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# Genetic testing for prevention of severe drug-induced skin rash (Protocol)

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[Intervention Protocol]

# Genetic testing for prevention of severe drug-induced skin rash

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## ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of prospective pharmacogenetic screening to reduce drug-associated skin reactions in a patient population.

## BACKGROUND

We have explained some terms we have used in a glossary. Please see Table 1.

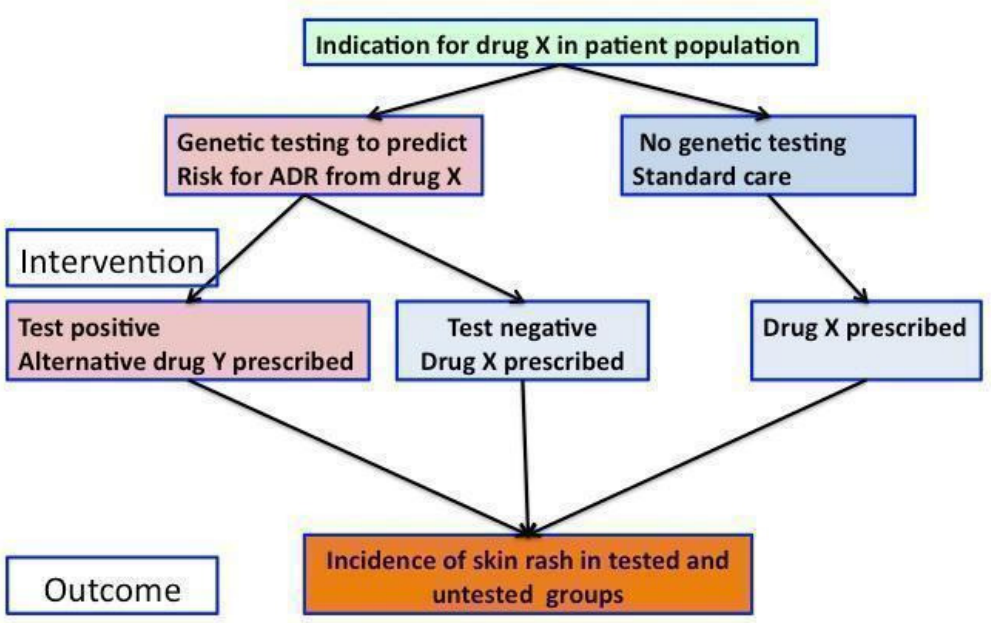
### Description of the condition

Some drugs may cause skin rashes that vary in their severity and incidence. Skin reactions caused by drugs, often termed 'drug-induced skin injury' (DISI), are common (carbamazepine-induced skin rash has a 10% incidence rate (Marson 2007)); they present with a range of clinical manifestations ranging from a mild maculopapular skin rash to life-threatening skin rashes such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (Pirmohamed 2004; Roujeau 1987). The most severe forms are very rare, but these may result in up to 30% mortality. Less severe forms of hypersensitivity reactions are troublesome and may prevent people from taking medications that are otherwise effective. The mechanisms involved in the pathogenesis of these drug-induced reactions are still poorly understood; however, immunogenetic and non-immune factors have been implicated. Recent evidence suggests that drug-specific T-cells can be identified in individuals who previously experienced adverse drug reactions (ADRs) to the culprit drug (Illing 2012).

### Description of the intervention

There is increasing evidence from clinical trials that pretreatment genetic testing may reduce the possibility of severe drug-induced hypersensitivity (Chen 2011; Mallal 2008).
Figure 1 represents a diagram of decision-making informed by genetic testing.

**Figure 1. Flowchart of interventions (genetic testing) and outcomes (skin rash) in a patient population prescribed drug X**




To date, the strongest association with drug-induced skin injury has been reported with genetic variants in the human leukocyte antigens (HLA) (Amstutz 2013; Chung 2004; Hetherington 2002; Hung 2005; Mallal 2002; McCormack 2011; Ozkaya-Bayazit 2001). Human leukocyte antigens are cell surface proteins involved in presenting antigens to the immune system. They are encoded by most polymorphic genes in the human genome. However, different genetic markers are associated with hypersensitivity in different populations, and the effect size varies in different ethnicities. Also, there is evidence that some common factors could predispose to DISI irrespective of the underlying drug aetiology. In addition, it is possible that different severity phenotypes can share the same predisposing factor.

Table 2 shows reported associations between hypersensitivity reactions, which include skin injury and genetic variants in HLA genes.

## How the intervention might work

Two recent clinical trials suggested that pretreatment genetic testing could reduce the possibility of severe hypersensitivity induced with an anti-AIDS drug, abacavir (Mallal 2008), and an antiepileptic drug, carbamazepine (Chen 2011).

Patients who have a clinical requirement for a particular drug treatment can be stratified on the basis of a genetic test. Those who test positive for the risk marker are not prescribed the culprit drug, while those who test negative are safe to take the medicine of interest. In this way, it may be possible to reduce the incidence of severe drug skin reactions in the genotyped group compared to the randomly assigned group of patients who are not offered genetic testing, but for whom decision on drug choice is based on traditional clinical and biochemical parameters.

## Why it is important to do this review

Adverse drug reactions affecting the skin are common; they can have high morbidity and mortality and are a burden for healthcare systems around the world. If we were able to predict them on the basis of a simple genetic test, it should be possible to prevent these reactions with one of the following approaches:

1. by prescribing alternative therapy if available;
2. by informing patients and healthcare providers; or
3. by informing drug developers in order to improve drug design and future drug development.

We aim to assess current research evidence to determine whether prospective pharmacogenetic screening is effective in reducing drug-associated skin reactions.

# OBJECTIVES

To assess the effects of prospective pharmacogenetic screening to reduce drug-associated skin reactions in a patient population.

# METHODS

## Criteria for considering studies for this review

### Types of studies

We will include randomised controlled trials (RCTs), which may be single-blind or unblinded.

### Types of participants

People (adults and children of either gender) who are prescribed drugs known to cause delayed type hypersensitivity reactions. These include antiepileptic drugs, antiretrovirals, antigout drugs, and antibiotics such as beta-lactams (penicillin, amoxicillin, piperacillin, cephalosporins) and sulphonamides (sulphamethoxazole and trimethoprim).

### Types of interventions

We will consider genetic testing for any genetic variants associated with hypersensitivity reactions using all available techniques to determine individual genotypes. The intervention is a randomly allocated genetic test; if the test is positive, a drug that can cause hypersensitivity is avoided.

### Types of outcome measures

We will base core outcome measures on several papers describing clinical classification of drug-induced skin reactions, including the recently published paper entitled 'Phenotype standardisation for immune-mediated drug-induced skin injury' (Pirmohamed 2011), as well as earlier papers by the RegiSCAR (European Registry of **S**evere **C**utaneous **A**dverse **R**eactions) consortium (Bouvresse 2012; Kardaun 2013; Sekula 2011).

We will assess clinically defined hypersensitivity reaction, immunologically confirmed hypersensitivity reaction (if skin patch testing or lymphocyte proliferation assay data are available), and long-term sequelae (including ophthalmologic, cutaneous, or liver damage, etc).

We have provided a full list of clinically relevant outcomes and distinction between primary and secondary outcomes in Appendix 1.

#### Primary outcomes

1. The incidence of severe drug-induced skin rash.
2. Long-term sequelae (including ophthalmologic, cutaneous, or liver damage, etc) up to 12 months after the severe drug-induced skin rash.

#### Secondary outcomes

1. Hospitalisation for drug-induced skin reaction within 3 months of exposure to the drug.
2. Clinical phenotypes of hypersensitivity reactions (organ specific and systemic manifestations) including the following:
   - SJS/TEN (Stevens-Johnson syndrome, toxic epidermal necrolysis);
   - AGEP (acute generalised exanthematous pustulosis); and
   - HSS (hypersensitivity syndrome).

Additional terminology for HSS includes the following: Drug-induced hypersensitivity syndrome (DIHS), Drug reaction with eosinophilia and systemic symptoms (DRESS), and Drug-induced delayed multiorgan hypersensitivity syndrome.

## Search methods for identification of studies

We aim to identify all relevant randomised controlled trials (RCTs) regardless of language or publication status (published, unpublished, in press, or in progress).

### Electronic searches

We will search the following databases for relevant trials:

- the Cochrane Skin Group Specialised Register;
- the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*;
- MEDLINE via OVID (from 1946);
- EMBASE via OVID (from 1974); and
- LILACS (Latin American and Caribbean Health Science Information database, from 1982).

We have devised a draft search strategy for randomised controlled trials (RCTs) for MEDLINE (OVID), which is displayed in Appendix 2. This will be used as the basis for search strategies for the other databases listed.

#### Trials registers

We will search the following trials registers:

- The metaRegister of Controlled Trials (www.controlled-trials.com).
- The US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov).
- The Australian New Zealand Clinical Trials Registry ( www.anzctr.org.au).
- The World Health Organization International Clinical Trials Registry platform (www.who.int/trialsearch).
- The EU Clinical Trials Register ( www.clinicaltrialsregister.eu/).

### Searching other resources

#### References from included studies

We will check the bibliographies of included studies for further references to relevant trials.

#### Adverse Effects

We will not perform a separate search for adverse effects of the target intervention. However, we will examine data on adverse effects from the included studies we identify.

## Data collection and analysis

We plan to include at least one 'Summary of findings' table in our review. In this, we will summarise the primary outcomes for the most important comparison. If we feel there are several major comparisons or that our findings need to be summarised for different populations, we will include further 'Summary of findings' tables.

### Selection of studies

Two review authors (AA and AJ) will independently assess studies for inclusion; they will independently screen all the titles and abstracts of publications identified by the searches to assess their eligibility. We will assess the full text of eligible citations for inclusion. We will exclude publications that do not meet the criteria at this stage and prepare a table of 'Characteristics of excluded studies' to clearly differentiate between those studies that are not at all relevant and those that may not fulfil the criteria for inclusion but may be considered relevant by some readers. We will reach consensus on the selection of trials and the final list of studies.

### Data extraction and management

Two authors (AA and AJ) will independently extract data from included studies and resolve disagreements by discussion. If consensus is not reached, they will consult a third author (MP). We will collect the following information on study characteristics and methods: study design; inclusion and exclusion criteria; setting; country; language of publication; ethnicity of participants; control population (exposed to the culprit drug or healthy population); description of genotyping techniques used; genotyping quality control, which will include deviation from Hardy-Weinberg equilibrium (Hardy-Weinberg equilibrium is a crucial concept in population genetics; it predicts how gene frequencies will be inherited from generation to generation and is used as a measure of quality of genetic tests) and genotype call rate; age; gender; concomitant medications; time from exposure to culprit drug to skin reaction; type of skin reaction; location of skin lesion; duration; treatment; sequelae; other manifestations indicating systemic involvement; and laboratory tests.

### Assessment of risk of bias in included studies

All review authors will assess the risk of bias of three studies as a pilot to ensure we are using consistent methods. AA and AJ will then independently assess the risk of bias in each trial according to the approaches described in the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Specifically, we will use The Cochrane Collaboration's tool for assessing risk of bias (Table 8.5.a in the *Cochrane Handbook for Systematic Reviews of Interventions*), which is based on seven domains (sequence, generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other issues). The tool allows for the risk of bias to be assessed as 'low', 'high', or 'unclear' (indicating lack of information or uncertainty over the potential for bias). An additional author (MP) will assess any disagreements.

### Measures of treatment effect

We will use statistical methods in accordance with the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) to measure treatment effect. We will use mean difference (MD) with 95% confidence interval (CI) for continuous data or indeed standardised mean difference (SMD) with 95% CI where all studies report an outcome using similar scales. We will use risk ratio (RR) with 95% CI for dichotomous data.

### Unit of analysis issues

We will take care to avoid a unit of analysis error due to repeated observations on participants, multiple treatments, or re-occurring events. We will also consider issues in cluster randomised trials, such as recruitment bias, baseline comparability of clusters,

and number of clusters, and make sure that appropriate statistical methods are used that take into account weighting, etc.

### Dealing with missing data

We will consider the possible different types of missing data. We will deal with missing studies and the associated risk of bias by assessing for publication bias, whilst we will deal with missing outcomes and the associated risk of bias by assessing for selective reporting (see Assessment of reporting biases section).
In the event of missing summary data, we will contact the study author if data required to calculate outcomes of interest are missing. If no further data are available, we will not include the study in the meta-analysis. However, we will report the limited results from the study in narrative form in the results section and consider whether they are consistent with the results of the meta-analysis for that outcome. Also, where appropriate, we will make assumptions about the missing data (e.g. assuming all missing values to have a particular value, e.g. an adverse event) and conduct sensitivity analyses to test how sensitive the analyses are to our assumptions. We will address the potential implications of the missing data in the Discussion section.

### Assessment of heterogeneity

We will assess the extent of heterogeneity using the $I^2$ statistic.
We will use the following thresholds for the interpretation of the $I^2$ statistic:

- 0% to 40% = might not be important;
- 30% to 60% = moderate heterogeneity;
- 50% to 90% = may represent substantial heterogeneity; and
- 75% to 100% = considerable heterogeneity.

If we do a meta-analysis, we shall report the $I^2$ statistic and interpret the two data together.

### Assessment of reporting biases

We will assess biases, including publication bias, 'time-lag' bias, outcome reporting bias, language bias, and citation bias. We will use a funnel plot, Begg test, and Egger test to evaluate publication bias (Begg 1989; Egger 1998). We will only carry out tests for funnel plot asymmetry when there are at least 10 studies included in the meta-analysis, because when there are fewer studies, the power of the tests is too low to distinguish chance from real asymmetry.

### Data synthesis

If there is no significant clinical heterogeneity, we will synthesise the results in meta-analyses. We will synthesise data according to type of intervention (e.g. genotype test). We will use a random-effects model.
Where events are rare, a random-effects approach may be inappropriate. Where events are rare, extra care will be taken to adopt appropriate methods of meta-analysis as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (section 16.9), since many meta-analysis methods are suboptimal where events are rare through results being biased, confidence intervals being too wide, or power being too low. Choice of method will be guided by control group risk, likely treatment effect size, and consideration of balance in numbers of treated and control participants in the constituent studies. Where the control groups differ, e.g. they are drawn from a healthy population or from a population of people treated with the culprit drug but without any adverse effects, we will conduct separate analysis. We will use Review Manager to undertake the meta-analyses.

### Subgroup analysis and investigation of heterogeneity

Where there is substantial heterogeneity, we will explore the causes by way of subgroup analyses. Indeed, some HLA genetic variants are associated with a high risk of drug-induced skin reactions, so interventions would only be given to the appropriate subpopulation.
We will consider the following:

- participant factors (age, ethnicity, ADR classification, and comparability of participant groups); and
- trial design issues (genotyping methodology and quality control, blinding, drugs included, and drug dosage and duration of use).

### Sensitivity analysis

We will evaluate the robustness of the results of the meta-analyses by removing trials of low methodological quality as defined by their risk of bias.

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* *Indicates the major publication for the study*

# ADDITIONAL TABLES

**Table 1. Glossary of terms**

| Term | Explanation |
|---|---|
| Allele | One of two or more alternative forms of a gene at corresponding sites (loci) on homologous chromosomes |
| Hardy-Weinberg equilibrium | This states that allele and genotype frequencies in a population will remain constant from generation to generation in the absence of other evolutionary influences |
| HLA | Human leukocyte antigen: a group of protein molecules located on bone marrow and other cells that can provoke an immune response |
| Hypersensitivity | A state of altered reactivity in which the body reacts with an exaggerated immune response to a foreign substance, such as a drug |
| Polymorphic | A variation in the DNA that is too common to be due merely to new mutation. A polymorphism must have a frequency of at least 1% in a population |
| Maculopapular rash | A rash with both macules (flat and coloured like a freckle) and papules (a small raised spot) |

**Table 2. Associations between drug-induced skin injury and genetic variants in the HLA genes**

| Drugs associated with skin injury | Class of drug | HLA allele | Population | Reference |
|---|---|---|---|---|
| **Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)** | | | | |
| Allopurinol | Antiuric acid | B*5801 | Han Chinese | Hung 2005 |
| - | - | - | Thai | Tassaneeyakul 2009a |

**Table 2. Associations between drug-induced skin injury and genetic variants in the HLA genes** (*Continued*)

| | | | | |
|---|---|---|---|---|
| - | - | - | Japanese | Kaniwa 2008 |
| - | - | - | Malay | Ding 2010 |
| Carbamazepine | Antiepileptic | B*1502 | Han Chinese | Cheung 2013; Chung 2004; Chong 2013; Hung 2006; Man 2007 |
| - | - | - | Thai | Kulkantrakorn 2012; Locharernkul 2008; Tassaneeyakul 2010; Tangamornsuksan 2013 |
| - | - | - | Malay | Ding 2010 |
| - | - | - | Indian | Mehta 2009 |
| - | - | A*3101 | White | Amstutz 2013; McCormack 2011; |
| - | - | A*3101 | Japanese | Ozeki 2011 |
| Phenytoin | Antiepileptic | B*1502 | Han Chinese | Hung 2010; Man 2007 |
| - | - | - | Thai | Locharernkul 2008; |
| Oxicam | Non-steroidal anti-inflammatory drug (NSAID) | A2, B12 | White | Roujeau 1987 |
| Sulphamethoxazole | Antibiotic | A29, B12, DR7 | White | Roujeau 1986 |
| **Hypersensitivity syndrome (DIHS or DRESS)** | | | | |
| Abacavir | Antiretroviral | B*5701 | White | Hetherington 2002; Hughes 2004; Mallal 2002; Mallal 2008; Martin 2004 |
| - | - | - | African Americans | Hughes 2004a; Saag 2008 |
| Aminopenicillins | Antibiotic | A2, Drw52 | White | Romano 1998 |
| Nevirapine | Antiretroviral | DRB1*01 | White - Australian | Martin 2005 |
| - | - | DRB1*01 | White - French | Vitezica 2008 |

**Table 2. Associations between drug-induced skin injury and genetic variants in the HLA genes** (*Continued*)

| | | | | |
|---|---|---|---|---|
| - | - | Cw8, B14 | White - Italian | Littera 2006 |
| - | - | Cw8 | Japanese | Gatanaga 2007 |
| - | - | B*3505 | Thai | Chantarangsu 2009 |
| - | - | Cw4 | Thai | Likanonsakul 2009 |
| - | - | C*0404 | Black African | Carr 2013 |
| - | - | Cw*04 | Chinese | Gao 2012 |
| Aspirin | NSAIDS | DRB1*1302, DQB1*0609 | - | Kim 2005; Palikhe 2008 |
| - | NSAIDS | DR11 | - | Quiralte 1999 |
| Iodine contrast media | - | DR | White - Spanish | Torres 2008 |
| Paraphenylenediamine | Hair dye | DP | White - German | Sieben 2002 |
| Gold sodium thiomalate | Treatment of rheumatoid arthritis | DR5 | White - Spanish | Rodriguez-Pérez 1994 |
| Lamotrigine | Antiepileptic | B*5801, A*6801 | White | Kazeem 2009 |
| Trichloroethylene | Industrial solvent, dry cleaning | B*1301 | Japanese | Li 2007; Watanabe 2010 |
| **Fixed drug eruptions** | | | | |
| Co-trimoxazole | Antibiotic | A30, B13, Cw6 | White - Turkish | Ozkaya-Bayazit 2001 |
| Feprazone | Analgesic | B22 | - | Pellicano 1997 |

# APPENDICES

## Appendix 1. Outcomes adapted from Pirmohamed 2011

Primary outcome:

- Drug-induced skin reaction (yes, no)

Secondary outcome:

- Clinical phenotype:

**SJS/TEN** (Stevens-Johnson syndrome, toxic epidermal necrolysis)

- Skin detachment 1% to 10% (SJS), 10% to 30% (overlap syndrome), and > 30% (TEN)
- Severe, often hemorrhagic, erosions of mucous membranes
- Other manifestations indicating systemic involvement (e.g. fever, liver chemistry elevations, intestinal and pulmonary manifestations, or the presence of lymphopenia)
- Severe pain and tenderness in the skin
- Target lesions, representing the degree of epidermal necrosis

**AGEP** (acute generalised exanthematous pustulosis)

- Acute widespread edematous erythema followed by a sterile pustular eruption. Often the pustules are first localised in the neck, groin, and axillae, and later become widely disseminated
- Fever (temperature > 38 °C)
- Neutrophilia with or without a mild eosinophilia

**HSS** (Hypersensitivity syndrome)

- Additional terminology includes Drug-induced hypersensitivity syndrome (DIHS), Drug reaction with eosinophilia and systemic symptoms (DRESS), Drug-induced delayed multiorgan hypersensitivity syndrome
- Variable skin manifestations; exanthema are most common
- Increased liver function tests, hepatitis, cholestasis
- Colitis
- Nephritis
- Pneumonitis
- Aseptic meningitis, encephalitis, inappropriate antidiuretic hormone syndrome
- Myocarditis
- Myositis
- Lymphocytic thyroiditis
- Eosinophilia, atypical lymphocytes, agranulocytosis, thrombocytopenia, haemolytic anaemia, aplastic anaemia
- Lymphadenopathy, pseudolymphoma

## Appendix 2. MEDLINE (OVID) search strategy

1. exp Exanthema/
2. exanthema.ti,ab.
3. (rash or rashes).ti,ab.
4. drug induced skin injury.ti,ab.
5. exp Drug Hypersensitivity/ge, pc [Genetics, Prevention & Control]
6. (drug adj2 hypersensitivit$).ti,ab.
7. hypersensitiv$ reaction$.ti,ab.
8. hypersensitivity syndrome.ti,ab.
9. drug eruption$.ti,ab.
10. exp Drug Toxicity/ge, pc [Genetics, Prevention & Control]
11. drug toxic$.ti,ab.
12. adverse drug reaction$.ti,ab.
13. toxic epidermal necrolysis.ti,ab. or exp Epidermal Necrolysis, Toxic/

14. stevens johnson syndrome.ti,ab. or exp Stevens-Johnson Syndrome/
15. exp Acute Generalized Exanthematous Pustulosis/
16. Acute Generalized Exanthematous Pustulosis.ti,ab.
17. erythema multiforme.ti,ab. or exp Erythema Multiforme/
18. dress syndrome.ti,ab.
19. "Drug Reaction with Eosinophilia and Systemic Symptoms".ti,ab.
20. "Drug Rash with Eosinophilia and Systemic Symptoms".ti,ab.
21. or/1-20
22. exp Genetic Testing/
23. genetic test$.ti,ab.
24. exp Pharmacogenetics/
25. (pharmacogenomic$ or pharmacogenetic$).ti,ab.
26. screening.ti,ab.
27. patch test$.ti,ab.
28. exp Patch Tests/
29. exp HLA Antigens/
30. hla allele$.ti,ab.
31. exp Polymorphism, Genetic/
32. genetic polymorphism$.ti,ab.
33. exp Genetic Variation/
34. (genetic variant$ or genetic variation$).ti,ab.
35. or/22-34
36. randomized controlled trial.pt.
37. controlled clinical trial.pt.
38. randomized.ab.
39. placebo.ab.
40. clinical trials as topic.sh.
41. randomly.ab.
42. trial.ti.
43. 36 or 37 or 38 or 39 or 40 or 41 or 42
44. exp animals/ not humans.sh.
45. 43 not 44
46. 21 and 35 and 45

## WHAT'S NEW

| Date | Event | Description |
|---|---|---|
| 19 May 2014 | Amended | The Declaration of interest section was updated (clinical referee's statement added) |

## CONTRIBUTIONS OF AUTHORS

AA was the contact person with the editorial base.

AA co-ordinated the contributions from the co-authors and wrote the final draft of the protocol.

AA, AJ, and MP worked on the methods sections.

AA, MP, and BM drafted the clinical sections of the background and responded to the clinical comments of the referees.

AJ responded to the methodology and statistics comments of the referees.

MP, AJ, BM, and LHS contributed to writing the protocol.

LHS was the consumer co-author and checked the protocol for readability and clarity. She also ensured that the outcomes are relevant to consumers.

AA is the guarantor of the final review.

Disclaimer

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, NHS or the Department of Health, UK.

## DECLARATIONS OF INTEREST

Ana Alfirevic: none declared.

Munir Pirmohamed: none declared.

Branka Marinovic: none declared.

Andrea L Jorgensen: none declared.

Linda Harcourt-Smith: none declared.

Olivier Chosidow, clinical referee, works in a department that is a referral center for toxic and auto-immune blistering diseases, and he has participated in the RegiSCAR (European Registry of Severe Cutaneous Adverse Reactions) group.

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