The UK-Irish **A**topic eczema **S**ystemic **T**her**A**py **R**egister (**A-STAR**)

A PROJECT OF THE BRITISH ASSOCIATION OF DERMATOLOGISTS

Study Sponsor: King's College London & Guy's and St. Thomas' NHS Foundation Trust

IRAS Number: 237309

UK REC Number: 18/WA/0200

Protocol Approval

Authorised by Chief Investigator:

Signature: **Date:**

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Principal Investigator agreement declaration:

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Organisation: _____

Signature: _____

Date: _____

General Information

This document describes the A-STAR observational register and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoir or guide for the treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the study, but centres entering patients for the first time are advised to contact the Study Co-ordinating Centre at St John's Institute of Dermatology, Guy's & St Thomas' NHS Foundation Trust and King's College London to confirm they have the most up to date version. Clinical problems relating to the study should be referred to the Chief Investigator.

The protocol defines the participant characteristics required for study entry and the schedule of follow-up. Participant recruitment and follow up will be undertaken in compliance with this document.

Statement of Compliance

This study will be carried out in accordance with the latest World Medical Association Declaration of Helsinki (2024 amendment) and will be conducted in compliance with the protocol. Participants, or in the case of children their parents/carer, need to provide written consent at study enrolment.

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1 GLOSSARY

ACT	Asthma Control Test
AE	Adverse Event
AR	Adverse Reaction
AZA	Azathioprine
BP	Blood pressure
BR	Bioresource Committee
CDLQI	Children's Dermatology Life Quality Index
CI	Chief Investigator
CNS	Central Nervous System
CPRD	Clinical Practice Research Datalink
CRF	Case Report Form
CS	Corticosteroids
CsA	Ciclosporin
DFI	Dermatology Family Index
DLQI	Dermatology Quality of Life index
DMC	Data Monitoring Committee
DOB	Date of Birth
EAMS	Early Access Medicine Scheme
EASI	Eczema Area Severity Index
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EQ-5D	European Quality of Life measure score-5D
FLG	Filaggrin
GP	General Practitioner
HRA	Health Research Authority
HES	Hospital Episode Statistics
HRQOL	Health related quality of life
IDQOL	The Infant's Dermatitis Quality of Life Index
IGA	Investigator Global Assessment
ISF	Investigator Site File
MEDDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
NICE	National Institute for Health and Care Excellence
NIHR CRN	National Institute for Health Research Clinical Research Network
NHS	National Health System (UK)
NRS	Numerical Rating Score
PI	Principal Investigator
PID	Personal Identifiable Data
PML	Progressive Multifocal Leukoencephalopathy
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life-years
QOL	Quality of Life
R&D	Research & Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RN	Research Nurse. When RN is referred to in this protocol it means either the RN or someone who has been delegated that duty
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SCC	Study Co-ordinating Centre
SCORAD	SCORing Atopic Dermatitis severity index
SSC / SC	Study Steering Committee / Steering Committee
SMG	Study Management Group
SmPC	Summary of product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TCS	Topical corticosteroids
TPMT	Thiopurine Methyltransferase
TREAT	Treatment of severe Atopic eczema Taskforce
UAR	Unexpected Adverse Reaction

2 PROTOCOL SUMMARY AND STUDY SCHEDULE

Study title:	The UK-Irish **A**topic eczema **S**ystemic **T**her**A**py **R**egister (A-STAR)
Protocol Short Title/Acronym:	A-STAR
Sponsor:	King's College London & Guy's & St Thomas' NHS Foundation Trust
Chief Investigator:	Professor Carsten Flohr
IRAS number:	237309
Study design:	Multicentre, prospective, observational clinical registry of paediatric and adult patients on systemic immuno-modulatory therapies.
Study participating centres:	Although we will initially start in highly specialised tertiary dermatology departments, all dermatology departments in the UK and Ireland are invited to express an interest to become a study participating centre.
Population:	Children (no lower age cut off) and adults with atopic eczema (UK Working Party diagnostic criteria), starting on or switching to another systemic immuno-modulatory therapy (e.g. CsA, AZA, MTX or biologic treatments). The study aims to monitor patients for at least 12 months but if possible for 10 years.
Study Duration:	A-STAR is a long-term study, with the aim to continue study activities for as long as funding is available.
Primary Objective:	To establish the short- and long-term effectiveness of systemic immune-modulatory therapies in adults and children.
Secondary Objectives:	<u>Clinical data collection:</u> - To assess the short- and long-term safety (pharmacovigilance) of these therapies, for instance with regard to malignancy risk, serious infections and cardiac and CNS abnormalities. - To establish a collection of health economic data for cost-effectiveness research. <u>A-STAR Bioresource:</u> -To establish a collection of biomaterial for molecular and stratification studies.
Sample Size:	We aim to extend the register to research active dermatology departments in the UK and Ireland, aiming to recruit at least 4,000 patients on conventional systemic therapy and 2,000 patients on novel biologics/small molecules.
Study conduct and schedule:	The study is observational and does not involve a study-specific intervention.

	During the observation period, participants will be assessed on a regular (3-6 monthly basis) to collect data on disease severity and other clinical outcomes (such as quality of life), adverse events, reasons for potential changes in therapy and key healthcare resource use (e.g. hospitalisations, specialist and GP visits, and drug use). The latter will form part of the health economic feasibility assessment, which will also examine the potential use of HES and CPRD data for health economic evaluation purposes. [The study outcomes are based on the results of a recent international consensus exercise – TREatment of severe Atopic eczema Taskforce (TREAT).] The first study visit occurs at enrolment (Baseline Visit, V1). V2 and V3 will be scheduled for 4 weeks and 16 weeks and there will be three-monthly visits thereafter while on systemic therapy up to V6. After V6, patients will be seen at 6-monthly intervals.
Data collection:	We will use a purpose-built online data entry platform to prospectively collect study data (eCRF). Individual participants will only be identifiable by their unique study ID number. Enrolment data containing patient identifiers will be held separately. Data capture includes: - A staff member -completed CRF relating to age at time of disease onset, past topical and systemic treatments, objectively assessed disease severity (including body surface area involvement), Investigator Global Assessment (IGA), current treatments, adverse events, as well as co-morbidities. - Patients and/or their carers will be asked to complete questionnaires relating to disease severity and quality of life, satisfaction with their treatment, and disease control (number of well-controlled weeks) since the last visit. Data security and Patient Identifiable Data (PID): The pseudo-anonymised study data will be hosted on a secure server with tightly regulated user access, and/or in the ISF. PID needed for long term follow up will be stored separately with access restricted to clinicians in direct care of the patient and the study administrative team. Data linkage: With fully-informed consent, patient identifiable data will be needed to provide linkage to data held by national NHS bodies and national providers of healthcare data for long term follow up. The minimum amount of identifiable data will be used as sufficient to provide a robust linkage, often only NHS number (or equivalent outside England), DOB, and postcode, avoiding patient name where possible. Patients can opt out at any time. Recallability: Identifiable data will also be used by the central study team to contact patients willing to be invited to take part in further research.

	Paper CRFs: If the online data entry platform is temporarily unavailable, alternative data entry on paper will be possible. Paper CRFs will be used for subsequent data transcription to the eCRF. Paper CRFs can also be used as primary source data collection tool. All identifiable data will be kept separate.
Sample collection for bio-banking:	Optional participation in a separate bio-analytic module on biomarkers, mechanistic, genetic and pharmacogenetics studies.
Study endpoints/measures (see also study schedule below):	Treatment effectiveness: - Change in EASI (Eczema Area and Severity Index), EASI-50, EASI-75 and IGA (Investigator's Global Assessment) - Change in POEM (Patient Oriented Eczema Measure) score - Change in quality of life (DLQI/CDLQI/IDQOL) (Dermatology/Children's Dermatology Life Quality Index)/EQ-5D) - Change in ACT (Asthma Control Test) score in patients with a diagnosis of asthma - Disease control as totally or well-controlled weeks - Drug survival, and long-term control of disease (e.g. time to discontinuation of treatment). Pharmacovigilance/safety reporting: All (S)AEs will be captured and MedDRA (Medical Dictionary for Regulatory Activities) coded, including malignancy (melanoma, non-melanoma skin cancer, lymphoma), serious infections (e.g. TB), cardiac and CNS disorders. Relationship to studied drugs and any reason for change in treatment dose and/or change to different treatment will be recorded. We will make use of data linkage to available registers (see above). Cost-effectiveness analysis: We will calculate the mean costs and assess generic quality of life with the EQ-5D (which is the health benefit measure preferred by NICE), estimated at different follow up times, for each treatment group/pathway to inform the development of an economic model. This will be in adherence to NICE (2013) methods guidance – whose objective is to estimate (i) long-term cost and QALYs for each treatment options, and (ii) incremental cost-effectiveness estimates to assess the value for money of each intervention. Value of information analysis will be used to identify those areas for further research which have the highest return in terms of population health. Standardised biorepository of blood, leucocytes and serum for genetic and biomarker analyses as well as skin biopsies (>16 years), tape stripping for cutaneous cytokine profiles, and skin swab samples for microbiome work (optional).
Data analyses:	Descriptive and exploratory data analyses will be conducted on a 6-monthly basis. All participating centres will receive a summary report of all patients as well as their own.

Version and date of protocol amendments:	V2.0 (26-FEB-2019) V3.0 (09-AUG-2021) V4.0 (01-JUL-2022) V4.1 (12-MAR-2024) V5.0 (08-APR-2025)

Study visits and assessments	**V1** **Baseline** (-28 days)	**V1b** **Day 1**[h]	**V2** **4 weeks** (+/- 2 wk[i])	**V3** **16 weeks** (+/-4 wk[j])	**V4** **6 months** (+/-4 wk)	**V5** **9 months** (+/-4 wk)	**V6** **12 months ** and subseq. Visits** (+/-4 wk)	**Baseline 2, 3, 4 etc. (where applicable) *****
Informed consent	X							
Inclusion/exclusion criteria	X							
Demographics	X							X
Personal/family history	X							
Smoking and alcohol consumption	X		X	X	X	X	X	X
Atopic Eczema and treatment history	X		X	X	X	X	X	X
Co-morbidities (including immediate and delayed allergies)	X		X	X	X	X	X	X
Concomitant medication	X		X	X	X	X	X	X
Physical examination [a]	X		X	X	X	X	X	X
Blood pressure (if applicable)	X		X	X	X	X	X	X
Treatment (prescribed)	X		X	X	X	X	X	X
Adverse events			X	X	X	X	X	X
Safety bloods [b]	X		X	X	X	X	X	X
EASI, EASI-50, EASI-75	X		X	X	X	X	X	X
IGA	X		X	X	X	X	X	X
POEM	X		X	X	X	X	X	X
Itch severity (numerical rating score)	X		X	X	X	X	X	X
CDLQI/DLQI/IDQOL[c]	X		X	X	X	X	X	X
EQ-5D-5L (adults) EQ-5D-Y (4-15 years old) [c]	X		X	X	X	X	X	X
ACT [c,d]	X			X			X	X
RECAP [c]	X		X	X	X	X	X	X
Collection of blood for FLG mutation and other genetic analysis (optional) [e]	X							
Collection and storage of blood samples for mechanistic studies, drug metabolite and trough level analyses (optional) [f]	X[g]		X	X			X	X
Skin biopsies (optional, ≥16 years) [f]	X[g]		X	X				
Skin swab samples (optional) [f]	X[g]		X	X				
Tape stripping (optional) [f]	X[g]		X	X				
Systemic immuno-modulatory therapy start		X[h]						

****** Follow up will be six-monthly whether the patients are on or off of systemic therapy treatment.

******* If patient switches their main systemic treatment or restarts the same systemic treatment after a decision for discontinuation by the treating physician has been made (excluding short-term breaks in treatment), Baseline 2 (or if applicable: Baseline 3, 4 etc.) assessments will be performed and then further visits will continue as per original schedule (D1, W4, W16, 6M, etc.).

a - Includes height at baseline and weight at all timepoints. For minors, height at all timepoints.

b - Full blood count, renal and liver function are recommended at all study visits. Other bloods to be done according to local practice (e.g. Hep B, Hep C and HIV). An additional blood sample at week 1 for patients in MTX may be collected according to local practice.

c - After 12 months of participation, questionnaires to be done every 6 months regardless of treatment.

d - For subjects with a diagnosis of asthma of ≥ 12 years old.

e - Can be collected at any time during the study.

f - Timepoints are subject to change if decided by the Study Steering Committee.

g - For patients participating in the bioresource, severity assessments (EASI, IGA, POEM, itch severity and A-STAR Bioresource CRF) need to be performed on the same day as the collection of biomaterial.

h - To be conducted as close to the baseline visit/assessments as possible, in particular for participants consenting to the collection of biomaterial for mechanistic studies. For patients only participating in the observational aspects of the study therapy needs to start within a maximum of 28 days following the baseline assessment.

i - For patients participating in the bioresource, the visit 2 window is +/- 1 week.
j - For patients participating in the bioresource, the visit 3 window is +/- 1 week with +/- 2 weeks in exceptional circumstances.

Participants will be followed up for as long as possible until withdrawal.
While on systemic therapy, follow up is three-monthly after the first 4 weeks up to Visit 6 (12 months). Then follow up will be every six months (for example: Visit 7 will be at 18 months, Visit 8 will be at 24 months and so on).
Once off systemic treatment, patients will be seen every six months.
Patients will be followed up for as long as possible, even if they stop treatment.
The following target visit windows apply: V2 +/-2 weeks (i.e. weeks 2-6), and then +/-4 weeks thereafter (i.e. V3 weeks 12-20 etc.).

EASI - Eczema Area Severity Index
IGA - Investigator Global Assessment
POEM - Patient Oriented Eczema Measure
IDQOL/CDLQI/DLQI - (Infant's, Children's) Dermatology Life Quality Index
EQ-5D - European Quality of Life measure score-5D
ACT - Asthma Control Test
RECAP- Recap of Atopic Eczema

3 BACKGROUND AND STUDY OBJECTIVES

3.1 Background

The prevalence of atopic eczema (syn. 'atopic dermatitis', 'eczema') has increased 2–3 fold during the last century, affecting up to 20% of children and 4-7% of adults in European countries (1, 2). Severe cases of atopic eczema can have a major impact on health-related QoL of patients and their families. Approximately 85% of cases begin in early childhood and up to 30% of early atopic eczema cases persist into adulthood. Atopic eczema has a strong and clinically relevant association with a range of inflammatory co-morbidities, in particular airway disease (asthma, hay fever), food allergies, atopic eye disease, clinical depression and attention-deficit hyperactivity disorder (3).

Atopic eczema is multifaceted and regulated by a complex array of genetic and environmental factors that lead to epidermal-barrier dysfunction and inappropriate up-regulation in pro-inflammatory immune responses (4, 5). There is increasing recognition that atopic eczema is a highly complex syndrome with multiple causes and mechanistic pathways that clinically can be distinguished by age of onset, severity of illness, ethnic modifiers, response to therapy, and extrinsic flare factors (e.g. infections, stress) (6). The search for objective molecular and laboratory disease severity and prognostic markers is still in its infancy but is essential to inform a personalised therapeutic approach.

Most children and adults with atopic eczema can be treated efficiently with emollients and topical anti-inflammatory agents. However, around 5% of patients require systemic immuno-modulatory therapies to induce disease remission and long-term control (7). Ciclosporin (CsA) is currently the only treatment approved in Europe, and only in adults (8). Its long-term use is limited due to the risk of renal toxicity. Alternative systemic immuno-modulatory therapies include methotrexate (MTX) and azathioprine (AZA) (2). Biologic treatments are also being actively researched in early phase trials (e.g. dupilumab and lebrikizumab), and dupilumab has now entered clinical practice, with others expected to enter clinical practice in a couple of years.

The current evidence to inform clinical management for severe atopic eczema stems from a small body of RCTs (9-14), and there is no long-term, comparative and real-world data on effectiveness and safety of these treatments in children and adults from a large-scale multi-centre registry study. The establishment of a UK register was consequently highlighted as a key translational research priority for atopic eczema research by a Delphi exercise conducted by UK TREND (15). In addition, several recent guidelines and a systematic review highlight these gaps (16-18) and lament the resulting lack of clear management guidance to inform clinical practice. Nevertheless, these immuno-modulatory treatments are frequently prescribed as off-label medicines in children and adults, as shown in our two recent surveys (European TREatment of severe Atopic dermatitis in children Taskforce (TREAT) survey (19) and a similar UK survey on the treatment of adult atopic eczema; currently under review). Moreover, the psoriasis literature indicates that approximately 30% of patients entered into registries would be ineligible for clinical trials (20) and data emanating from BADBIR further underscores the value of 'real-world' data (21).

A prospective multicentre registry study is therefore of vital importance to evaluate the real-world use of systemic immuno-modulatory therapies in paediatric and adult patients to provide effectiveness and drug adverse event data beyond the confines of short-term RCTs. Such a registry will ultimately inform treatment guidelines, act as a resource for biomarker discovery and pharmacogenetic and pharmacodynamic research, and ultimately improve patient care. With novel biologic treatment therapies having just entered our clinical practice, the timing for this project could not be better.

3.2 Rationale

Many patients with atopic eczema can be adequately treated with emollients and topical anti-inflammatory agents. However, a significant number require systemic immuno-modulatory therapies to induce disease remission and long-term control. The current evidence to inform clinical management for severe atopic eczema stems from a small body of RCTs, and there are currently no long-term 'real life' data on effectiveness and safety of these treatments from a large-scale multi-centre registry study. In the long-term, our registry data will allow us to design treatment pathways that are clinically and health economically more effective, leading to better outcomes for patients.

<u>The European TREatment of severe Atopic eczema Taskforce (TREAT Europe):</u>
A-STAR is directly linked to TREAT Europe, which links to UK TREND e-delphi and UK TREND strategy. TREAT Europe is an international initiative to harmonise the collection of observational data of atopic eczema patients who receive systemic therapy, which is led by Carsten Flohr (PI, UK), Alan Irvine (Ireland), Jochen Schmitt (Germany), Christian Apfelbacher (Germany), and Phyllis Spuls (PI, Netherlands). TREAT Europe recently conducted an international Delphi exercise among over 400 dermatologists from over 20 countries to find consensus on the core domains and domain items for national atopic eczema registries. The results of this consensus exercise have directly informed the design of the A-STAR data entry platform (see above study schedule in Table 1).

3.3 Objectives

A-STAR assesses treatment (cost-) effectiveness and drug safety as well as treatment impact on quality of life in children and adults with atopic eczema receiving systemic immuno-modulatory therapies in daily NHS and Irish Health Service practice.

The specific objectives are:

1. To assess short- and long-term effectiveness of these therapies, providing a basis for better shared decision making and guidelines.
2. To assess short- and long-term safety (pharmacovigilance) of these therapies.
3. To establish a collection of health economic data for cost-effectiveness research.
4. To establish a recallable biorepository to inform investigation of the cause, prognosis and treatment outcomes in atopic eczema.

4 SELECTION OF CENTRES/CLINICIANS

4.1 Centre/clinician inclusion criteria

Each participating centre (and Principal Investigator; PI) in the UK or Ireland will be identified on the basis of:

- Having at least one consultant dermatologist with an interest in, and responsibility for supervision and management of patients with moderate-severe atopic eczema
- Showing enthusiasm to participate in the study
- Ensuring that sufficient time, staff and adequate facilities are available for the study
- Providing information and training to all supporting staff members involved with the study or with other elements of patient management
- Acknowledging and agreeing to conform to the administrative and ethical requirements and responsibility of the study including adhering to GCP and other regulatory documentation
- Ability to access the eCRF with approval from local IT as needed
- Other important criteria are:
  a. Local R&D approval
  b. Signed contract between site and sponsor

4.2 Centre/clinician exclusion criteria

Not meeting the inclusion criteria listed above.

Study participating centres will be initiated once all global (e.g. local R&D approval) and study-specific conditions (e.g. training requirements) have been met, and all necessary documents have been returned to the Study Co-ordinating Centre. Study Initiation Visits will cover all requirements outlined in the protocol and manual(s), including severity assessment training and use of the CRF(s).

5 STUDY DESIGN

This is an observational register study of adult and paediatric patients with atopic eczema requiring systemic immune-modulatory therapy, either conventional systemic immuno-suppressive treatments (excluding oral corticosteroids) or a novel biologic or small molecule treatment.

Dupilumab has recently received approval from the EMA and FDA and other biologics and small molecules are being tested in clinical trials.

6 STUDY POPULATION

6.1 Inclusion Criteria

1. Paediatric and adult patients with atopic eczema who due to the severity of their disease and/or impact on quality of life are commencing on or switching to another systemic immuno-modulatory agent (e.g. CsA, AZA, MTX or biologic treatments), or who initiated their treatment within the last four weeks and have all required pre-treatment outcomes available.
2. Written informed consent for study participation obtained from the patient or parents / legal guardian, with assent as appropriate by the patient, depending on the level of understanding.
3. Participants consent to participate in long-term follow up and access to all medical records, including hospital admission records and linkage to data held by NHS bodies or other national providers of healthcare data.
4. Diagnosis of atopic eczema in keeping with the UK diagnostic criteria.
5. Willingness to comply with all study requirements.
6. Competent use of English language, according to patient's age (capable of understanding patient questionnaires).

There is no upper or lower age limit for participation. The decision to start systemic therapy or switch to another systemic agent will be the result of the treating dermatology consultant's decision, following discussion with the patient/parent/legal guardian, without using a pre-specified severity score cut off. It is the treating physician's responsibility to ensure that patients are suitable for the therapy, and that any standard of care treatment or assessments are provided alongside participation in the study as per local requirements.

6.2 Exclusion Criteria

1. Insufficient understanding of the study by the patient and/or parent/guardian.
2. Patients who are currently participating in a randomised clinical trial.

For further details on potential co-enrolment in observational studies and clinical trials see Section 7.6.

7 ENROLMENT

7.1 Recruitment and screening

Participants will be identified by the clinical team at each centre, most likely from their regular outpatient clinics. If deemed suitable for prescribing of a new systemic immuno-modulatory treatment, or if the patient has been prescribed a new systemic medication within the last 4 weeks and their pre-treatment outcomes are available, the patient and/or their parent/guardian will be asked if they are willing to participate in the study. A Patient Information Sheet and instructions on how to proceed if they are interested in taking part or finding out more about the study will be given to the patient and/or parent/guardian. They will be provided with the contact details to contact the research nurse if they wish to discuss or need further information. All patients and/or parent/guardian will be provided with a full explanation of the study, before obtaining informed written consent.

Patients can also self-refer to the study (using the details found on the study website or recruitment poster).

The time taken from initial contact and provision of information to obtaining written consent should be sufficient to enable appropriate discussions with the patient / family about the study, explanation of the protocol and procedures.

A patient and/or parent/legal guardian should be provided with the study information during their outpatient appointment and may be approached for consent during this visit if considered appropriate. Where the patient and/or parent/legal guardian feel that they have had adequate time to consider, enough information regarding the study and are happy to proceed, then consent can be sought and screening assessments can be undertaken on the same day as initial contact and provision of information.

Consenting can take place remotely using a postal consent form, by secure electronic mail communication (e.g. via NHS.net), or electronic data capture platform (e.g. REDCap). This consent form should be localised and can either be printed by the site team and posted to the patient, or can be emailed to the patient and returned to the site team with the patient's signature. If there are any queries regarding the study, site staff can address these during a telephone call. For postal consent, two copies of the consent form will be mailed to the participant. After signing both copies, the participant will return one copy in a pre-paid envelope (provided by the A-STAR team) and retain the other for their records. For consent via secure email, the participant will sign and return the form electronically, keeping a digital copy for themselves. When using the electronic data capture platform (REDCap), the consent will be stored within the database, and a copy will be emailed to the participant.

7.2 Baseline visit

The baseline visit of potentially eligible participants will take place following written informed consent to participate. Informed consent can also be taken prior to the baseline visit, and patients will have been provided with verbal and written study information beforehand, providing adequate time to consider the implication of taking part. A copy of the consent and assent forms should be kept in the ISF at the participating site, and the consent process documented in the medical notes. Data from clinical assessments undertaken as part of routine care prior to obtaining consent can be used (i.e. safety blood) for assessing eligibility.

The visit will include:

a. written informed consent will be obtained from the patient or parent/legal guardian
b. full medical history, including family history and personal history of co-morbidities (including delayed and immediate allergies), atopic eczema diagnosis and treatment history

c. alcohol and smoking consumption
d. assessment of eligibility criteria
e. review of concomitant medication
f. physical examination; including clinical phenotyping and eczema severity assessments (can be done by all team members who have completed the relevant training (see A-STAR study website under 'Training Resources') and who the local PI deems adequately experienced to conduct these assessments)
g. blood pressure at the local investigator's discretion
h. height and weight
i. safety bloods. To include full blood count, renal and liver profile, total IgE (if part of routine practice), as well as virology (Hep B, Hep C and HIV) as per local practice.
j. collection of demographic data
k. completion of EASI, EASI-50, EASI-75 and IGA and POEM, itch severity (NRS), IDQOL/CDLQI/DLQI, EQ-5D-5L (adults)/EQ-5D-Y (4-16 years' old), RECAP
l. completion of ACT in patients with diagnosed asthma of ≥ 12 years' old
m. optional: collection of blood for genetic analysis
n. optional: collection and storage of bloods samples for mechanistic studies, skin biopsies (≥16 years of age), and tape stripping for cutaneous cytokine analyses as well as sample collection for skin microbiome/metabolite work, using standardised operation procedures across all study participating centres that have the expertise and facilities to take part on this module.

In situations when a patient was recruited within the first 4 weeks after treatment initiation, the baseline visit will be recorded retrospectively, and dated as the day of systemic treatment initiation. This can only occur with all required baseline visit data is available to avoid key data missingness.

Baseline 2 (Baseline 3, Baseline 4, etc.) - If switching/restarting systemic treatment

If during participation in the study a patient starts a new systemic immuno-modulatory agent or restarts the same systemic treatment after a decision for discontinuation by the treating physician has been made (excluding short-term breaks in treatment), the patient will have a further 'Baseline' visit and retake all baseline assessments, with exception of family and personal medical history and collection of blood for genetic analyses. Baseline Adverse Events information will also be collected. A new signed Informed Consent will not be required but confirmation of continued consent should be documented in the medical notes. Following this new baseline, visits will be scheduled as per original schedule (Day 1, Week 4, Week 16, and so on). If a patient has simply started on a second systemic agent alongside another, then no baseline visit is required, just 3-monthly visits as per protocol.

7.3 Follow up visits

Follow up visits will occur at 4 weeks after the start of systemic immuno-modulatory therapy, 16 weeks and three-monthly thereafter whilst on systemic therapy up to Visit 6 (12 months). Then follow up visits will be every six months (for example: Visit 7 will be at 18 months, Visit 8 will be at 24 months and so on). Once treatment has been stopped, follow ups are also done six-monthly.

If a patient is recruited within the first 2 weeks after treatment initiation, visit 2 will happen at week 4 (±2 weeks), as per usual schedule of events. In situations when patient recruitment occurs 3-4 weeks after treatment initiation, visit 2 assessments will be conducted on the day of recruitment.

Follow up visit procedures:

a. Confirm informed consent status.

b. Review of co-morbidities and concomitant medication.
c. Review of systemic therapy (any changes since last visit/current dose) and disease control (number of controlled weeks).
d. If treatment has been switched: reasons for switching, and outcomes in patients at the point at which the subsequent treatment is initiated.
e. Reasons if discontinuing (lack of effectiveness, adverse events, patient preference, disease remission, other).
f. Smoking and alcohol consumption.
g. Review of adverse events experienced since the previous visit.
h. Any A&E, hospital, GP or healthcare skin-related visits, and whether due to disease exacerbations, including skin infection.
i. Days lost from usual activities due to skin disease (e.g. school, work).
j. Any further phototherapy (TL01, PUVA or other; number of doses).
k. Physical exam (at the discretion of the treating physician and with their oversight), including weight, and BP.
l. Safety blood samples are recommended at all study visits.
m. EASI, -IGA, POEM, itch severity (NRS), IDQOL/CDLQI/DLQI, EQ-5D-5L (adults)/EQ-5D-Y (4-16 years' old), and RECAP.
n. Completion of ACT in subjects with diagnosed asthma of ≥ 12 years' old*.
o. Optional: collection of blood samples, skin biopsies (≥16 years of age), and skin tape strips for mechanistic work and collection of skin microbiome/metabolite samples, using standardised operation procedures across all study participating centres that have the expertise and facilities to take part on this module.**

*ACT only done at 16 weeks and 12 months and then every six months.
**Only done at 4 and 16 weeks, as well as, one year into treatment.

Patients will be followed up for as long as possible, even if they stop treatment. The following target visit windows apply: V2 +/-2 weeks (weeks 2-6), and then +/-4 weeks thereafter, i.e. V3 weeks 12-20, etc. The date of the actual visit will be recorded in the CRF. For patients participating in the bioresource, the target visit windows are reduced to: V2 +/- 1 week and V3 +/- 1 week with +/- 2 weeks in exceptional circumstances.

7.3.1 Unscheduled visits

In some circumstances a patient may need to return to clinic outside of the suggested follow up visits, for instance due to a disease flare. Patient might also be admitted for severe disease exacerbations. If that is the case, data should be recorded on the eCRF. All data will be collected as if a routine follow up visit but with the addition of:

- Reason for return
- Adverse events
- Safety bloods (only collected if part of the reason for the unscheduled visit)
- Concomitant medications
- Blood pressure (only if part of the reason for the unscheduled visit)
- Outcome of the visit
- Severity assessment (EASI, EASI-50, EASI-75 & IGA, POEM and EQ-5D-5L (adults)/EQ-5D-Y (children)

7.3.2 Early Access Medicine Scheme

Retrospective enrolment of patients will be allowed if they are currently participating in an Early Access Medicine Scheme for a new atopic eczema treatment. All the relevant data that was previously collected for clinical or EAMS purposes will be entered into the eCRF at the appropriate timepoint, and the patient will continue prospective visits as per A-STAR schedule.

7.4 Patient transfer and withdrawal

Follow-up of patients who stop treatment or transfer to another hospital will be continued through the individual study participating centres, unless the participant explicitly withdraws consent for follow-up.

7.4.1 Patient Transfers

For patients moving from the area, every effort should be made for the patient to be followed-up at another participating centre and for this centre to take over responsibility for the patient.

The patient (or parent/legal representative) will have to sign a new consent form at the new site, and until this occurs, the patient remains the responsibility of the original centre. The Study Co-ordinating Centre should be notified in writing of patient transfers.

7.4.2 Withdrawal from the study

Patients are free to withdraw consent at any time without providing a reason. Cessation of systemic therapy for whatever reason is, however, not a reason to withdraw from study follow up. Patients may also opt to remain in the study but withdraw from specific aspects such as not to provide further samples, complete further questionnaires, or be contactable.

A withdraw form will be sought from the patient where subject will be able to indicate specifics of withdrawing. If consent is withdrawn completely then the reasons for withdrawal of consent will be collected (if possible) and reported. Participants who wish to withdraw consent for the study will have anonymised data collected up to the point of that withdrawal of consent included in the analyses and long term follow up data linked, unless the patient explicitly states in the form that this is not their wish. The patient will not contribute further data to the study, and the Study Co-ordinating Centre should be informed in writing by the responsible physician and a withdrawal CRF should be completed. If instructed by the patient, the Study Co-ordinating Centre should notify laboratories that are in possession of samples that belong to patients who have withdrawn and request that their stored samples should be destroyed. The destruction of the samples will be adequately documented.

7.5 Concomitant medications/treatments

A concomitant medication/treatment is any drug or substance administered between the baseline visit and the follow up visits, for atopic eczema or any other condition. All such medications should be reported to the investigator and recorded on the eCRF.

7.5.1 Medications in addition to systemic atopic eczema medication

It is expected that all study participants will be on concomitant topical therapy for their atopic eczema, in particular regular emollients but also potentially (antiseptic) bath additives and mild-to-potent topical corticosteroids (TCS) of the patient's/local investigator's choice. Topical calcineurin inhibitors and oral antihistamines and antibiotics as well as rescue oral corticosteroids will be recorded.

Any medication required for any ongoing illness, birth contraception and any rescue medications will also be recorded both during the treatment and follow up period.

It is the responsibility of the local PIs to check potential drug interactions with the systemic medication the patient is on for their atopic eczema.

Pregnancy testing should follow local clinical practice and SOPs and is the responsibility of the local PI and study team.

7.5.2 Medications precautions required

Advice on avoidance of live vaccines while on systemic immuno-suppressive therapy must be given, but is ultimately the responsibility of the local prescribing physician. All other advice/counselling provided to patients on any of the drugs prescribed should be in keeping with the SmPCs for each systemic medication.

7.6 Co-enrolment guidelines

Patients registered with A-STAR are not precluded from entering clinical trials. Where recruitment into another study occurs, it should be considered to be appropriate and without having any detrimental effect on the systemic medication. This should be recorded on the eCRF. The following procedure has been developed to deal with the various scenarios:

Procedure for handling data on patients who are registered with A-STAR who enter into clinical trials

i) If a patient registered with A-STAR enters into an un-blinded investigator sponsored clinical trial, the patient data may be collected and processed in the usual way. The medication or dosing regimen may need to be added to the eCRF dropdown.

ii) If a patient registered with A-STAR enters into an un-blinded clinical trial sponsored by a pharmaceutical company then subject to the consent of the pharmaceutical company the patient data may be collected and processed in the usual way. As A-STAR may have no formal contract with this pharmaceutical company, the relevant Principal Investigator would negotiate this with the pharmaceutical company and communicate the response to the Study Co-ordinating Centre.

iii) If a patient registered with A-STAR enters into a blinded clinical trial, the data would be censored at the time of entry onto the clinical trial. After discontinuation of the RCT, the patient could be reinstated as long as they continue to agree participation in A-STAR (to be documented in medical notes). If the blinding code has been opened, A-STAR would like to collect the data relevant to that period as long as permission has been given by the trial sponsor. The responsibility to obtain this permission would lie with the Principal Investigator as A-STAR may have no formal agreement with this pharmaceutical company.

7.7 Recall of patients

In cases where genetic or other biomarkers of disease and/or treatment outcomes require further phenotypic and biological validation we may wish to recall individual patients for collection of additional biological samples. This recall is entirely voluntary as stated in the Informed Consent Form. If it is necessary to contact the patient in the future a member of the study team will contact the subject by phone or approach them at their next clinic visit and ask if they are still willing to provide additional samples.

8 ASSESSMENTS AND PROCEDURES

8.1 Procedures for assessing effectiveness

Effectiveness of the study medications will be assessed throughout the period of the study using objective measures and patient-reported outcomes.

The primary outcome measure for the study is the change in atopic eczema severity from baseline, using the EASI score, conducted by a trained member of the study team. We will also assess severity with the IGA and POEM scores at baseline and all follow up visits**,** and ACT (for patients ≥12 years old who have a doctor-diagnosis of asthma).

8.2 Procedures for adverse events/pharmacovigilance

The following safety bloods and investigations will be performed to assess treatment safety and collect pharmacovigilance data:

a. Safety blood profiles (full blood count, renal function, and liver function) will be taken at screening/baseline, week 4 and week 16, and at every follow up visit thereafter while on treatment. Blood samples may be done at the local GP practice as long as the results can be provided to the treating centre. Other safety bloods may be done, in keeping with local clinical practice (e.g. IgE, hepatitis B and C as well as HIV screen). If it is not possible to obtain a safety blood sample (e.g. insufficient sample, participant refusal) at their visit, the assessments/procedures can be carried out as normal and the patient can continue in the study. However, the Investigator needs to assess whether it is safe for the patient to continue with their systemic drug treatment.

b. BP will be taken at baseline, 4, 16 weeks and then at every follow up visit while on systemic treatment, where change in BP is anticipated (e.g. ciclosporin).

c. Physical examination will be carried out at each visit.

d. A careful history of all potential adverse events since the last clinic visits will be taken and entered into the eCRF. This will cover in particular but not exclusively the following:
   - Specific prompt for serious infection (e.g. pneumonia, septicaemia, bone/joint infection, opportunistic infection, and soft tissue/skin infection, TB, respiratory (non-infectious), cardiac disorders, CNS disorders, haematological events, malignancy (skin cancer and non-cutaneous cancer), pregnancy, and death
   - Was patient on immune-modulatory/biologic treatment therapy at the time of onset of event?
   - Date of last treatment/injection
   - Did this result in death, hospitalisation or prolongation, loss of function, significant disability, congenital malformation or was in any other way life threatening?
   - Do you believe that there is a reasonable possibility that this event was related to the patient's immune-modulatory/biologic treatment therapy?
   The eCRF will remind the user that a yellow card /HPRA notification must be filled if applicable.

Data on adverse events, including severity, seriousness, and expectedness as part of pharmacovigilance will be recorded at each follow-up visit and entered into the eCRF. Requirements for pharmacovigilance reporting is detailed fully in Section 10 (Pharmacovigilance).

8.3 Other Assessments

8.3.1 Quality of Life

Quality of life assessments of the patient will be conducted via paper-based questionnaires and quality of life sheets or by electronic devices (for example: iPads or other secure mobile devices) directly entered onto an online platform by the patients/carers. If necessary the RN/member of the research team will provide guidance on how to complete the questionnaires and will collect them/the electronic device from the patients and carers at the end of the study visits.

The following quality of life questionnaires will be administered to the patient and/or parent/guardian:

DLQI
To be completed by all patients who are above 16 years.

CDLQI
To be completed by the patient (4 years – 16 years) during the visit. There is no difference between the questions of either the CDLQI – older children and the CDLQI – with cartoons. The researcher should assess which CDLQI questionnaire will be most appropriate for each individual child.

IDQOL
To be completed by the parent/guardian for patients who are below the age of 4 years during the visit.

EQ-5D-5L (adults) and EQ-5D-Y (children)
These generic quality of life scores will be completed by all patients or parents/guardian as indicated in the Study Schedule. The EQ-5D-Y is designed/validated for age 8-15 years only. There is a proxy version, which is designed for children without capacity and guidance advises that can be used for 4-7-year olds.

8.3.2 Health economics

There are two stages for the health economic investigations:

1. **Pilot Phase**: Information relating to the health economic component of the study, such as GP visits and attendance at other healthcare professionals, include required time off school or work, due to patients' atopic eczema will be gathered via the eCRF. This will allow us to assess the most relevant healthcare resource utilisation items for participants to record their healthcare contacts and which patient reported health-related quality of life instruments are most appropriate (particularly in the paediatric population). In order to identify the most efficient health economics data collection design, we will explore the feasibility of comparing direct patient reported data versus routine data linkage strategies (e.g. CPRD and HES) versus a mixture of the two. We will evaluate the cost, quality, accuracy and completeness of these data collection strategies for healthcare resource utilisation and health-related quality of life data collected prospectively via the eCRF. Furthermore, we will assess which of these strategies is best to estimate mean costs and patient reported health-related quality of life (including the EQ-5D data, the health benefit measure preferred by NICE) during the study period and for each eczema treatment option. Finally, our results will be used to identify a (health economics) core outcomes set for the assessment of eczema therapies, which can guide the design of the health economics component of future RCTs in eczema.

2. **Post-Pilot Phase**: These data will facilitate the cost-effectiveness assessment of alternative treatment strategies in the patient population recruited in the registry. Long term follow up data will be needed to develop a model-based health economics model describing the disease prognosis, the main clinical events experienced by patients, and associated costs and health related quality of life (HRQoL) implications. This

model will be used to generate costs and quality-adjusted life-years (QALYs). Statistical methods will be used to analyse the data collected in the registry and to account for the non-randomised study design. The model will be stochastic to reflect parameter and structural uncertainty surrounding our knowledge of the disease process and the impact of alternative therapies on patients' health status, health related quality of life (HRQoL) and healthcare contacts. Probabilistic sensitivity analysis (PSA), will be used to propagate parameters uncertainty through the model and to quantify their effect on the costs and HRQoL outcomes. The perspective for both analyses will be that of the NHS and Social Services for England and Wales. Life expectancy, costs and HRQoL will be discounted at 3.5% following NICE guidelines. More details will be provided in the health economics analysis plan, once additional funding for these analyses has been secured.

8.3.3 Research laboratory assessments for the Biorepository

Laboratory specimens will be collected from patients who give specific consent for this optional research, and this work will only be done at selected sites with the resources and expertise to take and process such samples.

Patients/parents/guardians will have the option to select which additional samples to provide. For example, they may opt into additional blood tests as these coincide with blood draws already needed for safety monitoring, but opt out of any of the skin samples. Adults will be invited to provide up to a maximum of 70 ml of venous blood at each of the 4 study visits, while paediatric blood volumes (patients up to 16 years of age) will be strictly kept in line with international recommendations and are based on body weight.

The main aims of the building of a biorepository are to study the association of biomarkers with drug effectiveness, adverse events, and disease progression and to increase our molecular and genetic mechanistic understanding of atopic eczema pathogenesis.

The collection of samples for the Biorepository will be only commence when the Laboratory manuals/SOPs and logistical processes are in place, as decided by the SMG and communicated to the study participating sites by the SCC.

8.3.3.1 All sites

Genetic analyses
We will collect venous blood for genetic markers. The mutational analyses will be conducted in Prof Irwin McLean's laboratory in Dundee, or another equally qualified laboratory.

In exceptional circumstances, where blood collection for genetic is not feasible (such as in the case of a recent blood transfusion), saliva sampling may be collected. A total of 2mls of saliva will be collected as per laboratory manual instructions.

All study participating centres can participate in the collection of genetic samples following patient's optional consent. Only one sample will be required, which can be collected at any time.

8.3.3.2 Selected sites

Only selected sites will participate in the collection of some or all of the following biological samples:

Biomarker analyses

Where patients opt into the voluntary bioresource and mechanistic sample collection, venous blood will be collected to obtain serum for metabolic work and biomarker analyses relating to cutaneous and inflammatory disease (e.g. periostin), as well as to isolate and cryopreserve PBMCs for Immunophenotyping.

Blood samples will be collected at baseline, 4 weeks, 16 weeks and 12 months (or at different timepoints if decided by the SMG or SSC upon emerging evidence) using standard phlebotomy techniques.

Epigenetics
Blood will be collected for epigenetics analyses.

Measures of drug exposure (PKs)
Poor concordance with therapy, intra-individual variation and development of drug antibodies in drug pharmacokinetics are known to impact on treatment response. The following samples will therefore be collected at bioresource centres **depending on therapy prescribed**, to ascertain drug levels in participants at baseline and three follow up visits:

- **Methotrexate:** Patients on methotrexate will provide whole blood for methotrexate polyglutamates.
- **Biological drug levels:** Patients on biologic treatment will provide blood for metabolites and anti-drug antibodies (ADA).

If a participant is due a follow up, the time of last dosing and interruptions in treatment must be recorded.

Skin biopsies and tape strip collection:
Tape strip skin samples can be collected in participants of all ages, and skin biopsies in those ≥16 years of age (≤ 5mm punch) will be taken on 3 occasions both from involved and uninvolved skin for various analyses such as expressed cytokine, RNA, and immunochemical assessment of atopic eczema. The time points of the skin sample collection are subject to change if decided by the SMG or SSC upon emerging evidence.

Not all participating sites will be involved in the collection of skin biopsies and tape strip samples.

Skin microbiome
Skin microbiome samples for bacterial DNA extraction, next generation or shotgun sequencing to identify bacteria or other micro-organisms (such as viruses and fungi) will be taken. This sampling method is non-invasive and will be collected through a skin swab.

Recallability: Where patients consent to be contacted for further research, such as molecularly stratified randomised control trials, the Study Co-ordinating Centre will be able to identify participants with specific genetic mutations or biomarkers. Lab researchers will not have access to patients' medical information or any personal identifiable data.

8.3.3.3 Laboratories for sample analysis

The different types of molecular and cellular analysis will be conducted in different laboratories of the study investigators, according to the specific expertise developed in each research centre/laboratory.

Moreover, due to the increasing international nature of scientific collaborations, this project may be done in close collaboration with industry partners, which are leading experts in providing highly specialised sample analysis. Anonymised materials may be shipped outside of the UK/Ireland and outside of Europe. If samples need to be shipped to any other than the A-STAR recruiting centres for further testing/scientific experiments, the Study Co-ordinating Centre and relevant A-STAR Consortium partners will ensure that adequate material

transfer and service level agreements are in place, before such shipments and experimental work is undertaken.

8.3.3.4 Sample handling

Processing of the samples can be carried out using the laboratory manual or site-specific laboratory manuals where no instructions are given (for example when analyses are specific to one particular centre). Sample collection, processing and shipment requirements are detailed in a laboratory manual, which will be provided to participating sites.

All samples will be labelled with a unique ID and initials in an anonymised form. The anonymised samples will be used in the study described in this protocol. No identifiable documents or labels will be sent with the samples.

If samples are used in future studies not covered by the present research proposal, the approval of the Research Ethics Committee will be sought.

8.4 Loss to follow-up

If any of the study participants are lost to follow up contact will initially be attempted through the PI or designated research staff at each centre. If the lead investigator at the study participating centre is not the participant's usual clinician responsible for their specialist care then follow up will also be attempted through this latter clinician. A final option will be for the Study Co-ordinating Centre to attempt if patient has provided contact details and consent to be contacted. Where possible, information on the reason for loss to follow up will be recorded.

8.5 Auditing of study conduct and research governance

The following coordinated program will ensure quality control:

a. Training of staff – including a program of training for research nurses/investigators in severity scoring and how to use the data entry platform will be provided by the Study Co-ordinating Centre.
b. An on-line manual on the use of the data entry platform will be provided to all study teams.
c. Quality checks on data entry will be performed centrally (e.g. with regard to data completeness, data entry errors and inconsistencies).
d. Selected serious adverse events (SAEs) will be checked against a set of predefined validation criteria.
e. On-site monitoring visits as per the Study Monitoring Plan.

8.6 Study closure

In the first instance, the study will be running for three years. However, sufficient financial resources permitting, we anticipate that recruitment and follow up will continue well beyond this time point. Premature study closure will be down to the discretion of the Steering Committee (SC), and ongoing clinical care will be at the discretion of the treating clinician. The definition of End of Study will be when all patients have discontinued and database is locked.

9 STATISTICAL CONSIDERATIONS

9.1 Primary endpoints

Change in disease severity between baseline and three months into treatment (V3), comparing the different treatment modalities with each other, using the EASI (Eczema Area and Severity Index).

9.2 Secondary endpoints

1. Change in EASI between baseline and six and twelve months in the different treatment groups
2. Change in POEM (Patient Oriented Eczema Measure) score, IGA (Investigator's Global Assessment) and quality of life (DLQI/CDLQI/IDQOL) between baseline and three months, six months and one year in the different treatment groups
3. Impact of *FLG* genotype on treatment effectiveness between baseline and three, six, and twelve months
4. Comparison of the drug adverse event profiles of all treatment groups (pharmacovigilance component of the study)

9.3 Sample size calculation

Treatment effectiveness:

Based on the results of the paediatric and adult severe AE treatment surveys we conducted in the UK [24], we expected that at least 200 patients on conventional systemic treatments needed to be recruited within 2 years and followed up for at least 12 months; 40% (80) of patients are expected to be on azathioprine, 35% (70) of ciclosporin, and 24% (50) on methotrexate. This takes a 10% loss to follow up into account. Should the pharmaceutical industry decide to support the A-STAR project financially, then we hope to be able to collect one year follow up data on patients on dupilumab during the life-time of this award.

Under these patient number assumptions, all comparisons of the EASI score (azathioprine vs ciclosporin, azathioprine vs methotrexate, ciclosporin vs methotrexate and dupilumab vs each of the other drugs) are able to detect differences that are below the published minimal clinically important difference (MCID) for each drug with high power (95%) [25]. Differences that can be detected are shown below alongside the MCIDs. Hence, with the projected patient numbers we will be able to detect differences between groups that are clinically meaningful.

	EASI score			
Comparison	Difference detectable with 95% power and expected sample sizes	Comparison	Difference detectable with 95% power and expected sample sizes	MCID
AZA vs CsA	3.5	AZA vs Dup	3.2	6.6
AZA vs MTX	3.9	MTX vs Dup	3.7	6.6
CsA vs MTX	4.0	CsA vs Dup	3.3	6.6

Treatment safety (pharmacovigilance):

Although we will not have adequate statistical power for a comparative analysis of rare and long-term latent adverse events of the different agents within the confines of this three-year project due to the relatively small patient numbers and short follow-up period, we will still be able to conduct a meaningful descriptive analysis of more common adverse events collected over an at least one-year period for each treatment modality.

The initial analyses will consist of comparisons in baseline status between the individuals in the treatment cohorts. For the purposes of analysis (initially) follow-up time will be censored in both cohorts if there is switching to another class of biologic therapy and censored in the standard therapy group if there is switching to a biologic agent. The adverse events of interest are calculated per person time of follow-up, after the start of therapy.

Sample size of the novel biologics/small molecule exposure group will be largely determined by external factors, including:

1) NICE technology assessments and resulting recommendations;
2) whether NICE indicates the need for pharmacovigilance and recommends patients are registered in our registry;
3) funding of by NHS, and
4) uptake by prescribing dermatologists.

The size of the comparison cohort will be more under our control. However, it is difficult to anticipate the magnitude of rate differences for adverse events between the cohorts as patients from all groups are likely to have had prior exposure to immunosuppressive drugs.

Assuming i) the risk of adverse event is proportional to the length of exposure with equal risk per year (note this may not be so), ii) power of 80%, and iii) a significance level of 5%, the following applies:

Annual adverse event rate	Rate ratio	Person years exposure per group
1/10,000	2	235,508
1/1000	2	23,590
2/1000	2	11,817
1/100	2	2,321
2/100	2	1,146
4/100	2	551
5/100	2	437
10/100	2	201

For guidance, the estimated risk of certain adverse events are as follows:

Squamous cell carcinoma with ciclosporin use 1 in 320
Non-melanoma skin cancer 1 in 1,000
Melanoma in high dose PUVA (phototherapy) 1 in 1,666
Melanoma in normal person 1 in 10,000

9.4 Statistical analyses

Treatment effectiveness:
Descriptive statistics, t-tests, regression and Kaplan-Meier survival analyses will be applied as appropriate to examine treatment effectiveness between drugs, adverse events, drug cost/QALY, and drug survival respectively. Primary treatment effectiveness variables are the mean EASI score, corrected for baseline scores. We will also compare the proportion of patients with an EASI reduction of 50%. For the purposes of analysis, follow up time will be censored in both cohorts if there is switching to another class of therapy and censored in the standard therapy cohort if there is switching to another systemic agent.

The potential effect of *FLG* genotype on treatment response:
In addition to the above analyses, we will conduct a subgroup analysis to investigate whether *FLG* genotype stratifies with treatment response, as *FLG* genotype is potentially an important biomarker but has not been investigated in the context of conventional systemic therapy for atopic eczema. We hypothesise that those with one or more *FLG* loss-of-function mutation(s) respond less well to therapy, as has been seen for the biologic treatment omalizumab [26]. Based on the available literature for patients with moderate-to-severe atopic eczema, we expect 40% of our participants to carry one or more *FLG* loss-of-function mutations. Under these assumptions, all treatment comparisons (AZA vs CsA, AZA vs MTX, CsA vs MTX, dupilumab vs any of the standard systemic medications) are able to detect an effect size as low as 20% difference in treatment responses that are close to the expected MCID* (=MCID x 80%) with 80% power. Further detail on the differences that can be detected are shown below alongside the expected MCIDs (MCID*).

The following assumptions are made in these calculations:
-Available sample sizes are Azathioprine (AZA): 32, Ciclosporin (CsA): 28, Methotrexate (MTX): 20, Dupilumab (Dup): 40 (expecting 40% of our study participants to carry a *FLG* mutation).
-MCID and corresponding standard deviation is for children and adults combined and reduced by 20% to 5.3.
-The analysis will use a 2-sample t-test to look at change in score (for the purposes of checking the sample size). The actual analysis will test interactions and therefore have lower statistical power.
-A 5% significance level (2-sided) will be used.

	EASI score			
Comparison	Difference detectable with 80% power and expected sample sizes	Comparison	Difference detectable with 80% power and expected sample sizes	MCID* (MCIDx0.8)
AZA vs CsA	4.4	AZA vs Dup	4.0	5.3
AZA vs MTX	4.8	MTX vs Dup	4.6	5.3
CsA vs MTX	4.9	CsA vs Dup	4.1	5.3

<u>Adverse events/pharmacovigilance:</u>
Drug adverse events are calculated per person time of follow up, after the start of therapy. Time-dependent regression analyses will be undertaken to compare event rates between groups, using standard multivariable analyses to reduce confounding. We will explore the use of other statistical techniques, including propensity score matching, to accommodate confounding by indication. As children and adolescents may have a different phenotype of atopic eczema compared to adults and may respond differently to systemic therapy, we will explore this further in comparative analyses.

Estimating the risk of rare adverse effects with a smaller signal, especially lymphoma will be facilitated by long-term linkage to the national cancer registry (in addition to the control group). The risk window for cancer being defined as once exposed always at risk. Where two biologicals have been used, the proportion of time spent on each will define its possible contribution to risk. Where the adverse event is rare or where a biological intervention is under-represented in the register, the numbers of patient's data can also potentially be increased by sharing data with other compatible registers such as those operating in Germany, Italy, Spain, France, Denmark, and the Netherlands.

The aim in the long-term is to recruit at least 4,000 patients on conventional treatments and also at least 2,000 on each biological intervention (depending on the uptake of these drugs in clinical practice). 4,000 patients in

each cohort, biologicals and conventional treatment would give an exposure of 12,000 patient years in each group. This would give power to detect at least a 3- or 4-fold increase in risk of events occurring at a frequency of 1 in a 1000 or 1 in 2000 patients. Rarer events would be detected if the relative risks were higher.

10 ADVERSE EVENT DEFINITIONS / PHARMACOVIGILANCE

10.1 Terms and Definitions

Adverse Event (AE)
Any untoward medical occurrence in a patient or clinical research subject which does not necessarily have a causal relationship with an investigational procedure or the medicinal product.

Adverse Reaction (AR)
Any untoward and unintended response in a subject which, in the opinion of the investigator, is related to the medicinal product or to an investigational procedure.

Unexpected Adverse Reaction (UAR)
An adverse reaction the nature and severity of which is not consistent with the information about the investigational procedure or medicinal product in question set out in: In the case of a product with a marketing authorisation, in the summary of product characteristics for that product.

Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)
Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:

- results in death
- is life-threatening* (subject at immediate risk of death)
- requires in-patient hospitalisation or prolongation of existing hospitalisation**
- results in persistent or significant disability or incapacity, or
- consists of a congenital anomaly or birth defect
- Other important medical events***

*'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.
***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Suspected Unexpected Serious Adverse Reaction (SUSAR)
An SAE occurring to a research participant where in the opinion of the Investigator the event was:
a. **related**: resulted from the administration of any of the research procedures or the medicinal product, and
b. **unexpected**: the type of event is not listed in the protocol or SmPC as an expected occurrence.

10.2 Notes on adverse event inclusions and exclusions

10.2.1 Include

- An exacerbation of a pre-existing illness

- An increase in frequency or intensity of a pre-existing episodic event/condition.
- A condition (even though it may have been present prior to the start of the study) detected after study drug administration.
- Continuous persistent disease or symptoms present at baseline that worsens following the administration of the study treatment.
- Laboratory abnormalities that require clinical intervention or further investigation (unless they are associated with an already reported clinical event).
- Abnormalities in physiological testing or physical examination that require further investigation or clinical intervention.
- Injury or accidents.

10.2.2 Do not include

- Medical or surgical procedures - the condition which leads to the procedure is the adverse event.
- Pre-existing disease or conditions present before treatment that do not worsen.
- Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery.
- Overdose of medication without signs or symptoms.
- The disease being treated or associated symptoms/signs unless more severe than expected for the patient's condition.

10.2.3 Reporting of pregnancy

Females of childbearing potential will be tested for pregnancy as per local clinical protocol. Any pregnancy that occurs will be reported, and it is the local PIs responsibility to discuss the need for cessation of the systemic medicine with the patient. All pregnancies that occur during treatment need to be followed up, until after the outcome. Verbal consent to report information regarding these pregnancy outcomes should be obtained from the mother and recorded in the medical notes.

Any pregnancies that results in complication will be reported to the MHRA (UK sites) or HPRA (Irish sites) by the patient's treating physician.

10.3 Notes severity / grading of adverse events

The assignment of the severity/grading should be made by the local investigator responsible for the care of the participant using the definitions below.

Regardless of the classification of an AE as serious or not, its severity must be assessed according to medical criteria alone using the following categories:

Mild: does not interfere with routine activities
Moderate: interferes with routine activities
Severe: impossible to perform routine activities

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in section 10.1, hence, a severe AE need not necessarily be a Serious Adverse Event.

10.4 Causality

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in table 2.

Table 2: Definitions of causality

Relationship	Description
Unlikely	There is none or little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the medication or study procedure). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Likely	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the medication or study procedure). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Confirmed	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

10.5 Expectedness

An AE whose causal relationship to the study drug or study procedure is assessed by the investigator as "likely" or "confirmed" is an Adverse Drug Reaction.

All events judged by the investigator to be "likely" or "confirmed" related to the therapy or study procedure, graded as serious and **unexpected** should be reported as a SUSAR.

Expected reactions to study procedures are:

- Blood testing: temporary discomfort from the needled in the arm, bleeding, bruising, swelling at the needle site, infection.
- Skin biopsy: bleeding, discomfort, infection, scarring, hyperpigmentation, intolerance reactions to local anaesthetic.
- Tape stripping: mild discomfort

Expected reactions to medicinal products

For further details or latest up-to-date list of events consult the latest SmPC.

10.6 Follow-up after adverse events

All adverse events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.

The investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes: resolved; resolved with sequelae (specifying with additional narrative); not resolved/ongoing; ongoing at final follow-up; fatal or unknown.

10.7 Reporting procedures

All adverse events should be recorded from initiation of treatment until withdrawn from study. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse

event reporting should be directed to the Study Co-ordinating Centre in the first instance. A table is given below to aid in determining reporting requirements.

10.7.1 Non-serious ARs/AEs

All such events, whether expected or not, should be recorded as Adverse Event on the eCRF.

10.7.2 Serious ARs/AEs/SUSARs

SARs, SAEs and SUSARs should be recorded on the eCRF. The eCRF form asks for the nature of event, date of onset, severity, outcome and causality.

All investigators will be informed of all SUSARs occurring throughout the study. Local investigators should additionally report any SUSARs and /or SAEs as required locally.

Reporting of AEs will be done according to table 3.

10.8 Responsibilities – Investigator

The Investigator is responsible for reporting all AEs in the eCRF that are observed or reported during the study, regardless of their relationship to study product. The participating investigators should share results of supplementary investigations into the adverse event (e.g. autopsy reports, admission records).

Patient safety incidents that take place in the course of research should be reported to the National Patient Safety Agency (NPSA) by each participating NHS/Irish Health Service Trust in accordance with local reporting procedures.

10.9 Responsibilities – Study Co-ordinating Centre

The Study Co-ordinating Centre will review adverse event data completeness and plausibility, and will query with the site any missing or inconsistent data.

The SCC will then produce safety reports for the different Committees and study partners, as per relevant agreements.

10.9.1 Safety reports

Safety reports will be generated during the course of the study, which allows for monitoring of SAE and AR reporting rates across sites and drug groups. The Study Co-ordinating Centre will generate pre-defined six-monthly safety update reports containing a list of all adverse events.

Any concerns raised by the SSC or the SMG or inconsistencies noted at a given site may prompt additional training at sites.

Additional training will also be provided if unacceptable delay in safety reporting timelines occurs. If any safety reports identify issues that have implications for the safety of study participants, the PIs at all institutions participating in the study will be notified.

Table 3: Safety reporting responsibilities for Principal Investigators

Event	When	How	To Whom
All AEs	Within 21 days	Via electronic CRF	Study co-ordinating centre
Drug-related SAR	Within 21 days	Electronic submission through: -Yellow card scheme for UK sites https://yellowcard.mhra.gov.uk/ -HPRA website for Irish sites https://www.hpra.ie/homepage/about-us/report-an-issue (Human Medicine Adverse Reaction) -Study co-ordinating centre: eCRF	MHRA (UK) or HPRA (Ireland). Study co-ordinating centre
AR for Medicines under additional monitoring [a]	Within 21 days	Electronic submission through: -Yellow card scheme for UK sites https://yellowcard.mhra.gov.uk/yellowcards/reportmediator/ -HPRA website for Irish sites https://www.hpra.ie/homepage/about-us/report-an-issue (Human Medicine Adverse Reaction) -Study Co-ordinating Centre: eCRF	MHRA (UK) and HPRA (Ireland). Study Co-ordinating Centre

a. Medicines under additional monitoring are those who display an inverted Black Triangle ▼ in the SmPC. The black triangle symbol identifies newly licensed medicines that require additional monitoring by the EMA. Such medicines include new active substances, biosimilar medicines, and medicines that the EMA consider require additional monitoring. The latest list can be found in: www.mhra.gov.uk/blacktriangle or EMA website.

11 ETHICAL CONSIDERATIONS

11.1 Ethical Considerations

The study will abide by the principles of the World Medical Association Declaration of Helsinki (2013 amendment) and the principles of GCP and in accordance with all applicable regulatory requirements. This protocol and related documents will be submitted for review to HRA and NRES.

There are no major ethical issues with this study, as it is observational in nature. However, the following points have been considered:

- **Medications under observation:** Whilst all drugs studied have potential side effects, in particular the conventional immuno-suppressive agents, they are used in standard clinical practice. Full information about possible risks and benefits of all medications will be provided to parents and participants and data on adverse events will be collected and monitored throughout the study. In addition, the treatment of severe atopic eczema in participants will not be compromised by participation in the study. The precise risks and benefits of participating in the study will be outlined in patient information sheets, to be formulated with service user involvement.

- **Blood testing:** The risks of taking blood include temporary discomfort from the needle in the arm, bleeding, bruising, swelling at the needle site and, in rare instances, infection.

- **Other tests for those who consent to the participation in the biorepository module (patients can individually opt into these investigations):**

- Skin biopsy: skin sample from lesional and non-lesional skin at baseline, V2 and V3. Every biopsy carries the risk of bleeding, discomfort, infection and scarring, and separate consent will be taken for this procedure. Local anaesthetic will be used to numb the skin beforehand, and intolerance reactions might occur but are very rare.

- Tape stripping: this involves several applications of a sticky disc (like Sellotape) to the skin and is not uncomfortable.

- Skin microbiome: taking skin microbiome samples (ideally the area immediately adjacent to and just before the biopsy, if taken). The sampling procedure is non-invasive and easy to perform, similar to taking a conventional skin swab for bacterial culture.

- **Consent in paediatric population:** Children up to the age of 16 will be eligible for enrolment in the study and age-appropriate Participant Information Sheets (PISs) will be prepared in line with current guidelines. See section 11.2 for further details.

- **Questionnaires:** Participants will be asked to complete a number of questionnaires, some of them which could be upsetting or considered burdensome. Patient will be informed that they can omit questions. Patients can also withdraw their consent to complete further questionnaires at any time.

11.2 Ethical approval

The study protocol will not be initiated until it has received the favourable opinion of a Research Ethics Committee (REC) and the HRA. Subsequent to this, it must also undergo independent review at R&D offices at participating sites. The local R&D office should be sent the appropriate site-specific information form complete with the necessary authorisation signatures, plus any other documentation requested for review. A copy of

local Research & Development (R&D) approval should be forwarded to the Study Co-ordinating Centre, before the site is initiated and patients recruited.

Children will be eligible for enrolment in the study. Proxy consent from the parent or legally acceptable representative should be obtained prior to each patient participating in the study. Age and stage-of-development specific Patient Information and Consent Forms will also be used and patient assent obtained where appropriate. The right of the parent/legal representative to refuse consent for the minor to participate in the study without giving reasons must be respected. After the patient has entered the study, the clinician is free to change to an alternative treatment at any stage, if he/she feels it to be in the best interest of the patient. However, the reason for doing so should be recorded and the patient will remain within the study for the purpose of follow-up and data analysis. Similarly, the parent/legal representative of the patient remains free to withdraw the patient at any time from the study treatment and study follow-up without giving reasons and without prejudicing the further treatment of the minor.

For children of school age, efforts will be made to arrange appointments outside of school hours whenever possible.

11.3 Informed consent process

Informed consent is a process initiated prior to an individual agreeing to participate in a study and continues throughout the individual's participation. Informed consent is required for all patients participating in the study. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

Discussion of objectives, risks and inconveniences of the study are to be provided to patients by medically qualified physicians, or delegated trained staff members with experience in obtaining informed consent. Age-and-stage-of-development appropriate Patient Information and Consent forms, describing the study and study procedures will be approved by a REC and the patient (parent/legal representative in the case of minors) will be asked to read and review the document.

Upon reviewing the document, the investigator/medically qualified physician, or delegated staff member will explain the research study to the patient (parent/legal representative in the case of minors). This information will emphasise that participation in the study is voluntary and that the participant may withdraw from the study at any time and for any reason. All participants will be given opportunity to ask any questions that may arise, should have the opportunity to discuss the study with their surrogates and time to consider the information prior to agreeing to participate. A contact point where further information about the study may be obtained will be provided.

Both the person taking consent (trained staff member on the delegation log) and the participant (parent or legal representative in the case of minors) must personally sign and date the form. A copy of the informed consent document will be given to the patient/their legally acceptable representative for their records. The other original copy will be filed in the Investigator Site File, and a further copy will go in the participants' medical notes.

Adequate time to consider study entry will be allowed before written consent of the participants/parent/legal representative is obtained by the responsible clinician. A patient and/or parent/legal guardian should be provided with the study information during their outpatient appointment and may be approached for consent during this visit if considered appropriate. Where the patient and/or parent/legal guardian feel that they have adequate information regarding the study and are happy to proceed then consent can be sought and screening assessments undertaken on the same day as initial contact and provision of information.

The patient may, without being subject to any resulting detriment, withdraw from the study at any time by revoking the informed consent. Similarly, the parent or legal representative may withdraw a minor under the same conditions. The rights and welfare of the patients will be protected by emphasising to them that the quality of medical care will not be adversely affected if they decline to participate in this study.

11.3.1 Consent for 16-year olds

A participant involved in the study who reaches the age of 16 (and is therefore no longer a minor) should be approached to provide consent as a competent adult at their next scheduled visit after their 16th birthday.

11.3.2 Assent in minors

If capable, and under appropriate circumstances, minors should be approached to provide assent by a delegated clinician with experience with minors. Age-and-state-of-development REC-approved Patient Information Sheet and Assent forms, describing (in simplified terms) the details of the study aims, study procedures and risks should be used. The minor should personally write their name and date the assent form, with a consent form then signed by the parent/legal representative and the researcher.

Assent forms do not substitute for the consent form signed by the patient's legally acceptable representative. Assent should be taken where appropriate and documented in the patient notes, however the absence of assent does not exclude the patient provided consent has been obtained from the parent/legal representative.

11.4 Study discontinuation

Even in the event that the study is discontinued, patients would still continue on the medication prescribed at their site under the standard care arrangement of their local hospital, under the discretion of their local treating clinician.

12 DATA CAPTURE AND DATA MANAGEMENT

12.1 Case Report Forms

The electronic study case report form (eCRF) is the data reporting instrument for the study. Primary source data will be collected through a mixture of paper CRFs, questionnaires, medical notes, and direct data entry by a clinician or nurse at point of care (hence eCRF can be source data). All mandatory and marked as 'required' fields on the eCRF must be completed within 21 days of original data collection. Patients, at clinics where iPads are available, will complete questionnaires electronically thereby generating an automatic entry directly on the data entry platform. A paper questionnaire will be used when iPads are not available. Training for site investigators and staff in the use of the data entry platform will be provided. All study data will be pseudo-anonymised by participant study ID. Enrolment data containing patient identifiers and any contact information will be collected and held separately. Study participation should be recorded in the hospital patient medical file and in a separate secure site master file that will contain patient identifiable data with the pseudo-ID study number along with confirmation of consent.

If online data entry platform is temporarily unavailable, alternative data entry on paper will be possible, and this data will have to be transcribed by the study team at the earliest opportunity.

Exceptional circumstances:
In case a face-to-face visit cannot be arranged at site, we allow data collection over the phone, via video calls/virtual visits and also by mail/email. The method of the data collection has to be written in the medical notes alongside the name of the staff member who collected the data. The answers given to the questionnaires can also be collected remotely, as described above, by the local study teams and transcribed into the eCRF.

12.2 Data protection

The study data will be protected by several means keeping data secure and accessible only to appropriate personnel. Data in the eCRF will only be identifiable by pseudo-anonymised patient study ID, with paper forms additionally marked with patient initials. The study database will be hosted on a secure server with tightly regulated user access. Patient identifiable data (PID) will be stored separately with access restricted to clinicians in direct care of the patient and the study administrative team. All data will be additionally stored on a secure backup server in case of data loss. If mobile devices (e.g. iPads) are being used, then data will be intermittently uploaded on the central server in an encrypted form and will be protected from manipulation through a signature, ensuring data integrity when the data is being transmitted. Only registered local PIs and delegated study members will have password-protected access to the data entry platform and only to the data of their own patients. Only the Study Co-ordinating Centre will have password-protected access to the database backend. Separate records containing patient identifiable data (PID) will only be transmitted on a secure format as needed to the central Study Co-ordinating Centre for study management and audit, and then to appropriate approved third parties for the purpose of data linkage and processing, in a secure and encrypted manner. Any identification for recall into follow up studies, if patients consent, will be done by site investigators.

12.3 Data audit and quality control

The data entry platform allows central auditing of data quality and completeness, which will be undertaken by a dedicated Data Manager. Any suspect data will be returned to the site in the form of data queries, electronically generated by the Study Co-ordinating Centre. Sites will respond to the queries providing an explanation/resolution to the discrepancies. Appropriate corrections will then be made on the database.

12.4 Confidentiality

Data will be stored in accordance with the Data Protection Act 1998 and the General Data Protection Regulation. Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

The Study Co-ordinating Centre will preserve the confidentiality of participants taking part in the study. Identifiable data may also be used by the site investigators or members of the central study team to contact patients willing to be invited to partake in further research or to reach those lost to follow-up or for whom data is missing.

All electronic CRFs and study data will be archived onto an appropriate media for long-term accessible storage. Where necessary, hard copies of data will be boxed and transferred to specially renovated, secure, premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

12.5 Linkage to National Healthcare Data Providers

It is recognised that there is potential for patients intended in the mid to long term to be lost to follow-up or for events to be missed during the data collection process. To mitigate against this risk, the study will link data to relevant datasets held by certain national providers of healthcare data for long term follow up and health economic research. These include Hospital Episodes Statistics (HES), mortality, Clinical Practice Research Datalink (CPRD), and NCRS (National Cancer Registry Service) such as by NHS Digital in England, for long term follow up. This data will supplement that acquired via the dermatology team and provide a more comprehensive picture of each participant's health. PID will need to be used for this purpose; this data will be encrypted and stored, and only the minimum amount of identifiable data will be used as sufficient to provide a robust linkage, often only NHS number (or equivalent outside the UK), DOB, and postcode, avoiding patient name where possible, being transferred to the relevant organisation for the purpose of linkage. The linkage will occur in a secure data environment and only de-identified data will be returned. Although this linkage will not happen immediately, consent of the participants will be sought right from the beginning. Patients can opt out at any time.

12.6 Archiving

Data will be retained intact in an appropriate format and storage facility according to relevant data legislation for a period of 5 years for adults, and 25 years for paediatric patients from the date of any publication which is based upon it. Where research data is not retained it will be disposed of according to King's College London and Guy's and St Thomas' Hospital guidelines. Each site will archive their patient data and ISF at local facilities as per local SOP.

13 FINANCIAL ARRANGEMENTS

A-STAR has been supported through a research grant from the British Skin Foundation in the first three years. Currently, A-STAR is supported by the British Association of Dermatologists Eczema Register Ltd (BADERL), a registered not-for-profit company within the British Association of Dermatologists. BADERL has received income from pharmaceutical companies for providing pharmacovigilance services on their therapies.

14 STUDY COMMITTEES

14.1 Study Management Group (SMG)

A Study Management Group (SMG) comprises of the Chief Investigator and members of the Study Co-ordinating Centre, in particular the Study Manager. The SMG will be responsible for the day-to-day running and management of the study and will meet regularly. Membership of the SMG might change over time but will always include the Chief Investigator and Study Manager.

14.2 Study Steering Committee (SSC)

The Study Steering Committee is chaired by someone other than the CI and consists of the Study Collaborators , including the statistician and health economist as well as PPI representatives. The role of the SSC is to provide overall supervision for the study. The ultimate decision for the continuation of the study lies with the SSC. The SSC will meet at least 3 times a year.

14.3 Data Monitoring Committee (DMC)

There was no DMC at the formation of the study but as time goes on and biologic treatments and other molecules enter general practice we will re-visit the need for such a committee.

14.4 Bioresource Committee (BR)

The broad remit of the BR is to plan and coordinate the collection and processing of biomaterial for mechanistic studies, reporting to the SSC. The BR consists of A-STAR collaborators who are actively participating in the collection and/or processing of biomaterial beyond the collection of venous blood for DNA analyses, and other members as per Terms of Reference. The BR will meet at least twice per year, either in person or via teleconference.

15 ROLE OF PHARMACEUTICAL COMPANIES

The goals of industry and the dermatology community are similar in seeking accurate estimates of efficacy and cost-effectiveness of systemic treatments for atopic eczema. Equally, both parties are interested in the long-term risk of adverse events of the therapies.

It may also be a pre-requisite for drug license approval, that a study such as A-STAR is established. It is accepted that it is beneficial that any study, such as the one proposed, should be independent of any direct industry involvement. Thus, decisions on analyses, interpretation and publication should be independent of any industrial contribution. Industry can have a crucial role in stimulating registration after licensing, and also contributing their experience into the nature and type of data to be collected. Aggregated data relating to a particular product will be shared with industry in confidence, though individual identifiable patient data will not be released. A participant company has the option of requesting specific analyses and will be shown drafts of any publications, reports, abstracts or other material prior to submission for presentation or publication. They can ask for clarifications or amendments to such material but the final decision on these would rest with the principal investigators and the SSC. All the principal investigators have to complete an annual 'Declaration of conflict of interests' form, which will be added to all publications. Should pharmaceutical companies become part of the project, there will be an annual joint pharmaceutical company meeting to discuss contractual issues and also to update on study progress.

16 PUBLICATION

The study results will be published in peer-reviewed journals and presented at national and international meetings, as well as in the study website (https://ppopderm.org/project/a-star/). A publication policy will be drawn up in due course to adequately reflect individual collaborators contributions.

The members of the SSC, BR and SMG should be listed with their affiliations in the Acknowledgements/Appendix of the main publications.

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