trigger will still be included if they meet eligibility criteria and case validation. For GBFDE, there must be multifocal, widespread, bullous-type fixed drug eruption characterised by sharply defined bullae at site of recurrent drug administration. Criteria for DRESS and AGEP are outlined in **Supplementary Tables 1** and **2**, respectively**.** The study design and biospecimen sampling schedule are outlined in **Figure 1 (25).**

At a later stage of the project, extended recruitment may include the following phenotypes, following approval by > 50% of principal investigators and the Project Steering Committee:

    a. **AIN** – Required hospitalization and biopsy proven with acute kidney injury (increase in serum creatinine by ≥ 0.3 mg/dl within 48 hours or increase in serum creatinine to ≥ 1.5 times baseline within 7 days or urine output < 0.5ml/kg/h for 6 hours) (26) with other common causes excluded. Non-biopsy proven cases with a single implicated drug, urinary and peripheral eosinophilia, acute kidney injury and resolution of renal disease post drug removal can be included.

    b. **DILI** – Required hospitalization and biopsy proven with $\geq 5x$ upper limit of normal (ULN) for ALT or ≥ 2 ULN for ALP, or ≥ 3 ULN for ALT with bilirubin ≥ 2 ULN (27). Non-biopsy proven cases with a single implicated drug, acute liver injury, autoimmune and other causes excluded and resolution of liver disease post drug removal can be included.

    c. **FDE** – Dermatologist confirmed, well-defined, circular, hyper-pigmented single or a few plaques that recur in fixed locations upon ingestion of drug (therefore requires 2 or more occurrences).

Biospecimen Collection and Analysis

Part 1. Clinical data and DNA collection

Following informed consent, baseline patient demographics, medical history and clinical data including histopathology and clinical photography will be collected from the patient and medical record and entered into a secure REDCap database. Consent may be obtained from the patient, parent/guardian or medical treatment decision-maker, as appropriate and subject to local or national law. A waiver of consent has been obtained for some participating institutions to collect clinical data retrospectively for patients that die prior to obtaining informed consent.

DNA will be collected for all patients enrolled prospectively: this will be extracted from saliva for patients who do not consent to additional sample collection or from whole blood or peripheral blood mononuclear cells (PBMCs) for patients who agree to additional blood collection. Genomic testing will be performed at the Institute for Immunology and Infectious Diseases (IIID), Murdoch University, Perth, Western Australia for HLA-A, HLA-B, HLA-C, DR/DQ/DP. Four-digit typing is performed on extracted DNA using the 454 FLX platform. Specific HLA loci are PCR-amplified using sample specific MID-tagged primers that amplify polymorphic exons from Class I (A, B, C Exons 2 and 3) and Class II (DQ, Exons 2 and 3; DRB and DPB1, Exon 1) MHC genes. Amplified DNA products from unique MID-tagged products (up to 48 MIDs) are then pooled in equimolar ratios and subjected to library preparation, quantitation and emulsion PCR suitable for entry into the 454 FLX sequencing pipeline. Clonally enriched beads are used for 454 Titanium chemistry based sequencing on the 454 FLX+ sequencer. Sequences are then separated by MID tags and alleles called using an in house accredited HLA allele caller software pipeline using the latest IMGT HLA allele database as the allele reference library. Further Genome Wide Association Studies (GWAS), RNA-seq and virologic assessment may be performed on stored DNA samples to determine if genetic and viral variants are associated with SCAR phenotype.

Part 2. Additional biospecimen collection

This part of the study is <u>optional for participating sites and for patients</u>. Samples will need to be stored at the participating site or at a collaborating AUS-SCAR site if there is capacity. Informed consent must be obtained for all samples requested. The sampling schedule is outlined below and in **Supplementary Table 3.**

Blood

For adults, an initial blood sample of 100 - 150 ml will be taken following informed consent. A reduced blood volume of 20 – 50 ml is taken for patients under 18 years of age. A convalescent follow-up blood draw of the same volume will be taken at 12 months post-SCAR onset for consenting patients. Repeat blood draws may be requested at both time points if the full volume was unable to be collected or cell viability is poor, subject to ongoing patient consent.

Skin biopsy

A 3-4mm punch biopsy may be taken from an affected area at the acute stage and 12 months post-SCAR onset. For a subset of patients, repeat biopsies may be requested for comparison studies.

Blister fluid

For patients with blisters present, blister fluid of any volume may be collected into a heparinised tube for the extraction of PBMCs. For patients whose blisters reform, additional fluid collection may be requested.

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Additional clinical samples

Additional clinical samples may be collected if considered to be of potential clinical relevance by the site investigator (e.g. cerebrospinal fluid, lymph node aspirate).

Sample processing

Samples are to be processed and stored at participating sites (or a collaborating AUS-SCAR site on request from participating site) and cannot be used in AUS-SCAR studies without written approval from the participating site. The participating site can choose to utilize these samples for any research project they have additional local ethics approval for, without consent required from AUS-SCAR investigators. The Doherty Institute for Infection and Immunity or Institute for Immunology and Infectious Diseases are available for assistance with sample processing where possible.

Part 3. Patient follow up

A 12-month follow-up will be performed to collect data regarding (i) drug utilization, (ii) health outcomes and (iii) quality of life **(Supplementary Materials)**. Whether the patient received a referral for further allergy/immunology evaluation (left to the discretion of the treating team) and the results of any allergy testing performed will be captured. Mortality/morbidity and prescribing data will be extracted from the medical record. For available patients, a quality of life assessment will be performed using the previously validated and adapted Drug Hypersensitivity Quality of Life Questionnaire (DrHy-Q) (28). A telephone script is provided with the DrHy-Q in Supplementary Materials. The questionnaire may also be sent out via email. Prescribing and mortality data may be obtained from PBS following approval or the participant's GP where not available from the medical record or patient.

Study Aims

1. To develop a national registry of SCAR to ensure continuous surveillance of new and emerging causative drugs and improve pharmacovigilance
2. To describe the causality and epidemiology of SCAR in Australasia
3. To determine patient, drug and clinical factors that predict SCAR phenotypes and which treatments improve outcomes
4. To determine the treatments employed for SCAR in Australasia and describe patient outcomes
5. To determine pharmacogenomic and genomic associations in SCAR.
6. To examine the long term impacts of SCAR including restricted medication use and QOL impact

Primary outcome measures

- Proportion (n, %) of SCAR secondary to antibiotics or non-antibiotics (addressed using the most likely implicated drug as determined through internal and external validation)
  o Proportion (n, %) for each drug class

Secondary outcome measures

- Proportion (n, %) of SCAR treated with a potentially disease-modifying therapy

- o Proportion (n, %) for each treatment type e.g. topical or systemic corticosteroids, intravenous immunoglobulin (IVIG), immunomodulators (e.g. rituximab), antivirals (e.g. ganciclovir)
        - o For each treatment type: Length-of-stay (days), inpatient mortality, all-cause mortality (90-day, 12-months), disease recurrence
    - ▪ Proportion (n, %) of SCAR referred for in vivo/ex vivo allergy testing
        - o Proportion (n, %) of each testing modality – patch testing, intradermal testing, *ex vivo* (LTT, ELISpot, other)
        - o Proportion (n, %) positive on skin testing
    - ▪ For each SCAR phenotype: Proportion (n, %) associated with inpatient and 12-month mortality
    - ▪ For each SCAR phenotype: Proportion (n, %) associated with relapse or drug re-exposure within 12 months
    - ▪ Risk factors associated with development of each SCAR phenotype
        - o Patient (host factors), drug (pharmacological class), clinical (disease factors)
    - ▪ Risk factors associated with SCAR mortality
        - o Patient (host factors), drug (pharmacological class), disease (phenotype)
    - ▪ For each SCAR phenotype and implicated drug: Genomic associations within HLA class I and/or II
    - ▪ Utility of *in vitro/ex vivo* diagnostics in assigning drug causality in SCAR
    - ▪ The long-term sequelae of SCAR

Sample size

Due to the registry study design, a sample size calculation is not required. The projected recruitment number over a 5-year period is 500 (80 cases are estimated over 5 years at a single institution (3) - allowing for 35% minimum case capture at 20 sites, the extrapolated numbers are 560 over this period).

Statistical analysis

Statistical analysis using Stata (StataCorp, Texas) will be performed by study investigators with the assistance of a biostatistician as required. Categorical variables will be summarized using frequency and percentage and compared using a chi-square test or Fisher's exact test. Continuous variables will first be assessed for significant skew using a Shapiro-Wilk test. They will then be summarized using mean and standard deviation (SD) or median and inter-quartile range as appropriate and compared using a t-test or Wilcoxon signed-rank / Mann-Whitney U test. Multivariable logistic regression modelling will be utilized to examine secondary objectives related to variables/factors predicting specified outcomes.

ETHICS AND DISSEMINATION

This study was registered on the Australian New Zealand Clinical Trials Registry (ANZCTR) on 19th February 2019 (Trial ID ACTRN12619000241134) and received ethical approval from the Austin Health Human Research Ethics Committee (HREC Number HREC/50791/Austin-19) in May 2019.

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An initial publication of pilot data is planned after the recruitment of 100 patients. Patient demographics, SCAR phenotype, implicated drugs, ELISpot and HLA results will be included. Principal investigators from each participating site will be included as authors. Authorship will be guided by the Project Steering Committee with reference to the International Committee of Medical Journal Editors guidelines.

Further results of this research project are planned to be published and/or presented in a variety of scientific forums and journals. The data presented will explore SCAR epidemiology in Australasia, drug causality, genomic predictors, diagnostic tools and potential treatments.

Authors' contributions

FJ is the Project Manager and Corresponding Author, responsible for providing central operational oversight of the study. JT, EJP, JY, MSYG, WT, CZ, DG and CK contributed to the initial design of the study and drafting of the protocol. FJ, MSYG, EM, SV, KC, NEH, AA, AMC, JFD, CZ, DG, HC, AD, JK, CK, FT, SB, JY, WT, WS, AC, TA, AL, JB, LM, AKA, EJP and JT contributed to pilot data acquisition informing the study design and substantial revision of the manuscript. JAT is the Coordinating Principal Investigator, providing overall responsibility for the study. All authors have read and approved the final manuscript.

Funding statement

Competing interests

None to declare.

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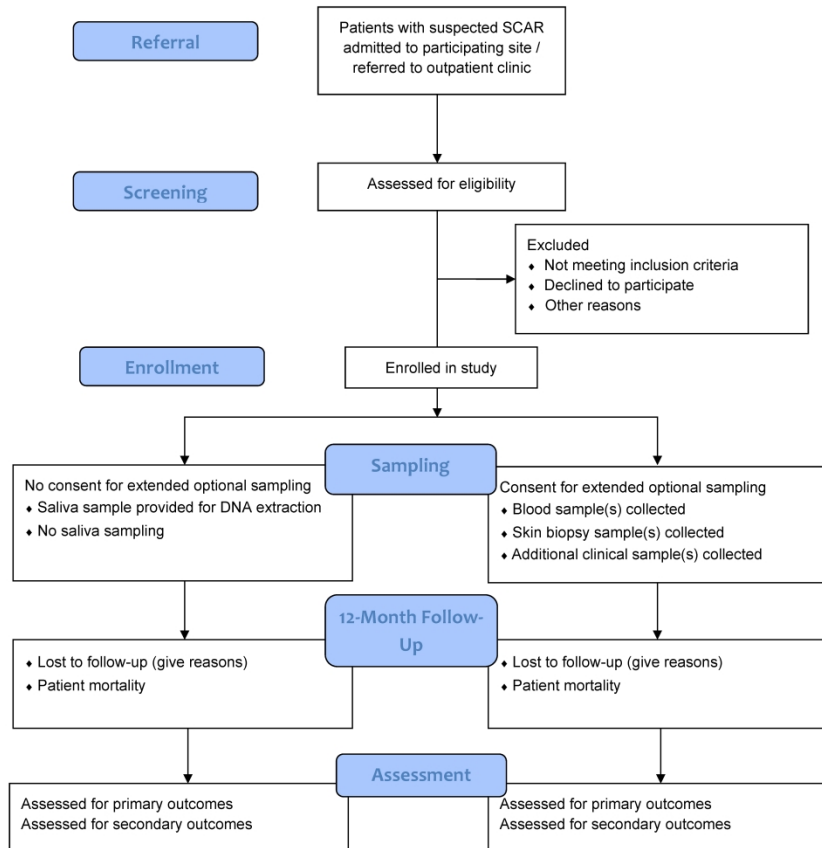
Figure 1. Overview of AUS-SCAR study design (adapted from Eldridge et al., 2010)28

215x279mm (600 x 600 DPI)

SUPPLEMENTARY MATERIALS

Supplementary Table 1. SCAR phenotype-specific criteria for Drug reaction with eosinophilia and systemic symptoms (DRESS). RegiSCAR scoring system (8, 22). Inclusion of cases with drug reaction with eosinophilia and systemic symptoms (DRESS) requires a RegiSCAR score of ≥ 4 and hospitalisation.

RegiSCAR Item		Present		Absent
Fever ≥38.5°C (101.3°F)		0		-1
Enlarged lymph nodes (>1 cm size, at least two sites)		1		0
Eosinophilia: ≥700 or ≥10 percent (leucopenia)	≥1500 or ≥20 percent (leucopenia)	1	2	0
Atypical lymphocytes		1		0
Rash ≥50 percent of body surface area		1		0
Rash suggestive (≥2 of facial edema, purpura, infiltration, desquamation)		1		0
Skin biopsy suggesting alternative diagnosis		-1		0
Organ involvement: one	two or more	1	2	0
Disease duration >15 days		0		-2
Investigation for alternative cause (blood cultures, ANA, serology for Hepatitis viruses, mycoplasma, Chlamydia) ≥3 done and negative		1		0

Supplementary Table 2. SCAR phenotype-specific criteria for Acute generalized exanthematous pustulosis (AGEP). AGEP validation score, EuroSCAR group (23). Inclusion of cases with acute generalised exanthematous pustulosis (AGEP) requires an AGEP score of ≥ 5.

Morphology	Score
Pustules Typical* Compatible** Insufficient***	+2 +1 0
Erythema Typical* Compatible** Insufficient***	1
Distribution/patter Typical* Compatible** Insufficient***	1
Post pustular desquamation Yes No/insufficient	1
Course	
Mucosal involvement Yes No	-2 0
Acute onset (≤10 days) Yes No	0 -2
Resolution	

Yes	0
No	-4
Fever ≥ 38	
Yes	+1
No	0
PMN ≥ 7000/mm^3	
Yes	+1
No	0
Histology	
Other disease	-10
Not representative/no histology	0
Exocytosis of PMN	+1
Subcorneal and/or intraepidermal non-spongiform or NOS ¹2 pustule(s) with papillary oedema or subcorneal and/or intraepidermal spongiform or NOS pustule(s) without papillary oedema (NOS½not otherwise specified)	+2
Spongiform subcorneal and/or intraepidermal pustule(s) ¹3 with papillary edema	+3

Supplementary Table 3. Schedule of assessments during study period.

Schedule of Assessments			
Procedure	**Visit**	**Timeline**	**Volume**
Part 1: DNA	Acute admission / outpatient visit	Acute	Saliva sample or additional 9mls blood
Part 2: Blood draws	Acute or follow-up admission / outpatient visit	Acute / convalescent	≤150mls blood (adults) OR ≤50ml (aged 12 – 18 years)
Part 2: Skin sample	Acute admission / outpatient visit	Acute / convalescent	3-4mm punch biopsy
Part 2: Blister fluid	Acute admission	Acute	Any amount
Part 2: Other relevant fluid samples (eg. CSF, urine, LN aspirate)	Acute or follow-up admission / outpatient visit	Acute / convalescent	Any amount
Part 3: Patient survey	Follow-up phone call / electronic mail-out	12 months post SCAR onset (convalescent)	N/A

Drug Hypersensitivity Quality of Life Questionnaire (DrHy-Q)

To be performed at 12 months post onset of rash. Assessment should be performed over the phone by a study investigator or via an online tool (REDCap) if they prefer.

If the patient doesn't speak English:

Page **2** of **4**

1
2
3   1. Prior to calling all patients, extract the data from the medical record as outlined above. During
4   the medical record review, check Emergency Department presentation notes medical record
5   to determine whether an interpreter was needed during any episodes.
6   a. If an interpreter was needed during the episode, the telephone interview should be
7   undertaken with the assistance of an interpreter.
8   b. If an interpreter was not used during hospital episodes, but a family member was
9   involved with the patient's care due to a language barrier, contact this person to
10   determine whether a suitable time can be set up to invite the patient to participate.
11   2. If a potential language barrier is not identified in the episode notes, telephone the patient as
12   outlined below. If during the telephone call, it is apparent that an interpreter is needed,
13   attempt to explain to the patient that you will organise an interpreter to assist with the
14   conversation or ask to speak with an English-speaking family member.
15   3. If a family member or professional telephone interpreter assists with the interview, note this
16   on the data collection form and the scanned medical record.
17
18
19
20   *Verbal consent script for patients discharged from hospital identified from AUS-SCAR database.*
21
22   "Hello could I please speak to (patient's full given name and surname)?
23
24   Hello, I am _____, a nurse or doctor at the _____ Hospital.
25
26   Before we proceed, can I please confirm your full name, your date of birth and address?
27
28   We are doing an audit to see how your health is following a recent episode of an adverse reaction you
29   had to a medication and managed at _____ Hospital. If you agree to be involved, we will ask you
30   some questions about yourself. Usually the interview takes about 10 minutes.
31
32   We initially obtained your consent to contact you for this survey and this will be your final
33   involvement in the study.
34
35   If you would prefer we can email you a link to a safe online version of the questions for you to answer
36   in your own time.
37
38   If patient is not home:
39
40   "Is there a time that I could call back to speak with (patient's name)?
41
42   If the patient is busy:
43
44   "Is there another time that I could call back that would be convenient?
45
46   **Questions:**
47
48   1. "Would you consider yourself allergic to any drugs?"
49   a. **If Yes** – "Could you please list them?"
50   2. "Did you have any allergy testing performed after your discharge from hospital"?
51   a. **If Yes** – "Do you know the results?"
52   3. "Did you receive a medical alert letter or card on discharge from the hospital"?
53   a. **If Yes** – "What is listed on this?"
54   4. "Have you had any recurrent rashes to drugs since discharge from hospital"?
55   a. **If Yes** – "Could you please list the drugs and describe the reactions"
56
57
58
59
60   **Phenotype-specific questions**

5. **If antibiotic associated SCAR** - "Have you received any antibiotics since the antibiotic allergy testing was performed?" (if antibiotic associated SCAR)
    a. **If Yes** – "Could you tell me which antibiotics, what they were given for and if you had any reactions?"
    b. **If Yes** – **"**Would you be happy with us contacting your general practitioner for these details?"
6. **If SJS or TEN** - "Do you have any ongoing issues with your eyes or vision?"
7. **If SJS or TEN** - "Do you have any ongoing issues of scarring or contractures?"
8. **If DRESS** – "Do you have any autoimmune problems since / after your reaction such as thyroid disease or diabetes"
    a. **If Yes** – "Diabetes" (Y/N), "Thyroid disease" (Y/N), "Lupus" (Y/N), "Other" (Y/N)

Drug Hypersensitivity Quality of Life Questionnaire (DrHy-Q) – as per previously published protocol (24) – Answer True or False

1. I would like an allergy doctor's opinion before taking drugs prescribed by other doctors
2. I feel different from others
3. Even a little discomfort is a problem for me
4. Since I am unable to take drugs every illness limits me more than other people
5. My allergy problems interfere with my sexual life
6. My family and partner are aware of my allergy problem
7. I am afraid of being administered a drug during an emergency to which I am allergic
8. For each infection I would be confident that there is a drug that I can take safely
9. I feel anxious due to my allergy reaction
10. I worry every time I take a drug different from ones that cause my allergic reactions
11. The idea of taking a medicine makes me feel anxious
12. My family doctor is aware of my adverse drug reaction
13. Experiencing an adverse reaction to drugs affects my life
14. I feel anguished due to my problem of allergy reaction
15. I am afraid I could not deal with the pain
16. I've given up leisure activities (sport, vacations, trips) because of my problem
17. I'm in a bad mood due to my problem of allergy reaction

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2,3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7,11-12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-8
Bias	9	Describe any efforts to address potential sources of bias	2
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	NA
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	NA
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	NA

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA

Discussion

Key results	18	Summarise key results with reference to study objectives	NA
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	NA
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	NA
Generalisability	21	Discuss the generalisability (external validity) of the study results	NA

Other information

| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 8 |

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.