Comparison of **AL**itretinoin with **P**UVA as the first line treatment in patients with severe chronic **HA**nd eczema

Version:	v 6.0
Date:	2nd August 2016
Sponsor:	University of Leeds
Sponsor Number:	DM14/11351
NIHR HTA Ref:	**12/186/01**
EudraCT Number:	2014-004741-27
REC Ref:	14/YH/1259
R&D Ref:	
ISRCTN Reg.	ISRCTN80206075

Chief Investigator Dr Miriam Wittmann
Chapel Allerton Hospital, LMBRU
Chapeltown Road
Leeds,
LS7 4SA
Tel: 0113 392 44 83
Fax: 0113 3924476
Email: m.wittmann@leeds.ac.uk

1. KEY CONTACTS

CHIEF INVESTIGATOR

Dr Miriam Wittmann
Chapel Allerton Hospital, LMBRU
Chapeltown Road
Leeds
LS7 4SA
Tel: 0113 392 44 83
Fax: 0113 3924476
Email: m.wittmann@leeds.ac.uk

CO-INVESTIGATORS

Prof Catherine Smith
Professor of Dermatology & Therapeutics
St John's Institute of Dermatology
Guy's & St Thomas's NHS Foundation Trust
Tel: 020 7188 6410
Email: catherine.smith@kcl.ac.uk

Dr John Lear
Central Manchester University Hospitals NHS
Foundation Trust (CMFT)
Tel: 0161 276 4173
Email: John.Lear@cmft.nhs.uk

Prof Steven Ersser
Dame Kathleen Raven Professor of Clinical Nursing
School of Healthcare, Baines Wing,
University of Leeds
Tel: 0113 343 6295
Email: S.J.Ersser@leeds.ac.uk

Dr Lesley Sunderland
Street Lane Practice
12 Devonshire Avenue
Roundhay, Leeds
LS8 1AY
Tel: 0113 237 1128
Email: LesleyS@nhs.net

Dr Cathy Green
Dermatology Dept
Ninewells Hospital
Dundee
DD19SY
Tel: 01382633901
Email: cathy.green@nhs.net

Dr Mark Goodfield
Department of Dermatology
Chapel Allerton Hospital
LS7 4SA
Tel: 0113 392 4371
Email: Mark.Goodfield@leedsth.nhs.uk

Dr Fiona Cowdell
Reader in Wellbeing in Long -Term Conditions
Faculty of Health and Social Care
University of Hull
Cottingham Road, Hull, HU6 7RX
Tel: 01482 463362
Email: F.Cowdell@hull.ac.uk

Dr Philip Hampton
Dermatology
Newcastle upon Tyne Hospital
Clayton Road
NE2 1JP
Newcastle upon Tyne
NE7 7DN
Tel: 01912 816 131
Email: Philip.Hampton@nuth.nhs.uk

PUBLIC INVOLVEMENT REPRESENTATIVES

Amanda Roberts
amandaroberts@ntlworld.com

Amy Barker
A.M.Barker@leeds.ac.uk

Damien Buckley
damian.buckley@sellafieldsites.com

HEALTH ECONOMIST

Dr Sandy Tubeuf
Ass. Professor in Health Economics
Academic Unit of Health Economics
Leeds Institute of Health Sciences
Charles Thackrah Building
University of Leeds
Leeds LS2 9LJ
Tel: 0113 343 0843
Email: s.tubeuf@leeds.ac.uk

CTRU STUDY MANAGEMENT:

Project Scientific Lead
Professor Jane Nixon
Clinical Trials Research Unit
Leeds Institute of Clinical Trials Research
University of Leeds
Leeds, LS2 9JT
Tel: 0113 343 1488
Fax: 0113 343 1471
Email: j.e.nixon@leeds.ac.uk

Project Delivery Lead
Dr Catherine Fernandez
Clinical Trials Research Unit
Leeds Institute of Clinical Trials Research
University of Leeds
Leeds, LS2 9JT
Tel: 0113 343 4895
Fax: 0113 34 31737
Email: c.fernandez@leeds.ac.uk

Data Manager
For data collection and data queries, contact:
Ms Catherine Reynolds
Clinical Trials Research Unit
Leeds Institute of Clinical Trials Research
University of Leeds
Leeds, LS2 9JT
Tel: 0113 343 0254
Fax 0113 343 1737
Email: c.reynolds@leeds.ac.uk

Senior Trial Co-ordinator
For site set up, regulatory approvals and trial conduct, contact:
Dr Victoria Goss
Clinical Trials Research Unit
Leeds Institute of Clinical Trials Research
University of Leeds
Leeds, LS2 9JT
Tel: 0113 343 4317
Fax: 0113 343 1737
Email: v.m.goss@leeds.ac.uk

Trial Statistician
Miss Isabelle Smith
Clinical Trials Research Unit
Leeds Institute of Clinical Trials Research
University of Leeds
Leeds, LS2 9JT
Tel: 0113 343 1477
Fax: 0113 343 1471
Email: i.l.smith@leeds.ac.uk

Supervising Statistician
Miss Sarah Brown
Clinical Trials Research Unit
Leeds Institute of Clinical Trials Research
University of Leeds
Leeds, LS2 9JT
Tel: 0113 343 1475
Fax: 0113 343 1471
Email: medsbro@leeds.ac.uk

Divisional Director
Professor Linda Sharples
Clinical Trials Research Unit
Leeds Institute of Clinical Trials Research
University of Leeds
Leeds, LS2 9JT
Tel: 0113 343 5616
Fax: 0113 343 1471
Email: l.sharples@leeds.ac.uk

Direct line for registration and randomisation: 0113 343 2290

Web address for registration and randomisation: https://lictr.leeds.ac.uk/webrand/

2. CONTENTS PAGE

Contents

3. SYNOPSIS

Title: ALPHA: **AL**itretinoin versus **P**UVA in **HA**nd eczema: Comparison of Alitretinoin with PUVA as the first line treatment in patients with severe chronic hand eczema

Primary Objective:

The primary objective is to compare Alitretinoin and psoralen combined with ultraviolet A (PUVA) as first line therapy in terms of disease activity at 12 weeks post planned start of treatment.

Secondary Objectives:

1. To compare Alitretinoin and PUVA in terms of disease activity over time with a focus on disease activity at 24 and 52 weeks post planned start of treatment.

2. To compare Alitretinoin and PUVA in terms of time to relapse.

3. To compare Alitretinoin and PUVA in terms of quality of life (QoL) and patient benefit over the 52 weeks duration post planned start of treatment.

4. To determine cost effectiveness of Alitretinoin compared to PUVA over the short and longer term.

5. To determine the educational need for individual patients.

6. To compare Alitretinoin and PUVA in terms of safety.

Exploratory objectives:

1. To compare scoring systems HECSI, mTLSS, DLQI and PGA used to monitor response to treatment in patients with severe chronic hand eczema (CHE).

2. To evaluate whether response to first line treatment is affected by the following parameters:

- duration of disease
- clinical phenotype
- disease severity
- presence of atopy
- filaggrin loss of function mutation and other potential emerging mutations affecting skin barrier or response to PUVA / Alitretinoin
- smoking history
- BMI
- foot involvement

3. To collect pilot data on clinical effectiveness of second line therapies, using HECSI and PGA.

4. To explore treatment responses in hand eczema (HE) subgroups defined by molecular inflammatory mediators determined in tape strips or washing solution.

5. To compare Alitretinoin and PUVA in terms of time in remission using different definitions of end of remission, including varying the extent of corticosteroid use.

6. To compare Alitretinoin and PUVA in terms of assessment of the nails

Study design:

The trial is a prospective, multicentre, open-label, two-arm parallel group, adaptive randomised controlled trial with one planned interim analysis.

A maximum of 780 consenting participants with severe CHE will be randomised on a 1:1 basis to receive either Alitretinoin (30mg per day) or immersion PUVA (twice weekly) in conjunction with concomitant topical corticosteroids, emollients and patient education.

The trial is an adaptive design with a planned interim analysis to re-estimate the sample size (see section 18.3) which may lead to fewer than the required 780 participants, although a minimum of 500 participants will be randomised.

Type of subjects: Patients suffering with severe CHE that is unresponsive to at least 4 weeks of treatment with potent topical corticosteroids.

Trial arms (including dosage regimen and dose levels): Participants will be randomised to receive either Alitretinoin at a dose of 30mg/day (may be reduced to 10mg if participants suffer with headaches and restored to 30mg dose once headaches cease) or immersion PUVA (3mg/L Meladinine® with ultraviolet A, twice weekly) for the 12 week interventional phase. Randomised treatment will be used in conjunction with concomitant topical corticosteroids, emollients and patient education. Partial responders in both arms will continue treatment regime for up to a further 12 weeks (treatment will be discontinued earlier if a clear or almost clear PGA is reached). Participants who relapse and non-responders will continue with 'standard clinical practice', as determined by the attending clinical team.

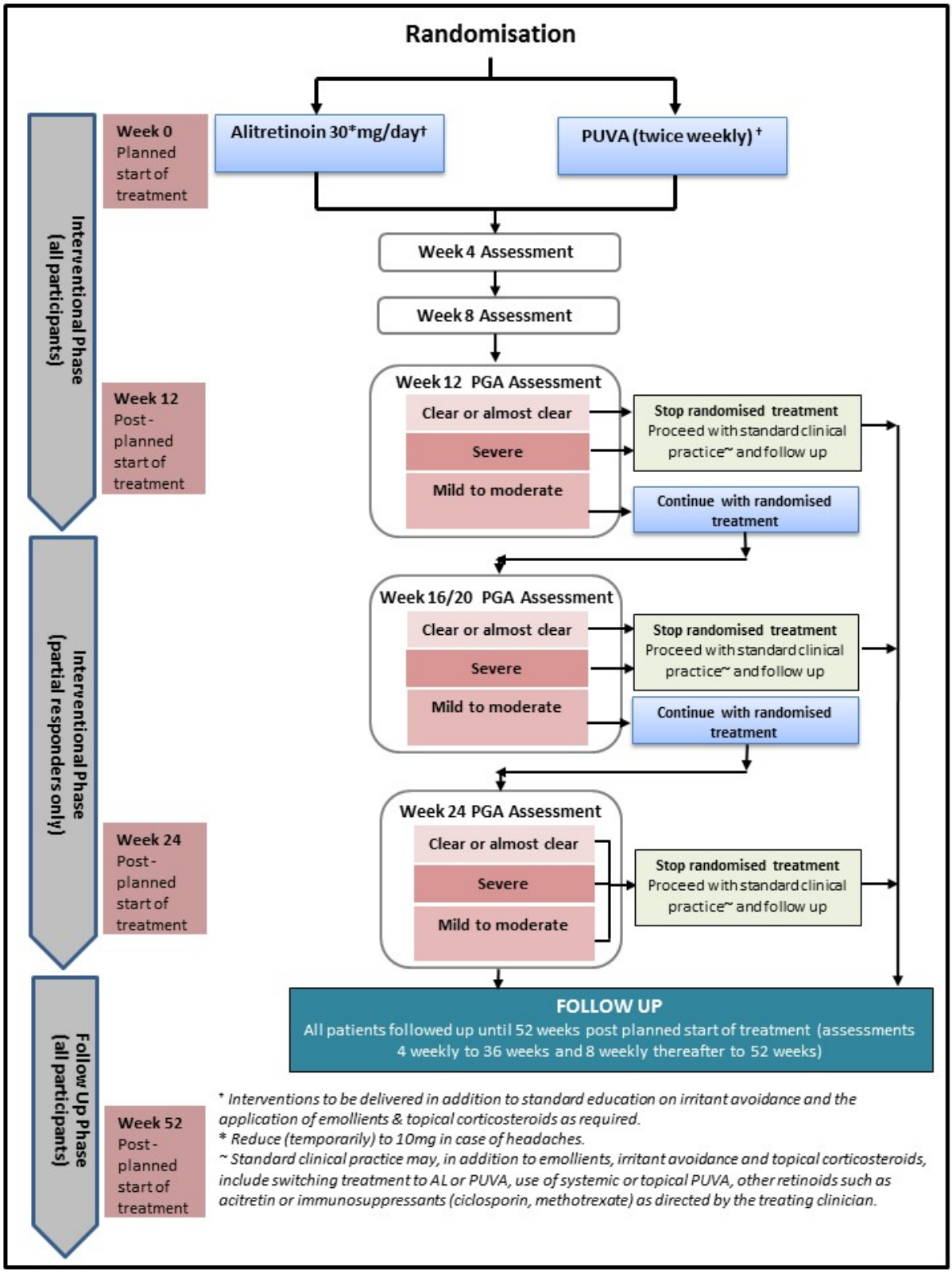
Drug supplies: Alitretinoin is used in routine clinical use and therefore generic 'off the shelf' supplies will be prescribed. Meladinine®, used in combination with ultraviolet A (PUVA), will be supplied free by Leeds Teaching Hospitals Pharmacy as trial stock.

Clinical safety laboratory evaluations: Local site laboratory services will analyse blood samples as per local practice.

Statistical analysis and reporting: Clinical Trials Research Unit (CTRU) and the Academic Unit of Health Economics (AUHE), University of Leeds.

Expected study duration: Total trial duration is 52 weeks post planned start of treatment. The interventional phase will last up to 24 weeks. Participants will receive their randomised treatment for 12 weeks at which point the follow-up phase of the trial will begin. However, partial responders will continue to receive their randomised treatment until a clear or almost clear PGA score or up to 24 weeks post planned start of treatment, whichever is the earliest time point. Participants who do not sufficiently respond to their randomised treatment and those who relapse will receive 'standard clinical practice'. During the follow up phase all participants will be assessed 4 weekly to week 36 post planned start of treatment and 8 weekly thereafter until week 52.

4. FLOW DIAGRAM



5. GLOSSARY OF TERMS

AE	Adverse Event
AUHE	Academic Unit of Health Economics
AL	Alitretinoin
BAD	British Association of Dermatology
CCL20	Chemokine (C-C motif) Ligand 20
CHE	Chronic Hand Eczema
CI	Chief Investigator
CRN	Clinical Research Network
CRFs	Case Report Forms
CsA	Ciclosporin A
cTIMP	Clinical Trial of an Investigational Medicinal Product
CTRU	Clinical Trials Research Unit
CV	Coefficient of variation
DMEC	Data Monitoring and Ethics Committee
DLQI	Dermatology Quality of Life Index
DSUR	Development Safety Update Report
EQ-5D-3L	EuroQol - five dimensions
GCP	Good Clinical Practice
GPwSI	GP with a Special Interest accreditation
HE	Hand Eczema
HECSI	Hand Eczema Severity Index
HTA	Health Technology Assessment
ICER	Incremental cost effectiveness ratio
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IgE	Immune Globulin E
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ITT	Intention to Treat
IL-18	Interleukin 18
IL-36	Interleukin 36
LICTR	Leeds Institute of Clinical Trials Research
MTX	Methotrexate
mTLSS	Modified Total Lesion Symptom Score
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NMB	Net monetary benefit
NRES	National Research Ethics Service
PASI	Psoriasis Area Severity Index
PBI-HE	Patient Benefit Index for chronic Hand Eczema
PeDeSI	Person-Centred Dermatology Self Care Index

PGA	Physician’s Global Assessment
PI	Principal Investigator
PIC	Participant Identification Centre
PIS/ICD	Patient Information Sheet/Informed Consent Document
PIN	Personal Identification Number
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PUVA	Psoralen combined with ultraviolet A (UVA) treatment
QALY	Quality Adjusted Life Years
QoL	Quality of Life
RN	Research Nurse
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TARC	Thymus and Activation-Regulated Chemokine/CCL17
TMG	Trial Management Group
TSC	Trial Steering Committee
TSLP	Thymic Stromal Lymphopoietin
UKDCTN	UK Dermatology Clinical Trials Network
UVA	Ultraviolet A
WCBP	Women of Child-Bearing Potential

6. BACKGROUND

Hand eczema (HE) is one of the most common skin disorders and an important cause of morbidity and occupational disability. The 1-year prevalence of HE is estimated to be up to 10% in the general population [3]. The proportion of patients who develop severe CHE is estimated to be 5-7% of all patients with HE [4].

The impact on daily life of sufferers is considerable [1, 2]. Patients suffering from severe CHE are significantly restricted in their work and social life. HE is characterised by severe itching and can be very painful. Many studies have shown the significant impairment of quality of life (QoL) in patients with HE [35, 36]. The physical and psychological burden for patients is comparable to that of patients with multiple sclerosis and migraine. HE is one of the most frequent work-related diseases. Psychosocial implications are highlighted by a high prevalence of anxiety and depression in patients with occupational HE [27]. Sick leave [1], lost productivity, frequent need of dermatology specialist treatment, vocational retraining and worker's compensation have marked economic implications for companies and social security systems [39]. HE is a persistent disease with a relapsing course and variable disease duration [36]. The long-term prognosis of HE is poor [37] especially in those with a long history. The severity of HE at initial diagnosis is predictive of disease prognosis [38].

HE treatment is challenging and often unsatisfactory, due to the fact that it is multiaetiologic with skin barrier impairment and (allergic) lymphocyte responses both playing an important role. Barrier impairment is addressed by avoidance of irritants and barrier-strengthening moisturisers; the lymphocyte response by immunomodulatory approaches.

Controversial opinion on the most effective treatment for HE is influenced by the following factors: (1) HE presents with several disease subgroups; (2) patients with different pathophysiology present with similar symptoms; and (3) the natural course of HE often follows a recurrent pattern [4, 5]. The currently proposed classification in the UK [5] and Europe [39] defines atopic HE, allergic contact dermatitis and irritant dermatitis, either alone or in combination. Discrimination of aetiologically distinct subtypes is a remaining clinical challenge also due to overlap/coexistence of different aetiologies [5]. In cases where aetiological factors are unknown HE is classified according to morphology (hyperkeratotic, hyperkeratotic-rhagadiform, dyshidrotic, pompholyx – which are for this study summarised as "predominantly hyperkeratotic" and "predominantly vesicular" due to reported different therapeutic outcomes of these 2 morphology groups). Subgrouping based only on morphology has so far not proven sufficiently useful for identification of the best suited therapy for a given patient. Therefore, a novel approach to subgrouping based on molecular / inflammatory markers may be useful.

Loss-of-function mutations in filaggrin, a protein important for the skin barrier, have repeatedly been shown to be associated with atopic eczema. Recent studies have also shown an association between the filaggrin null alleles and the subgroup of patients having both HE and atopic eczema [40, 41, 42-44]. It has been proposed by many experts [45] that any HE classification should consider the filaggrin genotype to enable better subgrouping and potentially targeted treatment. There are other emerging barrier related polymorphisms which could be of clinical relevance but are not fully explored yet and these include for example genes encoding for late cornified envelope [55] or tight junction proteins. Inflammation related molecular markers have not yet entered clinical diagnosis.

In clinical practice it is often difficult to determine the HE phenotype and distinguish hand psoriasis from hyperkeratotic HE if patients present without involvement of other body sites and if the condition has already been treated with topical corticosteroids. Clinicians are aware of “mixed” phenotypes named eczema-in-psoriatico or psoriasiform eczema; so far only skin biopsies can help to verify these mixed conditions. In the UK it is not current practice to biopsy lesions to verify diagnosis of HE or hand psoriasis. Mediators expressed by the uppermost layer of the skin, the epidermis, are of particular diagnostic interest as these skin layers are easily accessible (e.g. by tape stripping [17] or washing [19]). Described markers such as IL-36 or Thymic Stromal Lymphopoietin (TSLP) could improve subtype diagnosis and help to distinguish on a molecular level eczema subtypes. The identification of HE subgroups is extremely important. It has been highlighted in a number of expert opinion papers that disease heterogeneity contributes to overall unsatisfactory treatment outcomes. A better stratification of patients for the most appropriate therapy could significantly improve therapeutic results.

Currently available clinical evidence for the treatment of CHE is not compelling enough to guide clinical practice [5-7]. When patient education, irritant/contact allergen avoidance, skin moisturisation and application of topical corticosteroids are insufficient to control the disease, ultraviolet (UV) therapy or systemic immune-modifying drugs are used [5, 6, 7]. There is no treatment pathway generally accepted between UK dermatologists. However, most UK dermatology centres use phototherapy (mostly local PUVA) or Alitretinoin as first line treatment for HE refractory to topical corticosteroids (for review [5, 6]).

PUVA is used extensively across the NHS and comprises a photosensitising agent in combination with UV-A. It is effective in both vesicular and hyperkeratotic hand eczema [54]. The photosensitising agent 8-MOP (methoxsalen, 8-methoxypsoralen) is used world-wide and the most frequent delivery way for this compound in the treatment of hand eczema is topical (e.g. gel, cream, immersion) [6, 57].

The importance of topical PUVA was highlighted in a recent ‘consensus statement’ on the treatment of chronic hand eczema [5] as a widely used treatment option for the

management of chronic HE, although this is based more on clinical experience than on evidence. The British Photodermatology Group (BPG) produced guidelines on PUVA therapy in 1994 and updated these guidelines in 2000, where PUVA was described as playing an 'important part in dermatological therapeutics, being an effective and generally a safe treatment' [13]. PUVA treatment forms an important part of any published international guideline on hand eczema management including both Danish [52] and German guidelines [58] on the treatment of chronic hand eczema.

Alitrenoin (9-cis retinoic acid) is a naturally occurring vitamin A derivative (retinoid) and has recently become a licensed systemic agent for severe, CHE unresponsive to treatment with potent topical corticosteroids. If either PUVA or AL treatment fail, immunosuppressants such as Ciclosporin A (CsA) and Methotrexate (MTX) are used to treat these patients.

However, there is a lack of controlled clinical trials that directly compare treatments (eg comparison of PUVA to systematic immunomodulatory drugs) or demonstrate effectiveness under daily practice conditions, and the lack of clear evidence based data has been outlined by a number of national and international expert groups [8]. Given the high socioeconomic impact of the disease there is a pressing need for comparative studies on available first line treatments, and on long-term outcome of currently used therapies.

Our choice of comparator for Alitretinoin was based on published clinical trials [8], and on feedback from UK dermatologists, patients and the UK Dermatology Clinical Trials Network (UKDCTN). As research and audit data on treatment choices for CHE are unavailable, we performed a survey among 194 UK dermatologists; the most frequent first choice approaches for CHE were PUVA, oral corticosteroids and Alitretinoin. When asked which strategy was thought to be most efficient for long-term outcome 20% of clinicians indicated that they did not know whilst 43% of clinicians opted for Alitretinoin and 30% for PUVA. Therefore, we propose a multicentre, open, prospective, two arm parallel group, adaptive, randomised controlled trial comparing the response to the currently most common first line therapies in UK clinical practice, PUVA and Alitretinoin. In line with daily clinical practice (survey results) topical corticosteroids and emollients will be applied along with the randomised treatment. Frequent assessments will be performed for 52 weeks post planned start of treatment in order to collect data on long term outcomes.

This study will inform on the most effective first line therapy under daily practice conditions for patients suffering from corticosteroid resistant CHE, and will be the first to directly compare Alitretinoin to another treatment in CHE. It will inform on clinical and cost effectiveness and patients' benefit regarding short and long term outcomes and will report on duration of minimal disease activity (remission). The study will also provide pilot data on second line therapies. Comparison of HE studies is hindered by a confusing number of different assessment tools. We will therefore also compare

Physician's Global Assessment (PGA), modified Total Lesion Symptom Score (mTLSS) and Hand Eczema Severity Index (HECSI) and will inform on the most appropriate tool. An informative sub-study will increase our knowledge about inflammatory mediators defining HE subgroups. Results of this research will advance stratified treatment approaches for HE.

7. AIMS AND OBJECTIVES

The aim of this study is to determine the clinical and cost effectiveness of Alitretinoin and PUVA when used in conjunction with concomitant topical corticosteroids, emollients and patient education for the treatment of severe CHE which is unresponsive to treatment with potent topical corticosteroids alone.

7.1 PRIMARY OBJECTIVE

The primary objective is to compare Alitretinoin and PUVA as first line therapy in terms of disease activity at 12 weeks post planned start of treatment.

7.2 SECONDARY OBJECTIVES

1. To compare Alitretinoin and PUVA in terms of disease activity over time with a focus on disease activity at 24 and 52 weeks post planned start of treatment.

2. To compare Alitretinoin and PUVA in terms of time to relapse.

3. To compare Alitretinoin and PUVA in terms of quality of life (QoL) and patient benefit over the 52 weeks duration post planned start of treatment.

4. To determine cost effectiveness of Alitretinoin compared to PUVA over the short and longer term.

5. To determine the educational need for individual patients.

6. To compare Alitretinoin and PUVA in terms of safety

7.3 EXPLORATORY OBJECTIVES

1. To compare scoring systems HECSI, mTLSS, DLQI and PGA used to monitor response to treatment in patients with severe CHE.

2. To evaluate whether response to first line treatment is affected by the following parameters:

- duration of disease
- clinical phenotype
- disease severity
- presence of atopy
- filaggrin loss of function mutation (and other potential emerging mutations affecting skin barrier or response to PUVA/Alitretinoin)
- smoking history

- BMI
- foot involvement

3. To collect pilot data on clinical effectiveness of second line therapies, using HECSI and PGA.

4. To explore treatment responses in HE subgroups defined by molecular inflammatory mediators determined in tape strips or washing solution.

5. To compare Alitretinoin and PUVA in terms of time in remission using different definitions of end of remission including varying the extent of corticosteroid use.

6. To compare Alitretinoin and PUVA in terms of assessment of the nails

7. To explore the use of the photography guide for patients of non-Caucasian ethnicity

8. TRIAL DESIGN

The trial is a prospective, multicentre, open-label, two-arm parallel group, adaptive randomised controlled trial with one planned interim analysis.

A maximum of 780 consenting participants with severe CHE will be randomised on a 1:1 basis to receive either Alitretinoin (30mg dose per day – see section 12.2.1 for dose modifications) or immersion PUVA (twice weekly) in conjunction with concomitant topical corticosteroids, emollients and patient education. The trial is an adaptive design with a planned interim analysis to re-estimate the sample size (see section 18.3) and as such, the results of the interim analysis may lead to fewer than the required 780 participants, although a minimum of 500 participants will be randomised. All participants will receive their randomised treatment for a period of 12 weeks. Participants who have partially responded at 12 weeks will continue to receive their randomised treatment until a PGA assessment of clear/almost clear or up to 24 weeks post planned start of treatment, whichever is the earliest time point. Participants who do not sufficiently respond to their randomised treatment or those who relapse will receive 'standard clinical practice'. 'Standard clinical practice', in addition to concomitant topical corticosteroids, emollients and patient education, may include switching to the alternative randomised treatment, use of topical or systemic PUVA, use of other retinoids such as acitretin, or use of immunosuppressants such as CsA and MTX, at the discretion of the treating physician. All participants will continue to be followed up through 4 weekly visits to week 36, then 8 weekly up to 52 weeks post planned start of treatment in order to assess long term outcomes of Alitretinoin and immersion PUVA as first line treatment.

8.1 BLINDING

The trial is open-label as participants and investigators cannot be blinded to treatment allocation due to the nature of the PUVA intervention. However, the assessment of the HE severity scores (HECSI, mTLSS and PGA) will be undertaken by a clinical assessor who is blinded to the randomised treatment. This blinded assessor can be a

research/dermatology nurse or a clinician, and where possible, should be the same person at each assessment of a patient. Participants will be reminded not to reveal which treatment they have received to the blinded assessors in order to preserve blinding.

In addition, photographs will be taken, for 20% randomly identified, consenting Caucasian participants and all consenting participants of non-Caucasian ethnicity from each centre, at baseline and 12 weeks post planned start of treatment. A blinded central review of the photographs will be conducted in order to assess inter-centre differences in severity scoring and to gain documentation on the variety and variability of HE phenotypes across centres.

8.2 BIOMARKER SUB STUDY

A biomarker sub study on 100 consenting participants recruited from selected centres will be performed to further assess whether potential molecular markers for different inflammatory skin responses can improve subgroup definition with regard to therapeutic outcome. We will investigate the relationship of biomarkers including IL-36, Thymus and Activation-Regulated Chemokine/CCL17 (TARC), Chemokine (C-C motif) Ligand 20 (CCL20), Thymic Stromal Lymphopoietin (TSLP), and IL-18 with disease activity and response to treatment (see section 13.12 and 18.6).

8.3 NAIL ASSESSMENT SUB STUDY

Unlike for psoriasis, there is currently no nail scoring system available for hand eczema. However, there is some evidence to suggest that nails of patients with hand eczema show various nail changes [58] and that treatment with Alitretinoin can have a positive effect on nail involvement [59].

Clinical observational descriptive assessments of the nails from participants recruited only from St Luke's hospital, Bradford will be collected by the independent blinded assessor prior to the start of the randomised treatment, and at each follow up visit for the duration of the trial.

Information collected on nail descriptive assessments may be used to help develop a future score for nail involvement in HE.

8.4 INTERNAL PILOT STUDY

An internal pilot study has been planned in order to assess the feasibility of recruitment. The internal pilot target has been set to recruit 63 participants across 12 centres over the first 6 months of the recruitment period. This target represents 8% of participants recruited across 30% of centres after 25% of the recruitment period has been completed, and is based on a recruitment rate of 1 to 2 participants per month per centre taking into account a staggered opening of centres.

Providing the target of 12 centres open to recruitment and the overall number of participants recruited at 6 months is at least 63, the criteria for continuing the trial will be met. It will be considered feasible to reach the maximum sample size within the

planned recruitment period of two years. The decision to continue the trial will remain with the funder in the event that the target is not met.

9. ELIGIBILITY

9.1 INCLUSION CRITERIA

Patients meeting all the following criteria will be considered eligible for enrolment into the study:

1. Patients aged ≥18 years at the time of signing the Informed Consent Form
2. Patients suffering from uncontrolled, severe CHE defined as the presence of both of the following criteria:
   a) PGA score of severe
   b) Resistance to treatment with potent topical corticosteroids for ≥ 4 weeks prior to the point of eligibility screening.
3. Patient has provided written informed consent.
4. Patient is expected to comply with treatment and protocol schedule.

9.2 EXCLUSION CRITERIA

Patients will be excluded from the study for any of the following reasons:

Skin related:

1. Patients who have a clinically suspected infection (fungal, bacterial or viral) as cause for dermatitis of the hands.
2. Patients with known clinically relevant allergic contact dermatitis of the hands unless they had made a reasonable effort to avoid the contact allergen.
3. Patients suffering from atopic eczema covering more than 10% of body surface (excluding hands).
4. Patients who have skin conditions worsened by the sun i.e. do not tolerate UV-light (for example lupus erythematosus, porphyria).

Treatment related:

5. Patients who have received phototherapy/photochemotherapy in the last 3 months prior to randomisation
6. Patients who have received systemic vitamin A derivatives or other systemic immunosuppressants e.g. methotrexate or biologics treatment for HE in the last 3 months prior to randomisation
7. Patients who have received Ciclosporin A or systemic glucocorticoid steroid treatment for HE in the last 4 weeks prior to randomisation.
8. Patients receiving topical calcineurin antagonist treatment within 1 week prior to randomisation.
9. Patients receiving concomitant treatment with tetracyclines, or medication with potential for drug-drug interaction with Alitretinoin (e.g. CYP3A4 inhibitor ketoconazole) that cannot be suspended or switched to an acceptable alternative

10. Patients receiving concomitant treatment with relevant photosensitisers, when this treatment cannot be suspended for the duration of the intervention or switched to an acceptable alternative
11. Patients with a history of melanoma skin cancer, or patients with a history of non-melanoma skin cancer depending on history, location and “severity” of the non-melanoma skin cancer based on experience from routine practice.
12. Patients who have received prior treatment with arsenic agents or ionising radiation in the treatment area (e.g. hands).

General:

13. If female:
    a) Lactating
    b) Of child bearing potential (WCBP, Appendix 1):
        i. With positive pregnancy test (absence of pregnancy will be confirmed with a negative pregnancy test before randomisation)
        ii. Unwilling to follow pregnancy prevention program measures* (see below) whilst receiving treatment and after the last dose of protocol treatment as indicated in the relevant SmPC
14. Patients with hepatic insufficiency (alanine aminotransferase and/or aspartate aminotransferase > 2.5 times the upper limit of normal), known severe renal insufficiency, uncontrolled hyperlipidaemia (for all of the following: triglycerides, cholesterol and/or LDL cholesterol) or uncontrolled hypothyroidism in the 12 week period prior to randomisation.
15. Patients with known hypersensitivity to peanut, soya or vitamin A derivatives or with rare hereditary fructose intolerance as determined by patient history.
16. Patients currently suffering from hypervitaminose A as directed by clinical symptoms or patient history
17. Patients previously participated in the ALPHA trial

Eligibility waivers to the eligibility criteria are not permitted.

*Rigorous contraception for women of childbearing potential, unless exempt according to standard of care practice, is required 1 month before treatment, during the treatment period and 1 month after cessation of treatment as per usual standard practice.

10. RECRUITMENT, REGISTRATION AND RANDOMISATION

10.1 RECRUITMENT SETTING

Patients will be screened in secondary care dermatology outpatient, community hospital and General Practice settings. Formal eligibility assessment and recruitment will be undertaken in secondary care dermatology outpatient clinics. Research sites and participant identification centres (PICs) will be required to have obtained local,

ethical and management approvals and undertake a site initiation meeting with the CTRU prior to the start of recruitment into the trial.

10.2 RECRUITMENT PROCESS

10.2.1 DERMATOLOGY OUTPATIENT CLINICS

Potential patients will be identified in standard dermatology clinics, patch test clinics, occupational health clinics and phototherapy assessment clinics. Patients will then be approached during clinic appointments and provided with verbal and written details about the trial (ALPHA detailed Patient Information Sheet/Informed Consent Document PIS/ICD) by a member of the attending clinical team. This will include detailed information about the rationale, design and personal implications of the study.

Alternatively, patients identified by other means (such as review of waiting lists, case records, referrals and hospital databases) may be sent a personalised letter inviting them to take part. This letter will include a brief introduction to the study. Patients will be invited to contact the hospital research team to find out more information and to make an appointment to discuss the study further. Following information provision, patients will have as long as they need to consider participation and will be given the opportunity to discuss the study with their family and other healthcare professionals before they are asked whether they would be willing to take part in the study.

10.2.2 PRIMARY CARE AND COMMUNITY CLINICS

Potentially eligible patients will also be identified by primary care General Practices (GPs) and community hospitals, working as PICs. PICs will be responsible for the identification of potential patients for the trial, but will retain responsibility for the healthcare of the patients outside the research.

Patients will be approached during standard clinic visits and will be provided with details about the trial by the attending clinical team. A Patient Information Sheet (PIS) will be provided at this time which the patient will take away for consideration. If the patient is interested in taking part, the attending clinicians will refer potential participants to the research team based in one of the participating secondary care research sites for assessment and possible recruitment to the trial. Additionally, patients may be identified by other means (such as a database search) and sent a personalised letter from their GP asking them to consider taking part. This letter will include a brief introduction to the study and invite patients to contact their GP if they are interested in discussing the study further. If the GP assesses the patient to have severe hand eczema, the GP will send a referral to a participating hospital to assess suitability for the trial.

10.2.3 SELF-REFERRAL DROP-IN CLINICS

The Chief Investigator will run ‘drop-in’ chronic hand eczema clinics in a secondary care setting in order to identify potential patients. For patients under the care of their GP, the research team will arrange a secondary care referral from the GP for the patient.

Other participating recruiting secondary care hospitals may decide locally to proceed with this model for identifying potential patients, as required.

10.2.4 TRIAL INFORMATION

The ALPHA trial will be advertised using a series of ALPHA poster and leaflets as well as dermatology special interest websites such as the UK dermatology clinical trials network (UKDCTN) website (web links will be highlighted in ALPHA trial literature). Promotional material will be distributed to relevant locations including (but not limited to) dermatology departments, occupational health departments as well as GP surgeries, GPwSI dermatology clinics and community pharmacies. Details will be provided of how to contact the local research team in one of the participating research sites for further information so that interested patients can arrange an appointment to further assess their eligibility.

A specific ALPHA trial Twitter account accessed by ALPHA CTRU staff only will be used to advertise the trial to allow potential participants to become aware of the trial. Tweets used for the purpose of recruitment into the trial will be ethically approved prior to use.

In addition the study team will utilise an ethically approved video to explain and promote the ALPHA trial. The video will be available on various websites, including the CTRU website, University of Leeds YouTube and UKDCTN website. It will also be distributed to dermatology departments, occupational health departments as well GP surgeries and GPwSI dermatology clinics.

The study team will also utilise an ethically approved radio and television script to explain and promote the ALPHA trial on radio stations; this script will also be used to record a television piece to be broadcast in local areas. Where possible the trial team will engage with local and national newspapers to increase publicity about the trial. Patients will be directed to the ALPHA website for details about the trial and to work through the self-screening questionnaire process (section 10.2.5).

If eligible, patients will be invited to a formal eligibility assessment at one of the participating research sites which will take on the responsibility for seeking consent and undertaking trial research procedures.

A participant newsletter following an ethically approved format will be produced at regular intervals and offered to participants who are taking part in the study when they attend follow up visits; this will provide updates on the study progress and other relevant information. This newsletter will also be available on the ALPHA website.

10.2.5 ALPHA WEBSITE

ALPHA tweets, posters and leaflets will direct potential participants to the ALPHA web site which will contain the ethically approved ALPHA participant recruitment video and participant information document. The ALPHA website will contain an ethically approved self-screening questionnaire that will ask a series of questions to enable the

potential participant to assess their potential eligibility for the trial. The questions will be worded such that all responses will be 'yes' for those who are eligible for trial participation.

If the potential participant answers 'yes' to all questions, they will be directed to a list of participating research centres open to recruitment on the trial website. They will be advised to assess whether there is a participating centre that is convenient for them and read the participant information sheet before deciding whether they are interested in participating.

If the potential participant has assessed themselves as eligible and is interested in the trial, they will be directed to email an ALPHA specific email account to confirm that they have answered yes to all questions on the self-screening questionnaire, identify their local participating centre, and confirm that they can be contacted regarding the trial via email. The CTRU team will forward the email to the designated research nurse at the relevant participating centre.

The designated research nurse at the relevant participating centre will be responsible for contacting the potential participant and assessing their eligibility for trial participation. This may be done over the telephone, followed up by a clinic visit, or through a clinic visit in the first instance. If suitable for the trial, the research nurse will provide the potential participant with a secondary care referral for their GP to refer them to attend the dermatology clinic as per standard practice.

In the event that a potential participant emails the CTRU but has indicated that they have not answered yes to all eligibility questions, the CTRU team will contact the patient with a template email response advising the patient that unfortunately they are likely to be unsuitable for the trial and to advise them to visit their local GP for advice as the CTRU are unable to offer any medical advice.

In the event that a potential participant emails the CTRU but there is no hospital local to them participating in the trial, the CTRU team will contact the patient with a template email response advising the potential participant to keep checking the website for further information on updates as to which hospital sites are opened in the trial and to contact the CTRU again when a suitable site for them is opened. When the required number of sites has been reached, the website will clearly state that no further sites will be opened, so that potential patients are informed

10.3 SCREENING

Participating research sites and PICs will provide anonymous screening information. Participating PICs will be required to return details to the CTRU of the number of patients they have approached/sent letters for participation in the trial. Research sites will be required to complete an anonymised log of all patients aged 18 years and over with severe CHE who have been considered for the trial but not registered. Documented reasons for ineligibility or declining participation will be closely monitored by CTRU as part of a regular review of recruitment progress. These anonymised logs

should be returned to the CTRU on a monthly basis. Anonymised information collected will include:

- Age
- Gender
- Ethnicity
- Date screened
- How the patient first heard about the trial
- The reason not eligible for study participation, OR
- The reason eligible but declined.

10.4 INFORMED CONSENT AND ELIGIBILITY

The Principal Investigator (PI) retains overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki 1996.

The assessment of eligibility will be confirmed and the informed consent process will be undertaken by the PI or a designated medically qualified member of the clinical or research team (i.e. GCP trained and has been approved by the PI as detailed on the Authorised Personnel Log). The PI or designate will confirm consent by countersigning the informed consent form.

10.4.1 Eligibility bloods

As blood samples are required to confirm eligibility and atopy status prior to randomisation, a research site can choose to either use a one stage process to obtain full informed consent (using the detailed PIS/ICD) or a two stage consent process involving obtaining consent for blood sampling to confirm eligibility and atopy (using the shortened PIS/ICD) and then full informed consent (using the detailed PIS/ICD) for trial participation. If a period of greater than 12 weeks elapses prior to the baseline visit the eligibility blood test will have to be redone.

If available and within the 12 weeks prior to baseline visit, existing blood results (taken for other reasons) in participants' hospital notes can be used for "eligibility" screen. If existing atopy results (on presence/absence of specific IgE) are available in participants' hospital notes, a blood sample to confirm atopy status will not be required. Please note that a blood sample to screen for atopy (ie the genetic tendency to develop the classic allergic diseases (atopic dermatitis, allergic rhinitis (hay fever), and asthma)) is routine for all patients who have severe hand eczema.

10.4.2 Contraception requirements

As Alitretinoin is strictly contraindicated in pregnancy, women of childbearing potential will be required to follow a strict contraception prevention program, unless exempt

according to standard of care practice, 1 month prior the start of Alitretinoin treatment as per usual standard practice.

The research team will be required to use a two stage consent process using the shortened PIS/ICD to request women of child bearing potential to agree to use a reliable form of effective contraception, only if not currently doing so, for at least one month prior to randomisation.

If the participant is randomised to Alitretinoin, they will be required to continue to follow the strict pregnancy program throughout the trial and one month after cessation of treatment. If the participant is randomised to PUVA, it is not common clinical practice to ensure the participant follows the strict pregnancy program. However, the participant will be advised by the PI or a designated medically qualified member of the clinical or research team to use a reliable form of contraception and not become pregnant during the trial.

10.4.3 Shortened Consent

A shortened consent to the eligibility assessments can be obtained at the initial approach in clinic (i.e. screening visit) for the two following reasons:

i) For bloods to be taken immediately to confirm eligibility and atopy status (if existing blood results taken for other reasons and atopy results are not available in participants' hospital notes).
ii) To request that women of child bearing potential agree to use a reliable form of effective contraception, only if not currently doing so, for at least one month prior to randomisation (see Section 10.4.2).

Shortened consent can be taken using the Shortened PIS/ICD. The shortened consent for the blood sample and/or contraception may be taken by an appropriately qualified member of the trial team (including nurses and other health care professionals) who has received GCP training and is authorised on the trial delegation log to take this consent.

If the patient is found to be eligible, would like to take part in the study and has already been provided with the full PIS for the trial, at the next visit (baseline), assenting patients will then be invited to provide full informed consent for participation (using the detailed PIS/ICD) and undergo formal eligibility assessment. This must be confirmed prior to randomisation which must be within 12 weeks of the eligibility blood sample being taken. Informed consent for trial participation will be undertaken by the PI or an authorised, medically qualified member of the attending clinical or research team. If a participant has any concerns when attending clinic and requires more time to consider participation in the trial, more time can be offered prior to full consent being taken but a repeat blood sample will be required if randomisation does not take place within 12 weeks of the eligibility blood sample being taken. The shortened consent is purely for the purpose of carrying out eligibility assessments including contraception and a blood sample to assess eligibility and atopy status for randomisation (see section 10.6).

Participants who provide the optional shortened consent are not consenting to participate in the trial therefore trial-specific assessments not relating to eligibility, atopy status and contraception can only be carried out following full consent for the trial using the detailed PIS/ICD.

10.4.4 Full informed consent

Informed, written consent for the blood sample/s (if required) and contraception (as applicable) must be obtained prior to registration (using either the shortened PIS/ICD or detailed PIS/ICD) and full informed consent must be obtained prior to randomisation (using the detailed PIS/ICD, if not completed at registration). Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial and are not standard routine care at the participating sites (including the collection of identifiable participant data).

All patients will be provided with verbal and written details about the trial by the attending clinical and research team (detailed ALPHA PIS/ICD) for the patient to consider. This will include detailed information about the rationale, design and personal implications of the trial, including data collection burden. Following information provision, patients will have as long as they need to consider participation and will be given the opportunity to discuss the trial with their family and other healthcare professionals before they are asked whether they would be willing to take part in the trial. Patients will also be provided with a contact point where he/she may obtain further information about the trial.

All participants who consent (either optional shortened consent or full consent) will be registered into the trial.

Where the patient is able to provide full informed consent but is unable to sign or otherwise mark the consent form, provision for completion of the consent form by a witness will be made. This should be a carer, friend/family member, or a local member of the clinical team who is independent of the research team.

A record of the consent process detailing the date of consent and all those present will be detailed in the participant's hospital notes. The original consent form will be filed in the Investigator Site File at the hospital. A copy of the consent form will be given to the participant, a second copy filed in the hospital notes (as per local practice) and a third copy will be returned to the CTRU at the University of Leeds.

Where a participant is required to re-consent or new information needs to be provided to a participant, it is the responsibility of the PI to ensure this is done in a timely manner and according to any timelines requested by the CTRU.

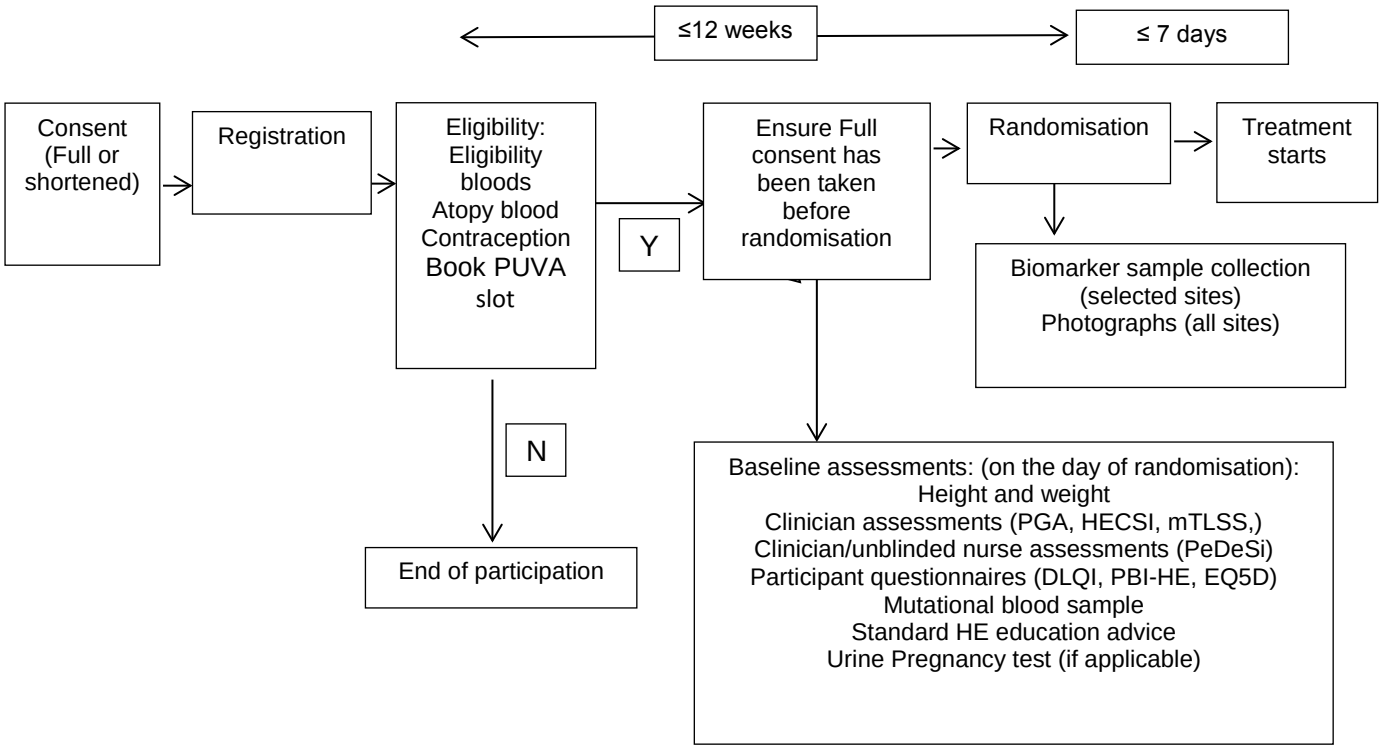
The right of the patient to refuse consent without giving reasons will be respected; furthermore the patient will be free to withdraw from the study at any time without giving reasons and without prejudicing any further treatment/care.

10.5 REGISTRATION

Timing of registration and randomisation

Recruitment of participants to the ALPHA trial will involve either a one or two step consent process depending on whether eligibility bloods and initiation of contraception are required. A maximum of 12 weeks between the screening visit and the baseline visit allows sites time to book a potential PUVA slot with their local phototherapy department (see Section 11.4.2), receive eligibility blood results, atopy status and at least 1 month duration of the contraception prevention program (if applicable) prior to randomisation. All participants who are consented must be registered into the trial. Participants are randomised into the trial within 12 weeks of the date that the eligibility blood sample was taken and/or at least 1 month (and less than 12 weeks) from the start of contraception. The order of events between consent and the start of trial treatment is shown in Figure 1.

Figure 1: Schedule of event between consent and start of trial treatment



Recruitment of participants to the ALPHA trial requires a blood sample taken within 12 weeks of the baseline visit, and at least 1 month duration of the contraception prevention program prior to randomisation (if applicable) to confirm eligibility. Patients will be registered after consent to either the shortened consent (for blood sample and/or contraception) or full consent (main trial) depending which consent is taken at the screening visit, by an authorised member of the attending clinical or research team. **At the point of registration participants will be issued a unique trial number. This unique five digit number together with the centre number will form the**

participant ID number. Please note this unique ID number will be required to complete the informed consent form.

Registration will be performed using either the 24-hour automated registration telephone system or via a web address based at the CTRU. For the telephone system, a site code, authorisation code and PIN will be required. To register using the web address then a staff site email address, a site code and Personal Identification Number (PIN) will be required. Authorisation codes and PINs will be provided by the CTRU. These codes will only be issued once a site has been fully approved and all the necessary documentation has been received at CTRU.

The person telephoning or accessing the web address to register the participant must have the completed Registration Case Report Form (CRF) available at the time of registration as the following additional information will be required:

- Participant details, including initials, date of birth, ethnicity
- Name of trial research site and site code
- Confirmation of date and type of written informed consent
- Personal authorisation codes and/or PIN

Direct line for 24-hour registration: 0113 343 2290

Web address for 24-hour registration: https://lictr.leeds.ac.uk/webrand/

Participants may only be registered into the trial by an authorised member of staff at the trial research site, as detailed on the Authorised Personnel Log.

The following information will be recorded on the Registration CRF but will not be required for the registration telephone call/web registration:

- Gender
- How the participant first heard about the trial

After trial registration the research site will:

- Add the unique participant ID number to all CRFs
- Return a copy of the completed consent form to CTRU
- Ensure that participants are notified of their appointment dates
- Book the PUVA treatment appointment for all participants. A time period between screening visit and baseline visit will allow time to schedule in the first PUVA treatment (as well as bloods for assessment of atopy (ie on presence/absence of specific IgE) should that information not be available in participants' hospital notes, and 1 month duration of the contraception prevention program, if applicable). Once a date of the PUVA treatment has

been confirmed, the baseline visit can be arranged with the participant, to occur **no earlier than 7 days** prior to the PUVA appointment. The participant will be randomised to receive either Alitretinoin or PUVA at the baseline visit, after all baseline assessments have been conducted. Please note, if the participant is randomised to Alitretinoin, the PUVA treatment appointment will no longer be needed for this participant, and the phototherapy department must be informed immediately to allow sufficient time for cancelled appointments to be re-used.

Following participant registration, CTRU will email a Participant Registration Notification to the research site.

10.6 RANDOMISATION

Participants who have previously been registered, have confirmation of eligibility and have provided full informed consent, will be randomised (within 12 weeks of the date the eligibility blood sample was taken and after 1 month duration of the contraception prevention program, if applicable) into the trial by an authorised member of the research team at the site using either the automated secure 24-hour telephone randomisation service or via a web address based at the CTRU. For the telephone randomisation, the same site code, authorisation code and PIN used for registration (refer to Section 10.5) provided by CTRU, will be required to access this system. For the web address randomisation, site staff email address, site code and PIN will be required. The person telephoning or accessing the web address to randomise the participant must be an unblinded member of the site research team and have the completed Randomisation CRF available at the time of telephoning/accessing the web, as the following information will be required:

- Participant's initials and date of birth
- Participant's unique trial number provided at registration
- Confirmation of date of written full informed consent
- Confirmation of participant's eligibility for the trial
- Confirmation of completion of baseline assessments
- Confirmation of participant completion of quality of life questionnaires
- Consent for sub-study: Yes or No (for selected centres)
- Consent for photographs: Yes or No

Patients will be randomised in a 1:1 allocation ratio, to receive either Alitretinoin or immersion PUVA using a computer-generated minimisation programme incorporating a random element to ensure treatment groups are well-balanced for the following participant characteristics, details of which will also be required for randomisation:

- Randomising site
- Disease duration (< 6 months / 6-24 months / >24 months)
- Clinical phenotype (predominately hyperkeratotic / predominately vesicular/ fingertip dermatitis)

- Presence of specific IgE (e.g. positive inhalant mix)
- DLQI (<15, ≥15)

Direct line for 24-hour and randomisation: 0113 343 2290
Web address for 24-hour randomisation:
https://lictr.leeds.ac.uk/webrand/

After trial randomisation the research site will:

- Provide each participant with a Trial ID card and inform them that it should be carried at all times and presented to medical staff should they be admitted to hospital during their time on trial.
- Ensure that participants are notified of their appointment dates.
- Notify the participant's GP of their participation in the trial using the approved ALPHA GP Letter.

Following participant randomisation, CTRU will fax or email a Participant Randomisation Notification to the member of the research team member who randomised the participant and pharmacy.

11. TRIAL MEDICINAL PRODUCT MANAGEMENT

Please refer to the ALPHA Pharmacy and IMP Management Study Site Operating Procedure (SSOP) for full details of the trial IMP management requirements.

11.1 INVESTIGATIONAL MEDICINAL PRODUCTS

Within the trial, the following are classed as investigational medicinal products:

11.1.1 ALITRETINOIN

Alitretinoin belongs to a class of medicines called retinoids which are related to vitamin A. It is only used if potent topical corticosteroids have not effectively controlled the HE.

- Alitretinoin is available as 10mg or 30mg capsules.
- The recommended starting dose for Alitretinoin is 30 mg once daily. A temporary dose reduction to 10 mg once daily may be considered in participants with Alitretinoin related headaches.
- Generic ('off the shelf') commercial stock of Alitretinoin is to be used as determined by individual hospital sites and according to standard of care.
- Please refer to the Summary of Product Characteristics (SmPC).

11.1.2 MELADININE®

Meladinine® (methoxsalen) will be used in combination with ultraviolet A (PUVA). PUVA treatment is recommended in numerous national and international guidelines [5, 6, 52]. As methoxsalen increases the skin's sensitivity to UV light, including

sunlight, it is used to improve the effectiveness of UV-A light therapy for moderate to severe eczema. Chemically, methoxsalen/8-methoxypsoralen belong to a class of organic natural molecules known as psoralens, or furanocoumarins which occur naturally in plants.

- Meladinine® 0.75% solution for local application in immersion PUVA: diluted to 3mg/L.
- Trial specific stock will be provided to sites free of charge by Leeds Teaching Hospitals Pharmacy. Refer to the Pharmacy Site File for Meladinine® ordering procedures.
- Methoxsalen 3mg/L solution is prepared by mixing 0.8ml of 0.75% Meladinine® solution in 2L tap water. The hands are soaked for 15 min followed by a 30 min delay before UVA exposure. Where delay is not feasible local routine practice can be followed (see section 12.1.3).
- Please refer to the Summary of Product Characteristics (SmPC) for all information except dosing (see above and section 11.2 below).

11.2 IMP FORMULATION, STORAGE AND PREPARATION

Formulation, storage and preparation of Alitretinoin are in line with the manufacturers' recommendations. For further details refer to the Alitretinoin Summary of Product Characteristics (SmPC).

Formulation and storage of Meladinine® are in line with the manufacturers' recommendations. For further details refer to the Meladinine® Summary of Product Characteristics (SmPC). A reference copy can be found in the Investigator and Pharmacy Site Files. However, Meladinine® will be used at a final concentration of 3mg/L i.e. as recommended in the British Photodermatology Group (BPG) guidelines, which suggest a final concentration of 3mg/L 8-methoxypsoralen for hand and foot immersion PUVA [13] and **not** those recommended in the Meladinine® SmPC. This is so that PUVA treatment in the trial will be administered in the same way as PUVA is administered within standard NHS practices.

11.3 IMP LABELLING AND HANDLING

Alitretinoin

Alitretinoin will be used as 'off the shelf' supplies. There is no requirement to ring-fence 'off the shelf' hospital supplies of this IMP. Alitretinoin will be used in accordance with the conditions set out in Regulation 46 (2) of the Medicines for Human Use (Clinical Trials) Regulations 2004 (and amended in 2006). As this IMP will be used within its routine indication, no special trial labelling requirements apply and this IMP may be labelled according to normal dispensing labelling requirements.

Meladinine®

Meladinine® trial supplies will contain a trial specific label, in line with Annexe 13: Investigational Medicinal Products (EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use) - please refer to ALPHA pharmacy and IMP SSOP. The trial site pharmacy will be responsible for completing individual participant details on each label.

11.4 IMP PRESCRIBING AND ADMINISTRATION

Details of the prescribing and dispensing of trial IMPs are given in the ALPHA Pharmacy and IMP Management SSOP. All drugs will be prescribed to eligible participants under the supervision of the PI or authorised treating clinician, and dispensed by hospital pharmacies.

For all treatment regimens, alterations in drug scheduling e.g. due to holidays is at the discretion of the local PI or treating clinician. All deviations to treatment regimen and drug scheduling should be fully documented in the participant's hospital notes, patient medication diaries and CRFs.

Participants receiving PUVA should be treated on an out-patient basis (or equivalent) only. Alitretinoin will be self-administered by the participant at home.

For details on all other medications, including prophylactics or concomitant medication please see Section 12.3.

11.4.1 ALITRETINOIN TREATMENT INITIATION

Participants randomised to Alitretinoin will be provided with a prescription at the randomisation/baseline visit and this will be dispensed as per standard care practice (e.g.hospital pharmacy/third party pharmacy). It is anticipated that the patient will take the first dose of Alitretinoin on the date of randomisation.

Prescriptions of Alitretinoin for all patients, except women of child bearing potential following the pregnancy prevention program, can be written to allow up to 5 week supply of treatment and continuation of treatment requires a new prescription. Prescriptions of Alitretinoin for women of child bearing potential following the pregnancy prevention program should be limited to a 4 week supply of treatment for each new prescription. Ideally, pregnancy testing (for those women of childbearing potential), issuing a prescription and dispensing of Alitretinoin should occur on the same day. Dispensing of Alitretinoin should occur within a maximum of 7 days of the prescription.

11.4.2 PUVA TREATMENT INITIATION

In order to avoid any significant delays in the start of PUVA randomised treatments, it is recommended that sites book a potential PUVA treatment slot with their local phototherapy department immediately after a patient has been assessed as potentially eligible at the screening visit (see section 10.5).

11.5 NON-INVESTIGATIONAL MEDICINAL PRODUCTS

Within the trial, there are no Non-Investigational Medicinal Products (NIMPs):

Please note, topical treatments for CHE, including emollients and topical corticosteroids will be used as prescribed by the treating physician according to standard clinical practice.

12. TREATMENT AND INTERVENTION DETAILS

12.1 DURATION AND FREQUENCY OF THE TREATMENT AND INTERVENTION

12.1.1 STANDARD HAND ECZEMA EDUCATION FOR EMOLLIENTS, IRRITANT AVOIDANCE AND CORTICOSTEROID USE (BOTH ARMS)

In both arms of the study it is expected that patients will follow good self-care practices in the use of emollients and irritant avoidance.

Education on HE in using emollients, avoiding irritants and relevant contact allergens will be delivered in a standardised way by the research nurse involved in the trial. The same education material will be handed to participants and the delivery of education will be face to face. The information material for participants will be based on sources used in clinical practise (British Association of Dermatology (BAD), National Eczema Society, Eczema Society patient information leaflets). Patient education will be delivered prior to randomisation.

Participants will be expected to use **emollients and soap substitutes and/or bath oils** on a daily basis throughout the study. There is no restriction regarding the frequency of emollient use and continuous use is recommended even in the absence of symptoms (National Institute for Health and Care Excellence (NICE) TA81). The choice of emollient is dependent on the clinical phenotype of the HE as well as on participant's preference. Non-urea containing emollient therapy in line with current most frequent clinical practice in the UK is recommended; however, participant's preference can override this recommendation.

In addition, **topical corticosteroids** may be used as required, as a reflection of standard clinical practice and will be documented by participant completed medication diaries. It is recommended that topical corticosteroids used should belong to the "potent" but not "very potent" group. Frequency of application (not exceeding once daily) is dependent on clinical symptoms –an "interval" scheme is recommended ("topical corticosteroids are used only intermittently to control exacerbations", NICE TA81).

12.1.2 ALITRETINOIN

According to standard clinical practice and NICE guidelines, Alitretinoin will be administered at a starting dose of 30mg, to be taken once daily with the main meal for 12 weeks. Participants will self-administer the treatment at home. Alitretinoin will be administered for 12-24 weeks as detailed below. After 12 weeks of treatment, participants' CHE will be assessed for their response to treatment (see section 12.1.4 for criteria of response during the intervention phase).

Dose adjustment of Alitretinoin down to 10mg or temporary cessation (i.e. dose interruption) may occur according to standard practice in participants who suffer from Alitretinoin related headaches (see section 12.2.1 for details).

12.1.3 PUVA

Hands will be immersed in a dilute solution of Meladinine® for 15 minutes followed by up to 30 minute delay (where delay not feasible local routine practice can be followed) before exposure to UV-A radiation (see section 11.1.2 for details of dilution). The exact dose of UV-A radiation that participants receive is individually tailored to the participant depending on phenotype (as per BAD guidelines) and the erythematous response of the skin following treatment.

It is standard practice for phototherapy units to regularly monitor the output of UV-A machines using UV meters. To ensure that patients enrolled in the study are treated with the same UV dose across different centres, meters should be accurately calibrated. Accordingly, a certificate of calibration (or equivalent) from UK medical physics departments will be required from sites prior to the start of recruitment.

The treatment will be performed in out-patient phototherapy departments within secondary care units and will be administered and supervised by the specialised nurses/dermatologists according to local policy. Treatments will be carried out twice weekly for 12 weeks as standard in most UK phototherapy units.

As most centres use immersion PUVA, this mode of administration has been chosen as the primary study intervention. Systemic and topical PUVA should **not** be given as primary study intervention but is a valid treatment option for non-responders or relapsing patients if part of local standard clinical practice.

After 12 weeks of PUVA treatment, participants' CHE will be assessed for their response to treatment (see section 12.1.4 for criteria of response during the intervention phase).

12.1.4 CRITERIA OF RESPONSE

Responders: defined as a PGA score of clear/almost clear at 12 weeks post planned start of treatment will discontinue randomised treatment and continue to receive 'standard clinical practice' and follow-up monitoring until 52 weeks post planned start of treatment.

Partial responders: defined as a PGA score of mild/moderate will continue with randomised treatment for up to 24 weeks post planned start of treatment. During this 12-24 week treatment period the patient will be monitored at 4 weekly intervals and the randomised treatment can be stopped at any time if the patient responds (PGA score of clear/almost clear) or if the symptoms worsen (PGA score of severe) and in the opinion of the attending clinical team there is no clinical benefit to continuation. All randomised treatment will be discontinued at the maximum 24 weeks treatment period and patients will continue to receive 'standard clinical practice' and follow-up monitoring until 52 weeks post planned start of treatment.

Non-responders: defined as a PGA score of severe at 12 weeks post planned start of treatment will discontinue randomised treatment and continue to receive 'standard clinical practice' and follow-up monitoring until 52 weeks post planned start of treatment.

12.1.5 STANDARD CLINICAL PRACTICE (BOTH ARMS)

As directed by NICE guidelines for Alitretinoin, the PGA score will direct treatment pathway decisions as determined by the treating clinician.

Patients achieving clear/almost clear PGA assessments at the end of the intervention (using randomised trial treatment) should be followed up with regular emollient use and a maximum of twice weekly (once a day) topical corticosteroid (maximum strength "potent") treatment at the discretion of the treating clinician.

At the end of trial treatment and during follow up, treatment will be at the discretion of the attending clinical team as per 'standard clinical practice', which in addition to concomitant topical corticosteroids, emollients, and irritant avoidance could include switching from PUVA to Alitretinoin and vice versa, using systemic or topical PUVA (as per local practice eg Psoralen), other retinoids such as Acitretin or immunosuppressants such as MTX and CsA. Relapsed participants could also return to the initial study intervention although PUVA should be administered as per local practice (eg Psoralen).

All participants will continue to be monitored to assess long-term first line treatment outcomes up to 52 weeks post planned start of treatment (12 months post planned start of treatment). All post interventional phase treatments will be recorded and will provide valuable pilot data on second line therapeutic approaches and will be useful in informing the choice of therapies in future trials.

CHE flare up events: For the purposes of this study, a "flare up event" is defined as return of symptoms for a short period (e.g. no longer than 3 days). Participants with unforeseen flare up events may be seen in clinics outside of their scheduled visit, according to local guidelines and procedures.

12.1.6 SCHEDULING VISITS

It is important, as far as possible, to ensure that participants in both arms receive the study intervention for similar periods of time i.e. an equivalent exposure. For the

purpose of ALPHA, the primary endpoint for the study is assessed at 12 weeks post planned start of treatment, with a -2 to +5 day assessment window permitted. The -2 to +5 day assessment window also applies to visits 4 and 8. All subsequent clinical assessment visits should then be arranged from the date of planned start of treatment within a time window of +/- 7 days.

Where a patient is unable to attend a visit, every effort should be made to reschedule the visits within the permitted time windows. However, if the week 4 or 8 visit does not occur within the -2 to +5 day assessment window, then where possible, the participant will be contacted by the research team via telephone, to obtain safety and treatment compliance information and to rearrange the next scheduled visit. Similarly, if a visit does not occur within the +/- 7 day assessment window (i.e. weeks 16, 20, 28, 32, 36 and 44), the participant will be contacted by the research team via telephone, where possible, to obtain safety and treatment compliance information and to rearrange the next scheduled visit.

If the week 12 visit does not occur within the -2 to +5 day assessment window (and every effort has already been made to arrange for the participant to attend the clinic visit within the permitted time window), the site will determine whether it is appropriate to contact the participant to administer the EQ5D-3L and DLQI questionnaires over the telephone within the visit time window. The health resource utilisation form will then be completed at the following week 16 visit (please see CRF guidance document for further detail).

If the week 24 or 52 visit does not occur within the +/- 7 day assessment window (and every effort has already been made to arrange for the patient to attend the clinic visit within the permitted time window), the site will determine whether it is appropriate to contact the participant to administer the EQ5D-3L and DLQI questionnaires over the telephone within the visit time window. The health resource utilisation form will then be completed at the following visit (except for week 52, where the health resource utilisation form will be completed over the telephone, where possible).

12.2 TREATMENT MODIFICATION OR DELAY - REASONS AND SCHEDULES

12.2.1 MODIFICATION OF IMP DOSAGE

All treatment modifications will be recorded on the CRF.

Alitretinoin

Alitretinoin related headaches:

Headaches are a common side effect of Alitretinoin and in many patients the dose adjustment is only temporarily necessary. Under these circumstances and according to standard practice, the dose of Alitretinoin can be reduced to 10mg/day. Participants taking a reduced dose of 10mg may increase their dose back to 30mg within a week. However, if this is not possible, 10mg can be maintained as a treating dose.

Alternatively, the dose may be temporarily ceased (i.e. dose interruption) for up to consecutive 7 days, at which point the participant should continue to take Alitretinoin. The greatest number of missed consecutive days will be recorded in addition to the number of missed days.

If adverse symptoms persist then Alitretinoin treatment may be withdrawn and the participant will continue with 'standard clinical practice' and will be followed-up as per the trial protocol.

Dose adjustments will be recorded on the relevant CRF.

Adverse reactions:
A temporary treatment interruption or dose reduction in Alitretinoin treatment may be required (managed at the discretion of the treating physician) under circumstances such as those described below:

- Abnormal cholesterol and triglyceride levels: Alitretinoin has been associated with an increase in plasma cholesterol and triglyceride levels. Serum cholesterol and triglycerides should be monitored. Please note that Alitretinoin should be discontinued if hypertriglyceridaemia cannot be controlled at an acceptable level or if symptoms of pancreatitis occur (see SmPC). Triglyceride levels in excess of 800mg/dL (9mmol/L) are sometimes associated with acute pancreatitis, which is a serious condition.
- Liver enzyme increase (alanine aminotransferase and/or aspartate aminotransferase > 2.5 times the upper limit of normal).

PUVA
As per standard practice, if there is a treatment interruption, PUVA should be recommenced (without dose increase) as per standard clinical practice and followed up as per the trial protocol. The maximum number of days between consecutive sessions will be recorded in addition to the number of missed sessions.

Alitretinoin and PUVA
Temporary cessation or discontinuation of treatment due to unexpected adverse events such as infection or unplanned surgery is at the discretion of the attending clinical team.

12.3 PRIOR AND CONCOMITANT TREATMENTS

All treatments being taken by the participants on entry to the trial or felt to be clinically indicated at any time during the trial in addition to the investigational medicinal product will be at the discretion of the treating physician as long as they are not contraindicated with the investigational medicinal products (please refer to the applicable SmPC). If contraindicated treatments are required for comorbid diseases, the treating physician will make a clinical decision on whether the participant will need to cease trial treatment.

The following concomitant treatments are <u>NOT</u> permitted during the interventional phase of the trial:

For all participants:

- Topical calcineurin antagonists
- Systemic corticosteroids for reasons other than hand eczema

For participants randomised to PUVA:

- Medication that may act as significant photosensitisers (e.g. tetracycline antibiotics).

For participants randomised to Alitretinoin:

- Systemic tetracycline antibiotics
- Other vitamin A derivatives.
- Other drugs with potential for drug-drug interaction (e.g. CYP3A4 inhibitor ketoconazole).

12.4 TREATMENT CESSATION

In line with standard clinical practice, cessation or alteration of regimens at any time will be at the discretion of attending clinicians or the participants themselves.
All participants who have been randomised will continue to be followed up to the end of the follow up phase (a maximum of 52 weeks post planned treatment start date) regardless of what treatment they have received, unless they withdraw consent for this (see section 12.5).

12.5 WITHDRAWAL OF CONSENT

By consenting to participate in the trial, participants are consenting to receive the randomised treatment (Alitretinoin or immersion PUVA), follow-up and data collection. Participants may withdraw consent from the trial at any time without explanation. If a participant explicitly states their wish to withdraw from the trial, CTRU should be informed by completion of the Withdrawal CRF. Participant withdrawal is categorised as follows:

a) Withdrawal of consent to the weekly text reminder service, but the participant is willing to continue randomised treatment (if applicable), and to be followed up according to the trial visit/ follow-up schedule and for further follow up information to be collected.
b) Withdrawal of consent for photographs to be taken as part of the trial, but the participant is willing to continue randomised treatment (if applicable), and to be followed up according to the trial visit/ follow-up schedule and for further follow up information to be collected.
c) Withdrawal of consent to the biomarker sub study, but the participant is willing to continue randomised treatment (if applicable), and to be followed up

according to the trial visit/ follow-up schedule and for further follow up information to be collected.

d) Withdrawal from further trial treatment, but the participant is willing to be followed up according to the trial visit/ follow-up schedule and for further follow up information to be collected.
e) Withdrawal of consent for further trial treatment (if not already completed treatment) and for the trial visit/ follow-up schedule, but the participant is willing to have any available follow-up information collected from healthcare records.
f) Withdrawal of consent for further trial treatment (if not already completed treatment) and for the trial visit/ follow-up schedule and for any further follow-up information to be collected.

For a), b), c) and d), trial follow up and data collection will continue for the duration of the trial, as if the participant remained on trial treatment. Completion of CRFs will continue as per the protocol schedule.

For e), only follow up data will continue to be collected on the CRFs if/ when it becomes available e.g. follow up data from standard clinic visits or the participant's medical records.

For f), no further follow up data will be collected past the point of withdrawal on participants who withdraw consent for trial treatment and further follow up data to be collected.

The PI or delegate should make every effort to ensure that the specific wishes of any participant who would like to withdraw consent for further involvement in the trial are defined and documented using the withdrawal CRF in order that the correct processes are followed by CTRU and site. Any outstanding data applicable to time points prior to withdrawal will continue to be requested from the trial site until it is received by CTRU. Data collected up to the point of withdrawal will be used as part of the final trial analysis. As this is a clinical trial of an investigational medicinal product (CTIMP), it should be made clear to any participant that data pertaining to safety will continue to be collected for regulatory reporting purposes even when the participant has withdrawn consent for further data collection and this data will be included in any safety analysis. In addition, it is suggested that the participant is made aware that if any significant new information becomes available with regards to the treatment they have received in the trial, it may be necessary to contact them in the future.

Participants who are willing to be followed up but do not receive or complete the allocated protocol treatment for a reason other than participant request, are **NOT** classed as withdrawals and will continue to be followed up. Details of any treatment will be recorded on the CRFs.

13. ASSESSMENTS AND DATA COLLECTION

All baseline and outcome measurements will be undertaken by a trained independent research nurse/clinician blinded to treatment allocation. Participants will be assessed by the blinded research nurse/clinician every 4 weeks for the first 36 weeks and then every 8 weeks to 52 weeks post planned start of treatment. Participants will also be assessed by the treating clinician (PGA) every 4 weeks for the first 36 weeks post planned start of treatment and then every 8 weeks to 52 weeks post planned start of treatment, to direct the treatment pathway. The assessment schedule is shown in section 13.2. In addition to the scheduled assessments, participants with unforeseen flare up events may be seen in clinics outside of their scheduled trial visits, where possible.

At each scheduled visit, clinical assessments will be conducted on both hands, however, at the baseline visit the research nurse/clinician will identify the participant's dominant hand and the hand which interferes with the participant's daily life the most - this information will be collected on the baseline CRF.

13.1 ASSESSMENTS, SAMPLES & DATA COLLECTION

Trial data will be recorded by site research staff and participants on paper CRFs. Participating sites will be expected to submit original paper CRFs to the CTRU at the University of Leeds and retain copies of all completed CRFs for the trial. Following receipt, the CTRU will contact trial sites to resolve any missing or discrepant data. Any outstanding CRFs will be chased by the CTRU until received or until the data is confirmed as unavailable.

It is the responsibility of each trial site to maintain a file of essential trial documentation (Investigator Site File), which will be provided by the CTRU, and to maintain their file of essential trial documentation on site during the trial and then at their designated archive facility.

Where central collection of reports is undertaken by the CTRU (i.e. for central monitoring purposes) it is the sites responsibility to obliterate all personal identifiable data prior to sending to the CTRU and use the Participant ID number plus date of birth and initials to identify the participant (plus any other required identifiers e.g. laboratory number).

Participants will be asked to complete a medication diary in order to monitor treatment compliance as well as topical corticosteroid use and will be required to bring the diary to each visit for review. Participants will be offered an optional text reminder service to aid diary completion. A single weekly text will be sent to remind patients to complete their medication diary.

13.2 SCHEDULE OF EVENTS

STUDY VISIT	1	2	3	4	5	6	7	8	9	10	11	12	13
WEEKS		Day 0*	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 44	Week 52
	Screening	Baseline	Interventional			Interventional/Follow-up (to be completed by all patients)			Follow-up (to be completed by all patients)				
STUDY VISIT WINDOW	**-≤12 weeks**		-2, +5 days	-2, +5 days	-2, +5 days	+/-7 days	+/-7 days	+/-7 days	+/-7 days	+/-7 days	+/-7 days	+/-7 days	+/-7 days
Eligibility screening log	X												
Informed Consent/ Shortened consent	X	X											
Registration	X												
Eligibility blood sample (haematology and blood chemistry)	X[1]												
IgE blood sample (to assess atopy)	X[2]												
Book PUVA appointment	X												
Start contraception prevention program (if applicable)	X[10]	X[11]											
Inclusion/exclusion criteria		X											
Medical history		X											
Height and Weight		X											
Clinical assessment (incl. HE phenotype)		X											
Urine pregnancy test (for WCBP only)[12]		X											
Record previous treatment for HE		X											
Gene Variant analysis blood sample		X[6]											
PeDeSI by treating clinician/unblinded nurse (pre randomisation at baseline)		X			X								X[9]
PGA by treating clinician		X	X	X	X	X	X	X	X	X	X	X	X
PGA by blinded assessor		X	X	X	X	X	X	X	X	X	X	X	X
HECSI by blinded assessor		X	X	X	X	X	X	X	X	X	X	X	X
mTLSS by blinded assessor		X			X			X			X		X
Nail assessment by blinded assessor (Bradford recruited participants only)		X	X	X	X	X	X	X	X	X	X	X	X
DLQI		X	X	X	X	X	X	X	X	X	X	X	X
PBI-HE		X			X			X			X		X
EQ-5D		X			X			X			X		X
Health resource utilisation questionnaire					X			X			X		X
Provide standard education for HE		X											
Randomisation		X											
Sub-study sample collection (tape stripping or washing) (for selected participants at selected centres only)		X[8]											
Photograph hands (for randomly selected participants only)		X			X								
Administration of randomised treatment[4]		X	X	X	X[3]	X[3]	X[3]	X[3]					
Notification of PUVA appointment (if randomised to PUVA)		X[7]	X	X	X[3]	X[3]	X[3]						
Dispense AL prescription (if randomised to Alitretinoin)		X	X	X	X[3]	X[3]	X[3]						
Issue medication diary		X	X	X	X	X	X	X	X	X	X[13]	X[13]	
Randomised treatment compliance (medication diary review)			X	X	X[3]	X[3]	X[3]	X[3]					
Topical corticosteroid usage (medication diary review)			X	X	X	X	X	X	X	X	X	X	X
Details of treatment under 'standard clinical practice'						X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]
Reportable Adverse reactions and Related SAEs/SARs/SUSARs			X	X	X	X	X	X	X	X	X	X	X

1 – Eligibility blood results/existing blood results must be within 12 weeks prior to baseline visit
2 – Only perform if IgE blood sample if appropriate results not available in participant's notes
3 – For partial responders only
4 – Randomised treatment administered according to the protocol
5 – Participants in follow up on Standard Practice (responders/non-responders to week 24, all participants to week 52)
6 – Blood sample to be obtained at baseline or as near as possible to baseline
7 – Cancel PUVA slot if participant randomised to AL
8 – Prior to start of randomised treatment
9 – Conduct at end of follow up if earlier than week 52
10 – All women of child bearing potential to use a reliable form of effective contraception, only if not currently doing so, for at least one month prior to randomisation
11- Alitretinoin participants to follow strict pregnancy program as per standard of care.
12 - Urine pregnancy test to be performed as per standard of care
13 – Issue 2 medication diaries to record required information prior to next visit
*Day 0 is the planned start of treatment from which all subsequent visits will be relative to

13.3 INFORMATION AND SCREENING VISIT

Following information provision, assenting patients will be screened for potential eligibility. The risk of pregnancy, concomitant therapies, relevant medical history and other eligibility criteria will be discussed with the patient and those who are potentially eligible will be asked to provide consent (either full consent for the trial, or shortened consent for blood sampling/contraception (if applicable) and further contact with the research team) and will be registered as potentially eligible for trial participation.

Where patients are assessed as clearly not eligible or eligible but not consenting at the screening visit, they will be recorded on the anonymous Non-Registered Patients log.

All participants will undergo screening within 12 weeks prior to baseline assessment unless otherwise indicated.

The following information will be recorded on the Registration CRF:

- Participant details, including initials, gender, ethnicity, date of birth, How the participant first heard about the trial Confirmation of date and type of written informed consent (full informed consent or shortened informed consent for blood sample and further contact)

The following procedures will be performed as part of the screening assessments:

- Eligibility blood sample will be taken for haematology (FBC), and blood chemistry (LFT (ALT), lipids, U+Es).
- Blood sample for specific IgE (serum) (e.g. positive inhalant mix) – to determine presence of atopy if above upper normal levels (not needed if already available in the participant's notes)

The attending research team member will record (for their local use only) the patient's name and contact details (including address, telephone and/or email, as preferred by the patient). These will be used to contact the patient with details of their blood sample result and to arrange the formal eligibility, baseline and randomisation visit.

For all patients, the PUVA treatment appointment must be booked at the screening visit – once a PUVA appointment date has been obtained, the baseline visit will be arranged with participant no earlier than 7 days prior to the PUVA appointment date (see section 11.4.2).

Where registered patients are assessed as clearly not eligible or eligible but not consenting (to the full consent) or withdrawing consent following the screening visit and will not be returning for a baseline visit, this information will be recorded on the Eligibility Checklist CRF as the reason for the participant not proceeding to be randomised into the study. The Eligibility Checklist CRF will then be returned to the CTRU.

13.4 BASELINE VISIT

The aim of this visit is to confirm that the participant is eligible for the study and to obtain full informed consent (if not obtained at the screening visit) and to undertake randomisation to investigational treatment. The baseline visit must be booked within 7 days of the first PUVA appointment, within 12 weeks of the eligibility blood sample and after at least 1 month duration of the contraception prevention program (if applicable).

Where registered patients who attend the baseline visit, are assessed as not eligible or eligible but not providing full consent, this information will be recorded on the Eligibility Checklist CRF as the reason for the participant not proceeding to be randomised into the study. The Eligibility Checklist CRF will then be returned to the CTRU.

The following information and procedures will be recorded and performed as part of the baseline assessments:

Please note, evaluations below marked with † should be performed by the same investigator during all visits throughout the study for each participant whenever possible to reduce potential investigator bias.

Baseline information and assessments will be recorded at the visit to confirm eligibility, prior to randomisation unless otherwise indicated:

- Full written informed consent for the study (if shortened consent taken at screening)
- Consent for sub study (at selected centres)
- Consent for photography
- Treating Clinician
- Mobile phone number for participants consenting to weekly text reminder service
- Relevant medical history – including inclusion/exclusion criteria and diseases, family history of relevant diseases, other eczema locations, previous treatments for HE (section 12.3) and exposure to irritants.
- Urine pregnancy test (for all WCBP)
- Date of HE diagnosis
- Smoking history (current or past; average number of cigarettes smoked per day)
- Height and Weight
- Dominant hand
- Hand which interferes with their daily life the most
- IgE results
- Visual assessment of HE clinical phenotype of the hands and assessment of potential foot involvement

- Physician Global Assessment (PGA) of HE disease activity by treating clinician.
- Physician Global Assessment (PGA), HECSI and mTLSS assessments of HE disease activity by blinded assessor.
- Nail assessment by blinded assessor (Bradford recruited participants only)
- PeDeSI by treating clinician/unblinded nurse
- Patient completed questionnaires (DLQI, PBI-HE, and EQ-5D)
- Gene Variant analysis blood sample**:** Blood should preferentially be taken at baseline (although also possible at any later visit) in order to obtain DNA for subsequent analysis for the filaggrin mutation and other skin barrier molecule polymorphisms (see section 13.15).
- Standard HE education advice

After recording the above data, randomisation* (see below) will take place and the following will subsequently be conducted/recorded, at the baseline visit:

- Sub-study sample acquisition (tape stripping or washing) in an identified subset of participants (see section 13.12)
- Photograph hands (see section 13.14) for randomly identified participants
- Investigational treatment allocation details (treatment allocated at randomisation and planned date of starting randomised treatment)
- Dispense Alitretinoin prescription (for participants randomised to Alitretinoin only)
- Participant medication diary issued

*Remember to cancel the PUVA appointment if the patient is randomised to Alitretinoin.

13.5 INTERVENTIONAL PHASE (0-12 WEEKS)

The following information/ assessments will be recorded at weeks 4, 8 and 12 post planned start of treatment assessment time points:

- Review of participant medication diary for HE topical corticosteroid usage by treating clinician/other clinician/research nurse, **but <u>NOT</u> the blinded assessor**.
- Review of participant medication diary and clinic records as applicable for randomised treatment compliance by the treating clinician/other clinician/research nurse, **but NOT the blinded assessor**
- Dispense Alitretinoin prescription (for participants randomised to Alitretinoin only)
- Adverse reactions (including SAEs) as described in section14.2

- Physician Global Assessment (PGA) (weeks 4, 8, 12) of HE disease activity and PeDeSI (week 12 only) by treating clinician (PeDeSI administration can be conducted by unblinded nurse)
- Physician Global Assessment (PGA) (weeks 4, 8 and 12), HECSI (week 4, 8 and 12) and mTLSS (week 12 only) assessments of HE disease activity by blinded assessor. †
- Nail assessment by blinded assessor (Bradford recruited participants only)
- Patient completed questionnaires (DLQI – weeks 4, 8 and 12)
- Patient completed questionnaires (PBI-HE, EQ5D and Health Resource Utilisation at week 12 only)
- Photography for randomly identified participants (at week 12 only)
- Reportable Adverse Reactions and Related SAEs/SARs/SUSARs. (Individual CRFs for Related SAEs/SARs/SUSARs must be returned to the CTRU within 24 hours of the research team becoming aware, please see section 14.0 for further details)

13.6 INTERVENTIONAL PHASE (12-24 WEEKS)

For participants who show a partial response (PGA mild/moderate) to randomised treatment at 12 weeks post planned start of treatment, the randomised treatment will continue to be administered for up to week 24 post planned start of treatment date. The following information/ assessments will be recorded at weeks 16, 20 and 24 post planned start of treatment assessment time points:

- Review of participant medication diary and clinic records as applicable for HE topical corticosteroid usage and randomised treatment compliance by treating clinician/other clinician/research nurse for CRF completion (**must NOT be reviewed by the blinded assessor**)
- Dispense Alitretinoin prescription (for participants randomised to Alitretinoin only)
- Adverse reactions (including SAEs) as described in section14.2
- Physician Global Assessment (PGA) (week 16, 20 and 24) of HE disease activity by treating clinician
- Physician Global Assessment (PGA) (week 16, 20 and 24), HECSI (week 16, 20 and 24) and mTLSS assessments (week 24 only) of HE disease activity by blinded assessor †
- Nail assessment by blinded assessor (Bradford recruited participants only)
- Patient completed questionnaires (DLQI - weeks 16, 20 and 24)
- Patient completed questionnaires (PBI-HE, EQ5D and Health Resource Utilisation at week 24 only)
- Reportable Adverse reactions and Related SAEs/SARs/SUSARs. (Individual CRFs for Related SAEs/SARs/SUSARs must be returned to the CTRU within 24 hours of the research team becoming aware, please see section 14.0 for further details)

13.7 FOLLOW UP (12-24 WEEKS)

For participants who have been assessed as responders (PGA clear/almost clear, with regular emollient use and a maximum of twice weekly (once a day) topical corticosteroid), and non-responders (PGA severe) at 12 weeks post planned start of treatment (to whom treatment according to 'standard local clinical practice' will apply), the following information/assessments will be recorded at weeks 16, 20 and 24 post planned start of treatment assessment time points:

- Details of HE treatments received
- Review of participant medication diary for HE topical corticosteroid usage compliance by treating clinician/other clinician/research nurse for CRF completion (**must NOT be reviewed by the blinded assessor**)
- Adverse reactions (including SAEs) as described in section14.2
- Physician Global Assessment (PGA) (week 16, 20 and 24) of HE disease activity by treating clinician
- Physician Global Assessment (PGA) (weeks 16, 20 and 24), HECSI (week 16, 20 and 24) and mTLSS (week 24 only) assessments of HE disease activity by blinded assessor
- Nail assessment by blinded assessor (Bradford recruited participants only)
- Patient completed questionnaires (DLQI – week 16, 20, 24)
- Patient completed questionnaires (PBI-HE, EQ5D and Health Resource Utilisation at week 24 only)
- Reportable Adverse reactions and Related SAEs/SARs/SUSARs. (Individual CRFs for Related SAEs/SARs/SUSARs must be returned to the CTRU within 24 hours of the research team becoming aware, please see section 14.0 for further details)

13.8 FOLLOW UP (28-52 WEEKS)

It is important that the blinded assessor remain blind to HE treatment other than topical treatment. The following information/assessments will be recorded at week 28, 32, 36, 44 and 52 post planned start of treatment assessment time points:

- Details of HE treatments received
- Review of participant medication diary for HE topical corticosteroid usage for CRF completion
- Adverse reactions (including SAEs) as described in section14.2
- Physician Global Assessment (PGA) (week 28, 32, 36, 44, 52) of HE disease activity and PeDeSI (week 52 only or at end of follow up period if earlier than week 52) by treating clinician (PeDeSI administration can be conducted by unblinded nurse)

- Physician Global Assessment (PGA) (week 28, 32, 36, 44, 52), HECSI (week 28, 32, 36, 44 and 52) and mTLSS (week 36 and 52 only) assessments of HE disease activity by blinded assessor †
- Nail assessment by blinded assessor (Bradford recruited participants only)
- Patient completed questionnaires (DLQI – week 28, 32, 36, 44, 52)
- Patient completed questionnaires (PBI-HE, EQ5D and Health Resource Utilisation at week 36 and 52 only)
- Reportable Adverse reactions and Related SAEs/SARs/SUSARs (Individual CRFs for Related SAEs/SARs/SUSARs must be returned to the CTRU within 24 hours of the research team becoming aware, please see section 14.0 for further details).

Blood tests for monitoring treatment safety and pregnancy tests (for participants randomised to Alitretinoin) throughout the study are the responsibility of the treating clinician and will be performed according to standard clinical practice.

13.9 CLINICIAN COMPLETED QUESTIONNAIRES

The **Hand Eczema Severity Index (HECSI)** [21] is a validated scoring system which resembles the clinically well-established Psoriasis area severity index (PASI) score and takes disease extent into account. Disease extent is an important prognostic factor for HE [22]. The HESCI scoring system, performed as an overall assessment of the hands (not of individual hands), divides the hands into 5 locations:

1. Fingertips
2. Fingers (except the tips)
3. Palm of hand
4. Back of hands
5. Wrists

At each location the intensity and extent of the following symptoms is scored:
1. Erythema
2. Infiltration/papulation
3. Vesicles
4. Fissuring
5. Scaling
6. Oedema

Intensity is graded according to the following scale:
0 = no skin changes; 1 = mild disease; 2 = moderate and 3 = severe

Extent is quantified by giving the affected area a score from 0 – 4, where
0 = 0%; 1 = 1–25%; 2 = 26–50%; 3 = 51–75% and 4 =76–100% for the extent of clinical symptoms at a given location.

The HECSI score is then calculated by multiplying the extent at each location by the total sum of the intensity score of each clinical symptom, to give a HECSI score from 0 to a maximum severity score of 360 points across both hands combined.

HECSI allows assessment of overall disease activity and accurate extent of disease and is used as an outcome measure for assessing relapse (see section 16.2).

The **Physician's Global Assessment (PGA)** [23] will be used in line with NICE guidelines to determine the HE severity and eligibility of patients for the study. The PGA has been used in all HE studies involving Alitretinoin. The PGA shows weakness regarding "extent of the disease" and is limited to a 5 step score (clear, almost clear, mild, moderate, severe). This score is thus not optimal to quantify and assess exact disease activity, in particular extent of the disease.

The PGA will be performed by the treating physician (not blinded) to assess the most affected side of the most affected hand to direct treatment pathway. The PGA will also be performed by the independent blinded assessor across the fingertips, palm and back of each hand to allow comparison with mTLSS and HECSI. A good correlation between PGA and mTLSS [12] as well as PGA and HECSI [24] has recently been reported.

Table 1. PGA assessment of disease severity

PGA Severity	Features	Intensity	Area Involved
Severe (NICE eligibility criterion)	**Erythema, Scaling, Hyperkeratosis/Lichenification**	**At least one moderate or severe**	**>30% of affected hand surface**
	Vesiculation, Oedema, Fissures, Pruritus/Pain	**At least one severe**	
Moderate	Erythema, Scaling, Hyperkeratosis/Lichenification	At least one mild or moderate	10%-30% of affected hand surface
	Vesiculation, Oedema, Fissures, Pruritus/Pain	At least one moderate	
Mild	Erythema, Scaling, Hyperkeratosis/Lichenification	At least one mild	Less than 10% of affected hand surface
	Vesiculation, Oedema, Fissures, Pruritus/Pain	At least one mild	
Almost clear (NICE stopping criterion)	**Erythema, Scaling, Hyperkeratosis/Lichenification**	**At least one mild**	**Less than 10% of affected hand surface**
	Vesiculation, Oedema, Fissures, Pruritus/Pain	**Absent**	
Clear (NICE stopping criterion)	**Erythema, Scaling, Hyperkeratosis/Lichenification**	**Absent**	**Not detectable**
	Vesiculation, Oedema, Fissures, Pruritus/Pain	**Absent**	

The **modified Total Lesion Symptom Score (mTLSS)** [23] has been used widely in the past and will be used in this study for reasons of comparability to previous studies on HE. Similar to the HECSI, the mTLSS considers eczema related symptoms. In

mTLSS scoring, disease is defined by the following symptoms; erythema, scaling, lichenification/hyperkeratosis, vesiculation, oedema, fissures and pruritus/pain. Each symptom is given a symptom specific score of between 0-3, where 0 means absence of symptom. However, mTLSS has not been chosen as the primary outcome measures due to weakness in relation to determination of extent. In addition, it has been criticised for being a composite of clinical signs (eczema symptoms determined by the physician) and "subjective" (pruritus, pain as determined by the patient) symptoms, which may cause an individual bias by overestimation of self-reports [20]. The mTLSS will also be performed by the independent blinded assessor across the fingertips, palm and back of each hand to allow comparison with the PGA and HECSI

Person-Centred Dermatology Self Care Index (PeDeSI) [10]. The PeDeSI is a validated 10 item questionnaire that measures the education and support needs of people with long-term skin conditions [33]. It is completed in collaboration between patient and practitioner/unblinded nurse and is quick and simple to use in practice. Each item has a score range of 0-3 and total scores indicate: 0 - 10 needs intensive education and support to develop knowledge, ability and confidence, 11 - 20 needs some education and support to develop knowledge, ability and confidence; 21 – 29 needs limited education and support to develop knowledge, ability and confidence; 30 has sufficient knowledge, ability and confidence to manage on their own.

13.10 PARTICIPANT COMPLETED QUESTIONNAIRES

This section details the **quality of life (QoL)** questionnaires that will be completed by participants. The timing of these questionnaires is detailed in section 13.2 – 13.8.

The **Dermatology Quality of Life Index (DLQI)** is a validated patient reported outcome measure of the effect of skin disease on a patient's daily activities [28] and is widely used [29]. The DLQI has a simple method of score interpretation: no impact (0-1), small impact (2-5), moderate impact (6-10), very severe impact (11-20) and extremely severe impact (21-30) [30]. The DLQI has been used in most large HE studies and is used in the definition of severe CHE.

Patient Benefit Index for chronic hand eczema (PBI-HE) [9]**.** The PBI [31] was developed based on the finding that the physician's perspective only partly corresponds with the patient's perspective when it comes to benefit measurements [32] . The validated PBI questionnaire has been developed specifically for the purpose of evaluating patient-defined benefits in dermatology treatment and the PBI-HE is a disease-specific patient reported tool for HE.

The PBI-HE is divided into two parts:
(1) The 'Patient Needs Questionnaire' (PNQ) is completed by the patient before therapy. It contains 27 standardized items on the patient's needs such as 'to no longer experience itching' and 'to be able to lead a normal everyday life'. The patient rates the

importance of each need on a 5-step Likert scale ranging from 0 = ‘not at all important’ to 4 = ‘very important’.
(2) The ‘Patient Benefit Questionnaire’ (PBQ) is filled in by the patient during or after therapy. It consists of the same items as the PNQ, but the instruction differs: the patient rates the extent to which the treatment needs have been fulfilled by therapy on a Likert scale ranging from 0 = ‘treatment didn’t help at all’ to 4 = ‘treatment helped a lot’.
The PBI score is then calculated from the importance of needs before therapy (rated in the PNQ) and the achievement of these needs (rated in the PBQ). The PBI ranges from 0 (no benefit) to 4 (maximal benefit).

All participants should complete the quality of life (QoL) questionnaires in clinic. An authorised member of the trial team will check that the forms have been completed fully and will be able to provide clarification only if requested by the participant. They will be trained to avoid directing patients in their responses.

It is acknowledged that on occasion, due to the nature of their condition, participants may be unable to or find it uncomfortable to hold a pen. In such circumstances, research staff are permitted to ask the participants the questions on the questionnaires and complete the questionnaires on the participants’ behalf. In the case of the Visual Analogue Scale in the EuroQoL-five dimensions (EQ-5D-3L) questionnaire (see below), participants should be asked to provide the research staff with a numerical value of between 0-100. The research staff should measure and complete the corresponding VAS accordingly. Site staff should contact CTRU whenever this is the case to ensure CTRU are aware.

13.11 HEALTH RESOURCE UTILISATION QUESTIONNAIRES

EQ-5D-3L questionnaire: The study will include the use of the EQ-5D questionnaire [26] for health economic evaluation (section 15). The EQ-5D is a generic instrument (www.euroqol.org) and forms part of the NICE reference case for cost per Quality Adjusted Life Years (QALY) analysis.

Health Resource Utilisation and Private Costs questionnaire will measure patient’s reported health care use, days off work and private costs due to HE using a bespoke short self-reported schedule adapted from forms already developed at the University of Leeds. Healthcare use includes the number of contacts with clinical staff (occupational health, primary care staff, dermatologists, etc) and medications as a result of HE.

13.12 BIOMARKER SUB STUDY

A subset of 100 participants recruited from selected centres will be asked to provide written informed consent to this optional sub study (see section 8.2) to consent to the following procedures, which will be collected prior to the start of the randomised treatment:

- **Tape stripping technique** involves an adhesive to bind and remove the top epidermal layers. This approach has been used as a non-invasive technique for direct sampling of skin [17, 18]. Tape stripping is generally rapid, and patient-friendly. For detailed instructions please refer to the biomarker sub study work instruction. Tape strips will be submersed in buffer solution and stored at site at -80^{o}C prior to sending to Dr Miriam Wittmann's laboratory (Section of Musculoskeletal Disease, Leeds Institute of Molecular Medicine, Wellcome Trust Brenner Building, St. James's University Hospital, Leeds).

- **Skin washing:** Where tape stripping is not possible due to acute inflammation, mediator content can be measured in skin washing fluids [47]. For detailed instructions please refer to the biomarker sub study work instruction. Buffer scrubs (washing fluid) will be stored at site at -80^{o}C prior to sending to Dr Miriam Wittmann's laboratory (Section of Musculoskeletal Disease, Leeds Institute of Molecular Medicine, Wellcome Trust Brenner Building, St. James's University Hospital, Leeds, UK).

13.13 NAIL ASSESSMENT SUB STUDY

Clinical observational descriptive assessments of the nails from participants recruited only from St Luke's hospital, Bradford will involve a simple method of scoring based on 0 (none), 1 (mild), 2 (moderate) and 3 (severe) for each of the following criteria: pits, ridges and plate thickening. Measurements will be collected by the independent blinded assessor prior to the start of the randomised treatment, and at each follow up visit for the duration of the trial.

13.14 PHOTOGRAPHY

In accordance with standard practice in HE studies [23, 6, and 25]; photographs will be taken at baseline if the participants have been identified during the randomisation phone call and whilst participants remain in clinic as well as at the week 12 visit using cameras supplied by the CTRU. Clinical photography will follow standard guidelines on patient's consent, data collection and storage. Standardisation of photographs will be in place across centres (e.g. distance, background colour, colour calibration procedures).

Photographs will serve as a quality control check for the inclusion criteria on severity of disease activity. CTRU will randomly identify 20% of consenting Caucasian participants and all consenting participants of non-Caucasian ethnicity for photographic assessment.

A standard study camera will be supplied to each site together with a work instruction detailing the use of a standardised photographic method including the use of calibration strips for colour measurement. For the purposes of consistency and interpretation of photographic data, it is imperative that only the study camera supplied is used to take photographs. In addition, the work instruction will provide clear

instructions on the anonymisation, secure transfer and deletion of the photographs (that is, there will be no local storage of photographs on the camera or National Health Service (NHS) computer). Central blinded review of the photographs will be undertaken by expert clinical dermatology specialists on the Trial Management Group (TMG).

Outwith the trial, consent will be sought from participants for the use of photographs for teaching or future research/publications purposes.

13.15 SKIN BARRIER MOLECULE POLYMORPHISMS

A blood sample will be collected at baseline from all participants for the purposes of DNA extraction and skin barrier molecule polymorphisms (including filaggrin mutational analysis). These samples will be anonymised and sent to Professor Ann Morgan's Molecular Rheumatology laboratory (Leeds Institute of Rheumatic and Musculoskeletal Medicine, Wellcome Trust Brenner Building, St. James's University Hospital, Leeds, UK) for DNA extraction.

For blood samples that have been damaged or classed as unusable during transit to the laboratory, the CTRU will contact research sites to request a replacement sample is obtained, if possible, from the participant at the next trial visit.

A proportion of extracted DNA will be sent to Professor Stephan Weidinger's laboratory (Department of Dermatology, University Hospital Schleswig-Holstein, Kiel, Germany) for assessment of skin barrier molecule polymorphisms (including filaggrin loss-of-function mutation). The remainder of the extracted DNA will be placed in long term storage (under suitable conditions) in the laboratory of Anne Morgan (Section of Musculoskeletal Disease, Leeds Institute of Molecular Medicine, Wellcome Trust Brenner Building, St James Hospital, Leeds UK) for potential future research. For example, there is evidence linking PUVA treatment and mutations in the vitamin D receptor and this sample set will provide an invaluable resource to delineate any causal link.

13.16 PREGNANCIES

Pregnancies occurring in participants randomised to Alitretinoin from the start of randomised treatment until after the last dose of trial treatment, represent a safety issue (refer to AL SmPC for time recommendations after the last dose) and must be prevented as effectively as possible.

All protocol treatment must be stopped immediately if a pregnancy occurs or is suspected in a participant taking Alitretinoin and must be reported to the CTRU (See section 14.5.1). Participants withdrawn from treatment will still attend for follow-up assessments unless unwilling to do so and CRFs will continue to be collected. Pregnant participants should be referred to an obstetrician/gynaecologist experienced in reproductive toxicity for further

evaluation and counselling. The pregnancy will be followed up until final outcome (termination, abortion, still birth, live birth (Healthy, congenital anomaly/birth defect)).

13.17 DEATHS

All deaths occurring during the trial must be recorded on the Notification of Death CRF and reported to the CTRU **within 24 hours** of the research team becoming aware of the event.

In addition, any deaths occurring during the trial and believed to be related to trial treatment or hand eczema should also be recorded using the SAE/SUSAR CRF and reported to the CTRU **within 24 hours** of the research team becoming aware of the event (see Sections 14.1 and 14.3).

13.18 DEFINITION OF END OF TRIAL

The end of the trial is defined as the date of receipt of the last participant's last data item.

14. PHARMACOVIGILANCE

14.1 GENERAL DEFINITIONS

'Adverse Event' (AE) – any untoward medical occurrence in a patient or clinical trial subject administered a medicinal (investigational or non-investigational) product and which does not necessarily have a causal relationship with this treatment and can include;

- any unintentional, unfavourable clinical sign (including an abnormal finding) or symptom
- any new illness or disease or the deterioration of existing disease or illness
- any clinically relevant deterioration in any laboratory assessments or clinical tests.

'**Adverse Reaction' (AR)** – all untoward and unintended responses to an investigational medicinal product related to any dose administered. This definition implies a reasonable possibility of a causal relationship which is supported by facts, evidence or arguments to suggest a causal relationship. This definition includes medication errors and uses outside what is foreseen in the protocol (i.e. if an AR occurs as a result of a medication error).

'Serious Adverse Event' (SAE) – any untoward medical occurrence or effect that at any dose:
- results in death,
- is life-threatening,
- requires hospitalisation or prolongation of existing hospitalisation,

- results in persistent or significant disability or incapacity,
- is a congenital anomaly or birth defect,
- other important medical event.

These characteristics/consequences have to be considered at the time of the event. For example, regarding a life-threatening event, this refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Medical and scientific judgement must be exercised in deciding whether an event is 'serious' in accordance with these criteria.

'Serious Adverse Reaction' (SAR) – Where an SAE is deemed to have been related to an IMP used within the trial the event is termed as a Serious Adverse Reaction (SAR). Reference is made to the criterion of 'Seriousness' above in relation to SAE. (Any suspected transmission via a medicinal product of an infectious agent is also considered a SAR.)

'Suspected Unexpected Serious Adverse Reaction' (SUSAR) – means an adverse reaction, the nature and severity of which is not consistent with the applicable product information:
- In the case of a product with a marketing authorisation, in the summary of product characteristics for that product,
- In the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.
Severity describes the intensity of the event.

Medical and scientific judgement must be exercised in deciding whether an event is serious (see protocol section 14.6 for Responsibilities). These characteristics / consequences must be considered at the time of the event and do not refer to an event which hypothetically may have caused one of the above.

14.2 OPERATIONAL DEFINITIONS

This is a randomised controlled trial using well established medicinal products with well-known safety profiles. In recognition of this, events fulfilling the definition of an adverse event or serious adverse event will not be reported in this study unless they are defined as

1. Expected and related to trial treatment (see 14.2.2 below)

2. Related to hand eczema and classified as an SAE (section 14.2.4).

3. Related to trial treatment and classified as a SAR or SUSAR (section 14.2.4).

For example hospital admission for any co-morbidity not related to chronic hand eczema **will not be reported**, but a hospital admission due to severe infection of hand eczema or a serious reaction to the trial treatment would be reported.

It is important to note that in this study a participant may receive their randomised treatment for between 12 and 24 weeks. Once the randomised treatment has been stopped there is the possibility that a participant's disease deteriorates and therefore as part of standard clinical care the participant may go back on to the randomised treatment they previously received or the alternative randomised treatment. To accommodate this patient pathway expected ARs/related SAEs/SARs/SUSARs will continue to be reported until the end of follow-up i.e. 52 weeks.

14.2.1 EXPECTED AEs/ARs – NOT REPORTABLE

The following adverse events/reactions (not meeting the criteria of Serious) are known to be related to the randomised treatments and are expected in this study population and **will not be reported**:

Alitretinoin

- Headaches
- Dry skin on regions of the body other than the hands.

PUVA

- Erythema (mild to moderate)
- Itching of skin in PUVA treated skin locations.

14.2.2 EXPECTED ARs – STANDARD REPORTING

The following ARs are expected within the patient study population and will be reported from randomisation to end of follow-up on standard CRFs:

Alitretinoin

- Depressive mood swings

PUVA

- UV burn (including erythema (graded as severe), soreness and blistering) to the hands.
- Polymorphic light eruption
- PUVA pain*/PUVA itch**.

Please note:

*PUVA pain is characterized by a persistent, severe, prickling or burning pain easily differentiated from itching. Episodes of pain may last from 15 min to several hours, and can occur spontaneously or following scratching or pressure to the skin. Severe skin pain is an **uncommon** complication of PUVA therapy and the mechanism of PUVA-induced skin pain is unclear.

**PUVA itch refers to itch/pruritis, which is different from the “eczema” itch in terms of onset and severity, which often presents after in the second or third week of PUVA treatment.

As these ARs are expected within the study population they will not be subject to expedited reporting to the main REC and MHRA. They will however, be included in the annual safety report provided to the main REC.

14.2.3 UNEXPECTED SAEs – NOT REPORTABLE

Events fulfilling the definition of serious adverse event will not be reported in this study if they are **not related** to hand eczema or trial treatment. For example hospital admission for other co-morbid diseases **will not be reported.**

14.2.4 RELATED SAEs/SARs/SUSARs – EXPEDITED REPORTING

All SAEs/SARs/SUSARs which are related to hand eczema or trial treatment which occur from the time of first dose of randomised treatment to end of follow up must be recorded on the relevant Serious Adverse Event Form/Suspected Unexpected Serious Adverse Reaction Form and faxed to the CTRU within 24 hours of the site becoming aware of the event. Once the event has been resolved, the original form should also be posted to the CTRU, and a copy retained on site. Please ensure that each separate event is reported on a separate SAE/SUSAR CRF and not combined into one form.

During follow up, following completion of the randomised treatment, if the participant goes on to receive either of the randomised treatments then any SAEs/SUSARs related to either trial treatment should be reported as above until the end of follow-up i.e. 52 weeks.

For each related SAE/SARSUSAR the following information will be collected:

- full details in medical terms with a diagnosis, if possible
- its duration (start and end dates if applicable)
- action taken
- outcome
- causality (i.e. relatedness to randomised treatment), in the opinion of the investigator
- whether the event would be considered expected or unexpected

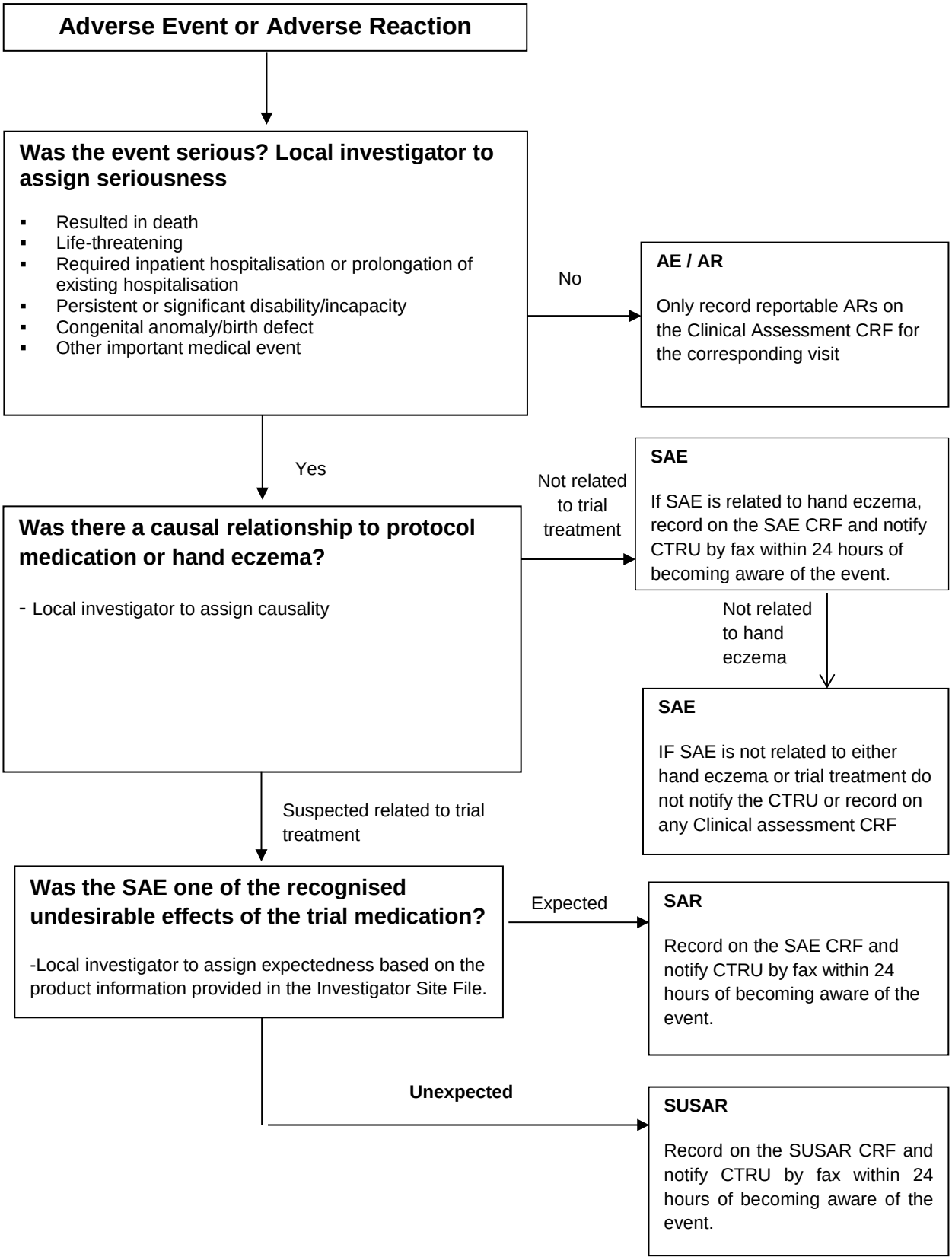
When determining whether an SAR is expected or not, please refer to the current version of the SmPC or Suppliers Fact Sheet for the trial IMPs supplied in the Investigator Site File (ISF).

Any change of condition or follow-up information should be faxed to the CTRU as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

All SARs assigned by the PI or delegate as both suspected to be related to the IMP-treatment and unexpected will be classified as SUSARs and will be subject to expedited reporting to the Medicines and Healthcare products Regulatory Authority (MHRA). The CTRU will inform the MHRA, the Sponsor and the main ethics within the required expedited reporting timescales i.e. 7 days.

Fax Number for reporting SAEs, SARs and SUSARs:
0113 343 1737

14.3. OVERVIEW OF THE SAFETY REPORTING PROCESSES



14.4 OTHER SAFETY ISSUES REQUIRING EXPEDITED REPORTING

14.4.1 PREGNANCY

All participant pregnancies with the estimated due date and participant suspected pregnancies must be recorded on the Notification of Pregnancy CRF and reported immediately to the CTRU by faxing. Where a pregnancy is known, this should be followed up until final outcome. The requirement for the initial reporting of pregnancies is from the time of start of protocol treatment until the end of the follow up phase of the study at a maximum of week 52. Any pregnancy resulting in a congenital anomaly or birth defect suspected related to randomised treatment should be reported as a SAR (see section 14.2.4).

14.5 RESPONSIBILITIES

PI / Authorised individual:

- Checking for AEs and SAEs during the treatment phase.
- Using medical judgement in assigning:
  - Seriousness
  - Relatedness
  - Expectedness
- Using the SmPC/Suppliers Fact Sheet for each interventional treatment:
  - To ensure all SAEs/SARs/SUSARs are recorded and reported to the CTRU within 24 hours of becoming aware and to provide further follow up information as soon as available. Ensuring that SAEs/SARs/SUSARs are chased with CTRU if a record of receipt is not received within 2 working days of initial reporting.
  - To report SAEs/SUSARs to local committees in line with local arrangements.
  - To ensure that ARs are recorded and reported to the CTRU in line with the requirements of the protocol.

Chief Investigator / delegate or independent clinical reviewer:

- Clinical oversight of the safety of trial participants, including an ongoing review of the risk / benefit.
- Using medical judgment in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.
- Immediate review of all SUSARs.
- Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
- Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs.
- Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).

CTRU:

- Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk/benefit according to the Trial Monitoring Plan.
- Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring & Ethics Committee (DMEC) and/or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
- Expedited reporting of SUSARs to the Competent Authority (MHRA in UK), main REC and Sponsor within required timelines.
- Notifying Investigators of SUSARs that occur within the trial.
- Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial.
  Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and main REC.

TSC:

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMEC regarding safety issues.

DMEC:

In accordance with the Trial Terms of Reference for the DMEC, periodically reviewing unblinded overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

15. ECONOMIC EVALUATION

The economic evaluation will estimate the incremental cost-effectiveness of Alitretinoin compared to PUVA in the management of severe chronic HE.
Two sets of economic evaluation will be undertaken:

- A within-trial analysis comparing the outcomes and costs up to 52 weeks follow-up using trial data.
- A long-term cost effectiveness analysis modelling outcomes and costs up to 10 years. The time horizon in the base-case analysis is 10 years as previous work demonstrated that the incremental cost effectiveness ratio (ICER) were likely to change marginally on higher time horizon (Paulden et al. 2009); an analytic 10-year horizon therefore appeared long enough to capture all the main costs and benefits of the treatment.

The evaluation will follow the reference case guidance for technology appraisals set out by NICE (NICE 2013).

15.1 MEASUREMENT OF OUTCOMES

The economic analysis will use quality-adjusted life-years (QALYs) to measure health outcomes. Health related quality of life will be estimated using responses from the EQ-5D-3L (EuroQol) [46] obtained from participants at baseline, at weeks 12, 24, 36 and 52 after randomisation as secondary outcomes of the trial. The standard UK tariff values will be applied to these responses at each time point to obtain utility. QALYs will be calculated as an “area under the curve” and form the main outcome measure of the within-trial analysis. A further analysis will use utility values obtained from the mapping of DLQI values to EQ-5D using algorithms already available [48]. A 3.5% discount rate will be used in the cost-effectiveness modelling, as per the NICE Methods Guide [46].

15.2 MEASUREMENT OF COSTS

The analyses will initially take the perspective of the UK NHS and Personal Social Services (PSS) perspective including costs incurred to the NHS in the provision of the treatment and other health care resource utilisation including medications over the trial follow-up, and a subsequent analysis will adopt a societal perspective and consider the out-of-pocket expenses including productivity costs to the participants.

NHS and PSS resource use will be collected through the health care resource utilisation questionnaire. The questionnaire will be administrated at weeks 12, 24, 36 and 52. Healthcare utilisation will be combined with appropriate unit cost information. Wherever possible, unit costs for resources will be obtained from national sources such as the British National Formulary and the PSS Research Unit Costs of Health and Social Care [49]. If national costs are not available we will consult with the finance departments of trusts recruiting patients to the trial to identify the mean unit cost.

These will be added to the treatment costs as identified through direct observation of the treatment provided within the study. Societal costs will be calculated by adding healthcare costs to the costs of lost production, based on days off work combined with wage rates and other reported private costs. A 3.5% discount rate will be used in the cost-effectiveness modelling, as per the NICE Methods Guide [51].

15.3 WITHIN-TRIAL ANALYSIS

The within-trial analysis aims to determine the intervention(s) that would maximise health outcomes both (1) within the NHS budget, and (2) within a societal perspective over the 52 weeks trial follow-up.

It will adopt an intention-to-treat (ITT) perspective and consists of a cost-effectiveness (cost-utility) analysis using an ICER which is calculated as the difference between the mean costs and difference in mean QALYs in each treatment.
We will use the NICE implicit cost per QALY threshold λ of £20,000 per QALY to determine cost-effectiveness. The more expensive intervention will be considered cost-effective so long as its ICER is within or below λ= £20,000 per QALY.

Uncertainty – Parameter uncertainty will be explored using probabilistic sensitivity analysis. The within-trial analysis will use the non-parametric bootstrap method to generate simulations of the mean costs and effects for each arm of the trial. The results of the analysis will be presented as the expected incremental cost-effectiveness of AL compared to PUVA. The results of the model will be presented as expected incremental cost effectiveness ratios and cost-effectiveness acceptability curves.

Net monetary benefit (NMB) will be calculated for each bootstrap estimates for a range of ceiling ratios λ as follows: NMB= (λ*QALYs) – Costs
The intervention with NMB>0 or with the highest NMB should be adopted taking into account an agency's willingness to pay threshold.
Mean net benefits will be reported with 95% bootstrap confidence intervals calculated using the bias-corrected method [50].

15.4 DECISION ANALYSIS MODELLING

We would use decision analytic modelling to compare Alitretinoin and PUVA in the management of severe chronic HE over a longer time frame. We will use a 10 year Markov decision model supplementing the within-trial results with findings from the literature to estimate the long term effectiveness of the treatment.

As far as possible parameters in the model will be specified using data collected within the trial. Other parameters, such as the long term 'natural history' will be parameterised using the published literature, and where necessary formally elicited expert opinion. The outcome measure for these analyses will be the QALY. The utility weights will be calculated using the EQ-5D data collected within the trial. Costs and outcomes will be discounted as per recommended good practice. One analysis will be conducted from the perspective of the NHS and Personal Social Services. A second analysis will be conducted from a societal perspective and take account of out-of-pocket expenses, productivity costs.

Parameter uncertainty will be addressed through probabilistic sensitivity analysis using Monte Carlo simulation. The outputs of the analysis will be presented as the expected ICER of Alitretinoin compared to PUVA, a scatter plot on the cost effectiveness plane and a cost effectiveness acceptability curve. We will also calculate the expected net benefit of AL for a range of values of lambda. The decision analytic cost effectiveness model will then be used to estimate the value of further research and identify those parameters for which further research would have the greatest value

Deterministic one-way sensitivity analysis will be performed to check the results over a plausible range of prior distributions placed on the time-varying model parameters. Multi-way deterministic sensitivity analyses will be undertaken by modelling optimistic ('best case') and pessimistic ('worse case') scenarios [51]. In addition, the time horizon of the model will be explored further in the sensitivity analysis and be extended up to 20 years.

16. ENDPOINTS

16.1 PRIMARY ENDPOINT

- Log (HECSI score) at 12 weeks post planned start of treatment.

16.2 KEY SECONDARY ENDPOINTS

- Log(HECSI score) over the 52 weeks post planned start of treatment
- mTLSS of the index hand and overall over the 52 weeks post planned start of treatment
- PGA of the index hand and overall at over the 52 weeks post planned start of treatment
- Time to relapse (HECSI score >75% baseline HECSI score of the index hand)
- DLQI over the 52 weeks post planned start of treatment
- PBI-HE over the 52 weeks post planned start of treatment
- PeDeSi over the 52 weeks post planned start of treatment
- Cost-effectiveness over the 52 weeks post planned start of treatment
- AEs and SAEs reported throughout the reporting period

For the purposes of secondary analysis the index hand will be used in addition to overall. The index hand is defined as the worst affected hand based on the hand which interferes with their daily life the most.

17. STATISTICAL CONSIDERATIONS

17.1 SAMPLE SIZE

A minimum of 500 and maximum of 780 participants are required to detect a relative difference of 1.3 (clinical opinion) in HECSI score between treatment arms at 12 weeks post planned start of treatment (80% power; 2-sided 5% significance level) assuming a coefficient of variation (CV) between 1.175 and 1.7 and allowing for 20% attrition. A sample size review will be carried out after 364 participants (precision of -0.132 and +0.168 assuming CV=1.2) have reached 12 weeks post planned start of treatment, to revise the CV and the final sample size.

17.2 PLANNED RECRUITMENT RATE

We estimate that we will need to screen 3200 patients of whom we expect 50% will be eligible and 50% of those eligible will consent. It is estimated that each centre will recruit 1-2 patients per month in order to recruit the maximum target of 780 participants within the 24 months period. Study sites will be supported by the Clinical Research Network (CRN).

In addition an internal pilot phase has been planned to inform on the feasibility of recruitment such that if the number of centres set-up and recruiting is at least 12 and

the overall number of participants recruited to the study is at least 63 at 6 months then it will be considered feasible to continue with the study. The decision to continue the trial will remain with the funder in the event the target is not met.

18. STATISTICAL ANALYSIS

18.1 GENERAL CONSIDERATIONS

Statistical analysis is the responsibility of the CTRU statistician. A full statistical analysis plan will be finalised and signed off before any data analyses are conducted.

The primary analysis will be on an intention-to-treat (ITT) basis where participants will be analysed according to treatment group randomised to receive. A per-protocol (PP) population will also be defined, which will include all eligible randomised participants according to treatment allocation received but will exclude major protocol violators. The PP population will be defined in agreement with the Data Monitoring and Ethics Committee (DMEC) and the Trial Steering Committee (TSC) members. Results from both the ITT and the PP analyses will be presented.

For analyses of the HECSI, PGA and mTLSS the assessments made by the blinded assessor will be used.

18.2 FREQUENCY OF ANALYSIS

Statistical monitoring of safety data will be conducted throughout the trial and reported at agreed intervals to the DMEC. One formal, blinded, interim analysis to review the sample size is planned (see section 18.3).

18.3 INTERIM ANALYSES AND STOPPING RULES

In order to demonstrate feasibility of site opening and recruitment a target of opening 12 centres and recruiting 63 patients over a 6 month time frame have been set. Any decision to continue the trial will remain with the funder in the event that the target is not met.

The results of the sample size review will be presented to the DMEC who will provide recommendations to the TSC. After 364 participants have reached 12 weeks post planned start of treatment, the pooled estimate of the coefficient of variation for the primary endpoint will be calculated and the sample size will be re-estimated. This will be done in a partially-blinded manner using coded treatment allocations in order to maintain the integrity of the trial. If the re-estimated sample size indicates that the study requires less than 500 participants, the final sample size will be set at 500 participants.

18.4 PRIMARY ENDPOINT ANALYSIS

A multivariable linear regression model will be fitted to the primary endpoint, log(HECSI), adjusting for minimisation factors duration of disease, clinical phenotype, DLQI, presence of specific IgE and ethnicity, and the covariates smoking history, BMI,

foot involvement [37, 38], filaggrin loss of function mutation, log of baseline score, and treatment group. Centre will be included as a random effect. The relative difference in the HECSI score at 12 weeks post planned start of treatment, corresponding 95% confidence intervals and p-values will be reported. The appropriateness of assuming a log-normal distribution of the HECSI score will be reviewed at the interim analysis (in a blinded manner) and if the log-normal distribution is not appropriate other distributions will be explored. This will be fully documented in the final statistical analysis plan.

18.5 SECONDARY ENDPOINT ANALYSIS

To compare Alitretinoin and PUVA in terms of providing a longer term treatment response over time with a focus at 24 and 52 weeks post planned start of treatment, multivariable multilevel repeated measures linear regression models of log (HECSI score) and mTLSS, and a multilevel repeated measures logistic regression model of the PGA over time will be fitted adjusting for the minimisation factors: duration of disease, clinical phenotype, DLQI, presence of specific IgE and ethnicity, and the covariates smoking history, BMI, foot involvement [37, 38], filaggrin loss of function mutation, relevant baseline measurement, and treatment group, as fixed effects. Centre, participant and participant-time interaction will be fitted as random effects. The parameter estimates, corresponding 95% confidence intervals and p-values will be reported; contrasts for the treatment effect at 24 and 52 weeks post planned start of treatment will also be reported.

Cox Proportional Hazard models will be used to analyse the duration of time to relapse adjusting for the same minimisation factors and covariates as for the primary endpoint analysis. The hazard ratio for the treatment effect, corresponding 95% confidence intervals and p-values will be reported.

In order to compare QoL, patient's education needs and patient's benefit over the 52 week duration, DLQI, PeDeSi and PBI-HE scores at baseline and over time will be summarised using descriptive statistics and plots by treatment group. Longitudinal data analyses will be conducted for each of DLQI, PeDeSi and PBI-HE adjusting for the minimisation factors: duration of disease, clinical phenotype, DLQI, presence of specific IgE and ethnicity, and the covariates smoking history, BMI, foot involvement [37, 38], filaggrin loss of function mutation, relevant baseline measurement, and treatment group, as fixed effects. Centre, participant and participant-time interaction will be fitted as random effects. The parameter estimates, corresponding 95% confidence intervals and p-values will be reported.

AEs and SAEs classified as related to treatment, hand eczema or resulting from administration of any research procedures will be listed and summarised by treatment group.

18.6 EXPLORATORY ENDPOINT ANALYSIS

Comparison of scoring systems: In order to compare scoring systems used to monitor response to treatment in patients with severe HE (HECSI, mTLSS, DLQI and PGA), correlations between scores will be produced where appropriate to assess the convergent validity of the scoring systems used to monitor response to treatment in patients with severe HE. Multilevel repeated measures modelling will also be used to explore relationships between scoring systems.

Exploratory sub-group analysis on duration of disease, clinical phenotype, disease severity, presence of atopy, filaggrin loss of function mutation, smoking history, BMI and foot involvement: In order to evaluate whether response to first line treatment is affected by duration of disease, disease severity (HECSI), clinical phenotype, presence of atopy, filaggrin loss of function mutation, smoking history, BMI and foot involvement, exploratory subgroup analyses will be conducted to compare treatment effects between these sub-groups. A regression model of log(HECSI score) at 12 weeks post planned start of treatment on baseline HECSI score, treatment group, disease duration and the covariates specified above will be fitted. An interaction term between treatment and disease duration will then be included in the regression model to determine if there is any differential effect of treatment with disease duration. Regression models will also be fitted to determine if there is a differential effect of treatment with disease severity, clinical phenotype, presence of atopy, filaggrin loss of function mutation, smoking history, BMI and foot involvement. Multivariable multilevel repeated measures linear regression modelling will also be conducted to explore sub group treatment responses over time.

Evaluation of biomarkers (IL-36, TARC, CCL20, TSLP, and IL-18) *or HE subgroups based on molecular inflammatory mediators*: Univariate and multivariable linear regressions models will be fitted to the response log (HECSI) at 12 weeks post planned start of treatment to assess the relationship between biomarkers on disease activity with and without adjusting for minimisation factors and covariates as for the primary analysis. Treatment group and an interaction term between treatment group and the biomarkers will be included in the models to determine if there is any differential effect of treatment in the presence/absence of these biomarkers. Multivariable multilevel repeated measures linear regression modelling will also be conducted to explore sub group treatment responses over time.

Pilot data on effectiveness of second line therapies: Descriptive statistics summaries on types of, dose and, response to second line therapies will be presented using HECSI and PGA.

Safety/Pharmacovigilance: Procedures will be established to monitor and report ARs, SAEs (related to HE), SARs and SUSARs in line with the Medicines for Human Use (Clinical Trial) Regulations, Sponsor and CTRU Standard Operating Procedures. Reasons for treatment discontinuation will be recorded and reported to the CTRU. This will include appropriate review by the Chief Investigator, Trial Management Group

(TMG) and Data Monitoring and Ethics Committee (DMEC) and expedited reporting to the MHRA and Ethics Committee in accordance with regulatory and ethical requirements.

Exploring the end of remission: Definitions such as the time point that patients are no longer clear/almost clear will be explored in conjunction with definitions of relapse. Descriptive statistics summaries on frequency of corticosteroid use will also be summarised and modelling will be conducted to further explore this data.

Exploring changes in nails: Descriptive statistics and plots to summarise data collected on nail assessments over time will be presented to explore observed changes in nails over time.

Exploring the use of the photography guide for patients of non-Caucasian ethnicity: This will be explored within the photography analysis (section 18.7).

18.7 PHOTOGRAPHY ANALYSIS

Agreement between the blinded assessor and the central review of photographs will be assessed using cross tabulations; kappa statistics will also be produced. These will be presented by time point and by ethnicity and will be considered at each DMEC meeting as part of quality control checks. Where discrepancies exist, the mTLSS will be explored for further information relating to pain and itch.

19. TRIAL MONITORING

A Trial Monitoring Plan will be developed and a Meeting Group Monitoring Schedule including primary endpoint and safety data will be defined and agreed by the Trial Management Group (TMG), TSC and DMEC.

19.1 DATA MONITORING AND ETHICS COMMITTEE

An independent Data Monitoring and Ethics Committee (DMEC) will review the safety and ethics of the study. Detailed reports will be prepared by the CTRU for the DMEC at approximately annual intervals. These reports will contain the information agreed in the data monitoring analysis plan. The formal interim analysis on the primary endpoint for re-estimating the final sample size will be reported to the DMEC after 364 participants have reached 12 weeks post planned start of treatment. Recruitment will continue to proceed whilst the results are being generated. The DMEC will be provided detailed reports including rates of occurrence of SAEs (related to HE), SARs and SUSARs.

19.2 DATA MONITORING

Data will be monitored for quality and completeness by the CTRU. Missing data will be chased until it is received, confirmed as not available or the trial is at analysis. However, missing data items will not be chased from participants. The CTRU/Sponsor will reserve the right to intermittently conduct source data verification exercises on a sample of participants, which will be carried out by staff from the CTRU/Sponsor. Source data verification will involve direct access to patient notes at the participating

hospital sites and the ongoing central collection of copies of consent forms and other relevant investigation reports.

19.3 CLINICAL GOVERNANCE ISSUES

To ensure responsibility and accountability for the overall quality of care received by participants during the study period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the TSC and, where applicable, to individual NHS Trusts.

20. QUALITY ASSURANCE AND ETHICAL CONSIDERATIONS

20.1 QUALITY ASSURANCE

The trial will be conducted in accordance with the principles of Good Clinical Practice (GCP) in clinical trials, as applicable under UK regulations, the NHS Research Governance Framework (RGF) (and Scottish Executive Health department Research Governance Framework for Health and Social Care 2006 for studies conducted in Scotland) and through adherence to CTRU Standard Operating Procedures (SOPs).

20.2 SUBMISSION OF TRIAL DATA

Case Report Forms

Trial data will be recorded by trial site research staff on trial-specific paper CRFs and submitted by post to the CTRU at the University of Leeds. Only the participant's trial number plus date of birth and initials will be added to CRFs in order to identify the participant. The trial site is responsible for obliterating all other personal identifiable data prior to sending CRFs and any other reports to the CTRU (with the exception of the patient consent form which will include the patient's signature). Following receipt, the CTRU will contact the trial site to resolve any missing or discrepant data queries.

The CTRU will seek to adopt all reasonable measures to record data in accordance with the protocol. Under practical working conditions, however, some minor variations may occur due to circumstances beyond the control the CTRU. All such deviations will be documented on the study records, together with the reason for their occurrence; where appropriate, deviations will be detailed in the published report.

20.3 SERIOUS BREACHES

Investigators are required to promptly notify the CTRU of a serious breach (as defined in the latest version of the National Research Ethics Service (NRES) SOP). A 'serious breach' is defined as a breach of the protocol or of the conditions or principles of GCP (or equivalent standards for conduct of non-CTIMPs) which is likely to affect to a significant degree the safety or physical or mental integrity of the trial subjects, or the scientific value of the research.

In the event of doubt or for further information, the Investigator should contact the Senior Trial Co-ordinator at the CTRU.

20.4 ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 52nd World Medical Association General Assembly, Edinburgh, Scotland, 1996. Informed written consent will be obtained from the patients prior to registration into the study. The right of a participant to refuse participation without giving reasons must be respected. The participant must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment. The study will be submitted to and approved by a main REC and MHRA and the appropriate Site Specific Assessor for each participating centre prior to entering patients into the study. The CTRU will provide the main REC and MHRA with a copy of the final protocol, patient information sheets, consent forms and all other relevant study documentation.

21. CONFIDENTIALITY

All information collected during the course of the trial will be kept strictly confidential. Information will be held securely on paper and electronically at the CTRU. The CTRU will comply with all aspects of the 1998 Data Protection Act and operationally this will include:

- Consent from participants to record personal details including name, date of birth, NHS number, hospital number, appropriate storage, restricted access and disposal arrangements for participant personal and clinical details.
- Consent from participants for access to their medical records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to trial participation.
- Consent from participants for the data collected for the trial to be used to evaluate safety and develop new research.
- Participants' names, date of birth and NHS number will be collected on the consent form when a participant is registered into the trial but the details will not be entered onto the database. The consent forms will be sent to the CTRU and stored separately from the clinical data.
- Patient mobile telephone contact details will be sent to the CTRU only with the participant's permission in order to send out weekly text reminders to aid diary completion.
- All other data collection forms that are transferred to or from the CTRU and AUHE will be coded with a trial number and will include two participant identifiers, usually the participant's initials and date of birth.

- Participant name, date of birth, NHS number and contact details will recorded by sites at the screening and information visit (subject to consent) and retained by them.
- Where central monitoring of photographs by CTRU is required the participant's name must be obliterated by site before sending.
- Where anonymisation of documentation is required, sites are responsible for ensuring only the instructed identifiers are present before sending to CTRU.

If a participant withdraws consent from further trial treatment and/or further collection of data will remain on file and will be included in the final study analysis.

21.1 ARCHIVING

At the end of the study, data will be securely archived in line with the Sponsor's procedures for a minimum of 15 years. Data held by the CTRU will be archived in the Leeds Sponsor archive facility and site data and documents will be archived at site. Following authorisation from the Sponsor, arrangements for confidential destruction will then be made.

22. STATEMENT OF INDEMNITY

This study is sponsored by the University of Leeds and the University of Leeds will be liable for negligent harm caused by the design of the study. The NHS has a duty of care to patients treated, whether or not the patient is taking part in a clinical study and the NHS remains liable for clinical negligence and other negligent harm to patients under this duty of care.

23. STUDY ORGANISATIONAL STRUCTURE

23.1 INDIVIDUALS AND INDIVIDUAL ORGANISATIONS

Chief Investigator (CI) – The CI is involved in the design, conduct, co-ordination and management of the trial. The CI will have overall responsibility for the design and set-up of the trial, the investigational drug supply and pharmacovigilance within the trial.

Trial Sponsor – The Sponsor is responsible for trial initiation management and financing of the trial as defined by Directive 2001/20/EC. These responsibilities are delegated to the CTRU as detailed in the trial contract.

Clinical Trials Research Unit – The CTRU will have responsibility for conduct of the trial as delegated by the Sponsor in accordance with relevant GCP standards and CTRU SOPs. The CTRU will provide set-up and monitoring of trial conduct to CTRU SOPs, and the GCP Conditions and Principles as detailed in the UK Medicines for Human Use (Clinical Trials) Regulations 2006 including, randomisation design and service, database development and provision, protocol development, CRF design, trial design, source data verification, monitoring schedule and statistical analysis for the

trial. In addition the CTRU will support main REC, Site Specific Assessment and NHS permissions submissions and clinical set-up, ongoing management including training, monitoring reports and promotion of the trial. The CTRU will be responsible for the day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting and all statistical analyses**.**

Central Laboratories:

Professor Ann Morgan's Rheumatology Laboratory (Leeds Institute of Rheumatic and Musculoskeletal Medicine, Wellcome Trust Brenner Building, St James University Hospital, Leeds) will have the responsibility for the isolation and storage of DNA from blood samples taken for subsequent analyses for skin barrier molecule polymorphisms (including filaggrin loss-of-function mutations).

Professor Stephan Weidinger's laboratory (Department of Dermatology, University Hospital Schleswig-Holstein, Kiel, (Germany) will be responsible for the assessment of skin barrier molecule polymorphisms (including filaggrin loss-of-function mutation analyses) from the extracted DNA sent from Ann Morgan's laboratory.

23.2 OVERSIGHT / TRIAL MONITORING GROUPS

Trial Management Group - The TMG, comprising the Chief Investigator, CTRU team, and co-applicants will be assigned responsibility for the clinical set-up, on-going management, promotion of the trial, and for the interpretation and publishing of the results. Specifically the TMG will be responsible for (i) protocol completion, (ii) CRF development, (iii) obtaining approval from MHRA and the main REC and supporting applications for Site Specific Assessments, (iv) submitting a Clinical Trial Authorisation (CTA) application and obtaining approval from the MHRA, (v) completing cost estimates and project initiation, (vi) nominating members and facilitating the TSC and DMEC, (vii) reporting of SAEs (related to HE), SARs, SUSARs (viii) monitoring of screening, recruitment, treatment and follow-up procedures, (ix) auditing consent procedures, data collection, trial end-point validation and database development.

Trial Steering Committee – The TSC, with an independent Chair, will provide overall supervision of the trial, in particular trial progress, adherence to protocol, participant safety and consideration of new information. It will include an Independent Chair and at least one other independent member. The Chief Investigator and other members of the TMG will attend the TSC meetings and present and report progress. The Committee will meet annually as a minimum.

Data Monitoring and Ethics Committee (DMEC) - The DMEC will review the safety and ethics of the trial by reviewing interim data during recruitment. The Committee will meet annually as a minimum.

24. PUBLICATION POLICY

24.1 AUTHORSHIP AND ACKNOWLEDGEMENT

The trial will be registered with an authorised registry, according to the International Committee of Medical Journal Editors (ICMJE) Guidelines, prior the start of recruitment.

The success of the trial depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributorship. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to:

- conception and design, or acquisition of data, or analysis and interpretation of data,
- drafting the article or revising it critically for important intellectual content,
- and final approval of the version to be published,
- and that all these conditions must be met (www.icmje.org).

In light of this, the Chief Investigator, co-applicants and relevant senior CTRU staff will be named as authors in any publication, fulfilling the above criteria and an appropriate first author agreed through discussion amongst the Trial Management Group (TMG) members. In addition, all collaborators will be listed as contributors for the main trial publication, giving details of roles in planning, conducting and reporting the trial.

Other key individuals will be included as authors or contributors as appropriate and at the discretion of the ALPHA TMG. Any disputes relating to authorship will be resolved by the TSC.

The Chairs and Independent members of the TSC and Data Monitoring and Ethics Committee (DMEC) will be acknowledged, but will not qualify for full authorship, in order to maintain their independence.

Relevant National Institute for Health Research (NIHR) Clinical Research Networks' (e.g. CRN) support should be acknowledged appropriately in trial publications.

To maintain the scientific integrity of the trial, data will not be released prior to the first publication of the analysis of the primary endpoint, either for trial publication or oral presentation purposes, without the permission of the TSC. In addition, individual collaborators must not publish data concerning their participants which is directly relevant to the questions posed in the trial until the first publication of the analysis of the primary endpoint.

24.2 DATA SOURCE

Data from the CTRU database in Leeds must be used for data analyses for all abstracts and publications relating to the questions posed within the trial protocol. Furthermore, the statistical team at the CTRU must perform all such analyses. If any additional analyses outside the remit of the protocol are to be performed, the statistical team at the CTRU should be involved if it involves data held on the CTRU databases.

Samples from the central laboratory will be analysed at Professor Stephan Weidinger's laboratory ((Department of Dermatology, University Hospital Schleswig-Holstein, Kiel, Germany) for the assessment of subsequent skin barrier molecule polymorphisms (including filaggrin loss-of-function mutation analyses). Results from the laboratory analyses will be sent to the CTRU for further statistical analysis.

24.3 DATA RELEASE

To maintain the scientific integrity of the trial, data will not be released prior to the first publication of the results of the primary endpoint analysis, either for trial publication or oral presentation purposes, without the permission of the DMEC and the TSC.

The TSC will agree a publication plan and must be consulted prior to release or publication of any trial data.

Individual collaborators must not publish data concerning their participants which is directly relevant to the questions posed in the trial until the main results of the trial have been published. Local collaborators may not have access to trial data until after publication of the main trial results.

24.4 PROCESSES FOR THE DRAFTING, REVIEW AND SUBMISSION OF ABSTRACTS AND MANUSCRIPTS

The agreed first author of abstracts is responsible for circulating these to the other members of the TMG for review at least 15 days prior to the deadline for submission.

The agreed first author of manuscripts is responsible for ensuring:

- timely circulation of all drafts to all co-authors during manuscript development and prior to submission
- timely (and appropriate) circulation of reviewers' comments to all co-authors
- incorporation of comments into subsequent drafts
- communication with the TSC (i.e. ensuring submission is in line with TSC publication plan, and ensuring TSC receive the final draft prior to submission)

The first author is responsible for submission of the publication and must keep the TMG and all authors informed of the abstract's or manuscript's status. The TSC will be kept informed of rejections and publications as these occur. On publication, the first author should send copies of the abstract or manuscript to the TSC, the TMG, the

Sponsor and to all co-authors, and ensure communication with the NIHR Health Technology Assessment (HTA) programme as outlined below.

24.5 FUNDER'S REQUIREMENTS

24.5.1 NIHR HTA PROGRAMME REQUIREMENTS

All material to be submitted for publication (written, audio/visual and electronic) will be prepared and submitted to the NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC) in accordance with the NIHR HTA programme's requirements at the time a publication is drafted. This applies to all publications regardless of whether or not the primary results have been published.

25. REFERENCES

1. Cvetkovski, R.S.*, et al.* Relation between diagnoses on severity, sick leave and loss of job among patients with occupational hand eczema. *Br J Dermatol* **152**, 93-98 (2005).
2. Fowler, J.F.*, et al.* Impact of chronic hand dermatitis on quality of life, work productivity, activity impairment, and medical costs. *J Am Acad Dermatol* **54**, 448-457 (2006).
3. Meding, B. & Jarvholm, B. Hand eczema in Swedish adults - changes in prevalence between 1983 and 1996. *The Journal of investigative dermatology* **118**, 719-723 (2002).
4. Diepgen, T.L.*, et al.* Management of chronic hand eczema. *Contact Dermatitis* **57**, 203-210 (2007).
5. English, J.*, et al.* Consensus statement on the management of chronic hand eczema. *Clin Exp Dermatol* **34**, 761-769 (2009).
6. Coenraads, P.J. Hand eczema. *N Engl J Med* **367**, 1829-1837 (2012).
7. Van Coevorden, A.M.*, et al.* Overview of studies of treatments for hand eczema-the EDEN hand eczema survey. *Br J Dermatol **151**, 446-451 (2004).*
8. Paulden, M.*, et al.* Alitretinoin for the treatment of severe chronic hand eczema. *Health Technol Assess* **14 Suppl 1**,39-46 (2010).
9. Blome, C., Maares, J., Diepgen, T., Jeffrustenbach, S. & Augustin, M. Measurement of patient-relevant benefits in the treatment of chronic hand eczema--a novel approach. *Contact Dermatitis* **61**, 39-45 (2009).
10. Cowdell, F., Ersser, S.J., Gradwell, C. & Thomas, P.W. The Person-Centered Dermatology Self-Care Index: A Tool to Measure Education and Support Needs of Patients With Long-term Skin Conditions. *Arch Dermatol* **148**, 1251-1256 (2012).
11. Ersser, S.J.M., S.; Nicol, N.;Penzer, R.; Peters, J. A best practice statement for emollient therapy. *Dermatological Nursing* **11**, S1-S19 (2012).
12. Dirschka, T.*, et al.* An open-label study assessing the safety and efficacy of alitretinoin in patients with severe chronic hand eczema unresponsive to topical corticosteroids. *Clin Exp Dermatol* **36**, 149-154 (2011)
13. Halpern, S.M.*, et al.* Guidelines for topical PUVA: a report of a workshop of the British photodermatology group. *Br J Dermatol* **142**, 22-31 (2000).
14. Tzaneva, S., Kittler, H., Thallinger, C., Honigsmann, H. & Tanew, A. Oral vs. bath PUVA using 8-methoxypsoralen for chronic palmoplantar eczema. *Photodermatol Photoimmunol Photomed* **25**, 101-105 (2009).
15. Katsarou, A.*, et al.* Tacrolimus 0.1% vs mometasone furoate topical treatment in allergic contact hand eczema: a prospective randomized clinical study. *Eur J Dermatol* **22**, 192-196 (2012).
16. Schnopp, C.*, et al.* Topical tacrolimus (FK506) and mometasone furoate in treatment of dyshidrotic palmar eczema: a randomized, observer-blinded trial. *J Am Acad Dermatol* **46**, 73-77 (2002).
17. Benson, N.R.*, et al.* An analysis of select pathogenic messages in lesional and non-lesional psoriatic skin using noninvasive tape harvesting. *The Journal of investigative dermatology* **126**, 2234-2241 (2006).
18. Morhenn, V.B., Chang, E.Y. & Rheins, L.A. A noninvasive method for quantifying and distinguishing inflammatory skin reactions. *J Am Acad Dermatol* **41**, 687-692 (1999

19. Wittersheim, M.*, et al.* Differential expression and in vivo secretion of the antimicrobial peptides psoriasin (S100A7), RNase 7, human beta-defensin-2 and -3 in healthy human skin. *Experimental Dermatology* **22**, 364-366 (2013).
20. Weistenhofer, W., Baumeister, T., Drexler, H. & Kutting, B. An overview of skin scores used for quantifying hand eczema: a critical update according to the criteria of evidence-based medicine. *Br J Dermatol* **162**, 239-250 (2010).
21. Held, E., Skoet, R., Johansen, J.D. & Agner, T. The hand eczema severity index (HECSI): a scoring system for clinical assessment of hand eczema. A study of inter- and intraobserver reliability. *Br J Dermatol* **152**, 302-307 (2005).
22. Meding, B., Wrangsjo, K. & Jarvholm, B. Hand eczema extent and morphology--association and influence on long-term prognosis. *The Journal of investigative dermatology* **127**, 2147-2151 (2007).
23. Ruzicka, T.*, et al.* Efficacy and safety of oral alitretinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, double-blind, placebo-controlled, multicentre trial. *Br J Dermatol* **158**, 808-817 (2008).
24. Agner, T., Jungersted, J.M., Coenraads, P.J. & Diepgen, T. Comparison of four methods for assessment of severity of hand eczema. *Contact Dermatitis* **69**, 107-111 (2013).
25. Coenraads, P.J.*, et al.* Construction and validation of a photographic guide for assessing severity of chronic hand dermatitis. *Br J Dermatol* **152**, 296-301 (2005).
26. Brooks, R. EuroQol: the current state of play. *Health Policy* **37**, 53-72 (1996).
27. Boehm, D.*, et al.* Anxiety, depression and impaired health-related quality of life in patients with occupational hand eczema. *Contact Dermatitis* (2012).
28. Basra, M.K., Fenech, R., Gatt, R.M., Salek, M.S. & Finlay, A.Y. The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. *Br J Dermatol* **159**, 997-1035 (2008).
29. Finlay, A.Y., Basra, M.K., Piguet, V. & Salek, M.S. Dermatology life quality index (DLQI): a paradigm shift to patientcentered outcomes. *The Journal of investigative dermatology* **132**, 2464-2465 (2012).
30. Hongbo, Y., Thomas, C.L., Harrison, M.A., Salek, M.S. & Finlay, A.Y. Translating the science of quality of life into practice: What do dermatology life quality index scores mean? *The Journal of investigative dermatology* **125**, 659-664 (2005).
31. Augustin, M.*, et al.* The patient benefit index: a novel approach in patient-defined outcomes measurement for skin diseases. *Arch Dermatol Res* **301**, 561-571 (2009).
32. Zschocke, I., Hammelmann, U. & Augustin, M. [Therapeutic benefits in dermatological therapy. Evaluation of therapy from the physician's und patient's perspective in psoriasis and atopic dermatitis]. *Der Hautarzt; Zeitschrift fur Dermatologie, Venerologie, und verwandte Gebiete* **56**, 839-842, 844-836 (2005).
33. Cowdell, F.E., S.; Gradwell, C.; Langford, A. The development, validity, reliability and field testing of the Person- Centred Dermatology Self-Care Index. *Arch Dermatol* **148**, 1251-1256 (2012).
34. Molin, S., Diepgen, T.L., Ruzicka, T. & Prinz, J.C. Diagnosing chronic hand eczema by an algorithm: a tool for classification in clinical practice. *Clin Exp Dermatol* **36**, 595-601 (2011).
35. Diepgen, T.L., Scheidt, R., Weisshaar, E., John, S.M. & Hieke, K. Cost of illness from occupational hand eczema in Germany. *Contact Dermatitis* **69**, 99-106 (2013).
36. Meding, B., Wrangsjo, K. & Jarvholm, B. Fifteen-year follow-up of hand eczema: persistence and consequences. *Br J Dermatol* **152**, 975-980 (2005).

37. Malkonen, T.*, et al.* Long-term follow-up study of occupational hand eczema. *Br J Dermatol* **163**, 999-1006 (2010).
38. Meding, B., Wrangsjo, K. & Jarvholm, B. Fifteen-year follow-up of hand eczema: predictive factors. *J Invest Dermatol* **124**, 893-897 (2005).
39. Diepgen, T.L.*, et al.* Hand eczema classification: a cross-sectional, multicentre study of the aetiology and morphology of hand eczema. *Br J Dermatol* **160**, 353-358 (2009).
40. Thyssen, J.P. The association between filaggrin mutations, hand eczema and contact dermatitis: a clear picture is emerging. *Br J Dermatol* **167**, 1197-1198 (2012).
41. Thyssen, J.P.*, et al.* Filaggrin null mutations increase the risk and persistence of hand eczema in subjects with atopic dermatitis: results from a general population study. *Br J Dermatol* ***163**, 115-120 (2010).*
42. Thyssen, J.P. Atopic dermatitis, filaggrin mutations and irritant contact dermatitis. *Br J Dermatol* **168**, 233-234 (2013).
43. Thyssen, J.P.*, et al.* Filaggrin mutations are strongly associated with contact sensitization in individuals with dermatitis. *Contact Dermatitis* **68**, 273-276 (2013).
44. Molin, S., Vollmer, S., Weiss, E.H., Ruzicka, T. & Prinz, J.C. Filaggrin mutations may confer susceptibility to chronic hand eczema characterized by combined allergic and irritant contact dermatitis. *Br J Dermatol* **161**, 801-807 (2009).
45. Giwercman, C., Lerbaek, A., Bisgaard, H. & Menne, T. Classification of atopic hand eczema and the filaggrin mutations. *Contact Dermatitis* **59**, 257-260 (2008).
46. National Institute for Clinical Excellence. Guide to the Methods of Technology Appraisal. Process and methods guide. NICE 2013. http://www.nice.org.uk/article/pmg9/resources/non-guidance-guide-to-the-methods-of-technology-appraisal-2013-pdf
47. Dolan P: Modelling Valuations for EuroQol Health States. *Med Care, **35**:1095-1108 (1997).*
48. Blome, C., Beikert, F. C., Rustenbach, S. J., & Augustin, M. Mapping DLQI on EQ-5D in psoriasis: transformation of skin-specific health-related quality of life into utilities. *Arch Dermatol Res, **305(4),** 197-204 (2013).*
49. Curtis L. Unit Costs of Health and Social Care 2012. *2012 [cited; Available from: http://www.pssru.ac.uk/publication-details.php?id=4378*
50. Efron B. Better bootstrap confidence-intervals. *Journal of the American Statistical Association **82**:171-85 (1987).*
51. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. *JAMA : the journal of the American Medical Association. **Oct 16;276(15):**1253-8 (1996).*
52**.** Menne et al. Hand eczema guidelines based on the Danish guidelines for the diagnosis and treatment of hand eczema. *Contact Dermatitis, **65**, 3–12 (2011)*
53. Stern, R.S. Psoralen and Ultraviolet A therapy for psoriasis *N. Eng. J. Med., **357:** 682-690, (2007)*
54. Schempp, C.M., Muller, H., Czech, W., Schopf, E. & Simon, J. C. Treatment of chronic palmoplantar eczema with local bath-PUVA therapy. *J A Acad Dermatol **34**, 733-737 (1997).*
55. Molin S., Vollmer S., Weiss E.H., Weisenseel P., Ruzicka T., Prinz J.C. Deletion of the late cornified envelope genes LCE3B and LCE3C may promote chronic hand eczema with allergic contact dermatitis. *J Investig Allergol Clin Immunol **21(6)**:472-9 (2011).*

56. Coenraads P.J., Christoffers W.A., Svensson A., Diepgen T.L., Blok J.L., Matterne U., Williams H.C. Cochrane review: Interventions for hand eczema. [In press]
57. Diepgen T.L., Elsner P., Schliemann S., Fartasch M., Kollner A.,Skudlik C., John S.M., Worm M. Management von Handekzemen, JDDG, 2009, S3, 1-16
59. Milanesi N., D'Erme A. M.,Gola M. Nail improvement during alitretinoin treatment: three case reports and review of the literature Clinical and Experimental Dermatology (2015) 40, 533–536
58. Yu M., Kim S. W., Kim M. S., Han T. Y., Lee J. H., Son S-J. Clinical study of patients with hand eczema accompanied by nail dystrophy. Japanese Dermatological Association (2013) 406-407

APPENDIX 1 - DEFINITION OF A WOMEN OF CHILDBEARING POTENTIAL

A woman of childbearing potential (WCBP) is:

- A sexually mature woman (i.e. any female who has ever experienced menstrual bleeding)

AND

- Who has not undergone a hysterectomy or who has not been postmenopausal for at least 24 consecutive months (i.e. who has had menses at any time within the preceding 24 consecutive months).