A Randomised Controlled Trial of Systemic Therapy for Vulval Erosive Lichen Planus

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SYNOPSIS

Title	A Randomised Controlled Trial of Systemic Therapy for Vulval Erosive Lichen Planus
Acronym	hELP (systemic t**h**erapy for vulval **E**rosive **L**ichen **P**lanus)
Short title	Adjunctive systemic therapy for Vulval Erosive Lichen Planus
Chief Investigator	Professor Kim Thomas
Objectives	To test whether hydroxychloroquine, methotrexate or mycophenolate mofetil are better than standard care with topical clobetasol propionate 0.05% plus a short course of oral prednisolone in patients with vulval erosive lichen planus that has been refractory to first-line therapy.
Trial Configuration	Four-armed, open-label randomised controlled trial.
Setting	Secondary care, multi-centre randomised controlled trial.
Sample size estimate	Assuming a control arm success rate of 10% and using a 1:1:1:1 allocation ratio, 17 patients per arm are required to detect a 40% absolute increase in the proportion of successes on the primary outcome, with 80% power at the two-sided 5% significance level. To account for a 10% drop out rate a total of 76 patients are therefore required for the analysis of this 4-arm trial. To control the familywise error rate (probability of any type I error) at the 5% level and maintain the power of each pairwise comparison at 80%, 96 patients will be required.
Number of participants	We will aim to recruit up to a maximum of 96 patients into the trial in order to have a definitive clinically relevant outcome. However, if time and resources are restricted recruitment will be targeted at 76 to give an outcome with limited power.
Eligibility criteria	**Inclusion criteria:** • Clinical diagnosis of erosive lichen planus affecting the vulval region (ELPV) • Histological examination of vulval tissue that excludes malignant/pre-malignant disease; biopsy to be repeated if clinically indicated prior to consideration of systemic therapy • Inadequate disease control despite first-line therapy with clobetasol propionate 0.05% for at least 3 months • Moderate or severe disease on Investigator Global Assessment • Microbiological swabs negative, or result that is not clinically relevant, at study entry • Willing and capable of giving informed consent

	• Willing to have clinical images taken • Female aged 18 years or over • Use of effective contraceptive methods in females of childbearing age for the duration of treatment • For participants receiving methotrexate to use effective contraceptive methods until 6 months after the end of treatment. **Exclusion criteria:** • Cases of lichen sclerosus/lichen planus overlap • Received one or more of the trial drugs within the last one month (excluding clobetasol propionate 0.05%) • Previous/current diagnosis of malignant disease (skin or internal) • History of or current diagnosis of pre-malignant vulval skin or cervical disease • Receiving concurrent medications that would preclude the use of any of the trial medications in normal practice • History of clinically significant renal or liver impairment or other pre-existing medical conditions that would preclude the use of any of the trial medications in normal practice • Administration of a live vaccine (BCG, Measles, Mumps, Rubella, Yellow Fever, Oral Polio, Oral Typhoid) within the last 2 weeks • Pregnancy or breast-feeding • Known allergy to any of the trial medications
Description of interventions	**Intervention:** Participants will be randomised to receive one of the three active interventions or to receive the comparator, clobetasol propionate 0.05% plus oral prednisolone, which is standard care: **<u>Comparators</u>** **Hydroxychloroquine**, oral administration, up to 6.5mg/kg lean body weight, maximum dose of 200mg BD (in conjunction with topical clobetasol propionate 0.05%). Treatment duration 6 months. **Methotrexate**, oral administration, dose commencing at 5mg/week and gradually increase as per protocol according to response to a maximum of 25mg/week (in conjunction with topical clobetasol propionate 0.05%. Treatment duration 6 months. **Mycophenolate mofetil**, oral administration, dose commence at 500mg OD and gradually increase as per protocol according to response to a maximum dose of 1.5g BD (in conjunction with topical clobetasol propionate 0.05%) Treatment duration 6 months. **<u>Standard Care</u>** **Clobetasol propionate 0.05%** (standard care)**,** topical application, once daily for one month and regimen reduced according to response. Maximum 60g over 6 months (British Association of Dermatologists guidance for the treatment of Lichen sclerosus). **Oral prednisolone** an initial 4 week course of on a reducing regimen of 20mg OD for 1 week, reducing by 5mg per week.

Duration of study	The overall duration of study is 24 months with a planned start date of May 2014. The duration of each participant will be 12 months.
Randomisation and blinding	This is an open-label trial; participants and treating clinicians will know the allocation of treatments. However, the primary endpoint is a composite measure and will include the assessment of blinded clinical images by an independent assessor. Randomisation to treatment allocation will be performed using minimisation with a random element of approximately 80%. Recruiting centre and disease severity will be used for the minimisation criteria. The randomisation sequence will be concealed until interventions are all assigned and recruitment, data collection and data cleaning are complete. Accessing the randomisation system will be by an internet-based system.
Outcome measures	**Primary outcome measure:** Proportion of participants achieving treatment success at 6 months; Treatment should be classed as successful if both criteria (a) and (b) are met. a. Patient Global Assessment score of 0 or 1 on a 4-point scale b. Assessment of improvement from baseline judged by clinical images **Secondary outcome measures:** 1. Reduction in pain/soreness 2. Global assessment of disease assessed through: a. Patient Global Assessment b. Investigator Assessment by treating clinician c. Assessment by blinded assessor using clinical images 3. Assessment of other affected mucosal sites by treating clinician 4. Psychological assessment using the Hospital Anxiety and Depression Scale 5. Assessment of sexual function 6. Health-related quality of life –using a. 'Skindex-29' b. 'Short Form 36' 7. Days of topical steroid use during treatment period 8. Treatment satisfaction – assessed as overall satisfaction plus number of participants continuing treatment post the primary endpoint 9. Adverse events (AEs) reported during the study, and discontinuation of medications due to AEs 10. Average cost of intervention in each treatment group per participant
Statistical methods	All outcomes will be analysed for each research arm against the control arm in separate pairwise comparisons. Binary outcomes will be analysed using an absolute risk difference. Continuous outcomes will be analysed using an absolute difference in means. All analyses will adjust for the minimisation factors. As this is a multi-arm trial, analyses with multiplicity adjustment will also be presented. Research arms that are better than the control arm will be compared to one another in exploratory analyses.

ABBREVIATIONS

ADR Adverse Drug Reaction
AE Adverse Event
BAD British Association of Dermatologists
BCG Bacille Calmette Guerin
BD Bis die (twice a day)
BHPR British Health Professionals in Rheumatology
BNF British National Formulatory
BSR British Society of Rheumatology
CF Informed Consent Form
CI Chief Investigator overall
CRF Case Report Form
DAP Data Analysis Plan
DMC Data Monitoring Committee
EOT End of Trial
ELP Erosive lichen planus
ELPV Erosive lichen planus affecting the vulva
GCP Good Clinical Practice
HCQ Hydroxychloroquine
HELP 'Therapy for vulval Erosive Lichen Planus' trial
MHRA Medicines and Healthcare products Regulatory Agency
MMF Mycophenolate mofetil
MTX Methotrexate
NHS National Health Service
OD Once daily
PI Principal Investigator at a local centre
PIS Participant Information Sheet
PO Per os – by mouth
REC Research Ethics Committee
R&D Research and Development department
SAE Serious Adverse Event
SAR Serious Adverse Reaction
SmPC Summary of Product Characteristics
SUSAR Suspected Unexpected Serious Adverse Reaction
TMG Trial Management Group
TSC Trial Steering Committee

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TRIAL / STUDY BACKGROUND INFORMATION AND RATIONALE

Background

Epidemiology, pathogenesis and clinical presentation

Erosive lichen planus (ELP) is a chronic, inflammatory, scarring skin condition that occurs predominantly on the mucosal surfaces of the mouth (oral ELP) and genital region. Other less commonly affected sites include the eyes [1], oesophagus [2], bladder, larynx and anus [3]. It is believed to be an autoimmune condition [4, 5] with T-cell mediated damage to basal keratinocytes [6], although at present, the exact pathogenesis remains unclear.

We have a particular interest in ELP affecting the vulvovaginal region (ELPV). This causes painful raw areas at the vaginal entrance; subsequent scarring leads to anatomical changes with narrowing of the vaginal canal. Symptoms lead to difficulty in normal daily activities such as walking/sitting, washing, going to the toilet and can prevent normal sexual function. There is risk of cancerous change in affected skin of 1-3% [8-10].

The incidence of ELPV is estimated at 0.01%, which equates to approximately 3000 women in the UK. However, this is likely an underestimate with many cases going undiagnosed for a number of reasons, such as patients failing to present to medical services [13]. As it is a chronic condition, 'clusters' of patients are managed by specialist centres and are therefore readily identifiable for consideration of participation in clinical studies.

ELPV is diagnosed by clinico-pathological correlation; a diagnostic dataset has been agreed through a recent international multidisciplinary consensus exercise [14].

Management

There is variation in management of ELPV. A Cochrane Systematic Review [15], found no randomised controlled trial (RCT) evidence on which to base treatment for ELPV. Evidence for treatments is mainly based upon retrospective case-series and case reports.

First-line therapy

First-line therapy in the UK is with a super-potent topical steroid, usually clobetasol propionate 0.05% [16, 17]. Non-randomised studies, mainly retrospective case series, have suggested that super-potent topical steroids can be an effective first-line therapy [10, 12, 18, 19]. However, in the only prospective published case series [10], one-third of patients responded poorly to super-potent topical steroids. Evidence to date suggests that super-potent topical steroids are a reasonable first-line therapeutic choice and qualitative work has shown that they are ingrained into clinical practice as an initial therapy for ELPV [20]. The rationale for using clobetasol propionate 0.05% in all groups is determined from collaboration with the British Society for the Study of vulvovaginal disease (BSSVD) and limited case series studies in the literature.

Intravaginal steroid preparations may be used for patients with erosive lichen planus affecting the vaginal canal as topical corticosteroids are difficult to apply to these regions.

Second-line therapy

There is no agreement for which second-line agents should be used [7, 17], despite the fact that one-third of patients fail first-line therapy. Most second-line therapies are used based upon expert opinion. Systemic agents described in case series and case reports consist of:

- oral corticosteroids
- systemic immunosuppressants including azathioprine, ciclosporin, methotrexate and mycophenolate mofetil
- systemic antibiotics, particularly tetracyclines
- hydroxychloroquine
- oral retinoids
- other anti-inflammatory agents including griseofulvin (an oral anti-fungal agent), colchicine (an agent traditionally used to treat gout) and dapsone.

Response to treatment

Response to treatment (both first and second-line) is variable and assessment consists of physician-assessed and patient-reported outcomes. There are no standardised outcome measurement sets for ELPV [16] and there are no outcome measure tools specific to the condition [21]. Focus groups have been run in preparation for this study and participants' views about the most relevant outcomes for the condition are reflected in the primary and secondary endpoints of this RCT.

Need for this research

Providing a high-quality evidence base for the treatment of ELPV has been prioritised by the British and International Societies for the Study of Vulval Disease and the most important question clinically is to determine the most effective second-line therapy for ELPV.

This is the first study of its sort in this rare condition. As there is currently no RCT evidence for any of the trial interventions it was impossible to pick one comparator alone to test in a traditional two-armed, placebo controlled RCT. As patient numbers are scarce and resources limited in this population this is a four-armed study.

It has been agreed by expert clinicians in the feasibility stages that the systemic treatments with the greatest success rates (anecdotally) when used in clinical practice are hydroxychloroquine, methotrexate mycophenolate mofetil and prednisolone. However, of these agents, there is no clear favourite and insufficient data within the literature to know which one is best to test in a two-armed RCT.

This study will be a four-armed randomised controlled trial design to test all of these agents in a single trial against a control group who will receive topical clobetasol propionate 0.05% with an initial short course of oral corticosteroids. This approach will allow information these four treatment regimens to be acquired more quickly compared with separate trials and will require smaller patient numbers than 3 separate placebo controlled RCTs. This approach is important to maximise information about ELPV which is a rare disease.

This will be the first therapeutic RCT for ELPV and results will contribute towards future evidence-based management guidelines and will help to standardise practice.

DETAILS OF INVESTIGATIONAL MEDICINAL PRODUCTS

All of the investigational products are familiar to Dermatology, have a well characterised safety profile and have been used as part of routine clinical practice for years. None are

licensed for ELPV as it is a rare condition but it is not anticipated that the side effect profile will be significantly different in the patient group under study.

As described in the previous section, the chosen investigational products have been shown to be part of normal practice in treating ELPV and anecdotally have the greatest success rates, although there is insufficient data in the literature to indicate which of these are likely to be the most effective. The reason for using all of the agents in a multi-armed RCT is to efficiently assess, in this rare group pf patients, whether use of these agents are better than standard care alone.

The treatment regimens to be used are as per usual practice following national guidelines for the individual medications.

Treatment groups

Participants will be randomised to one of four treatment groups:

Control group: standard care of topical clobetasol propionate 0.05% plus a short course of oral prednisolone. **N.B** Topical clobetasol propionate 0.05% will be used once daily for one month, alternate days for 1 month then twice weekly thereon. This is in conjunction with an initial reducing course of oral prednisolone (20mg per day to reduce by 5mg per week over 4 weeks until stop (i.e. 20mg/day for 1 week, then 15mg/day for 1 week, then 10mg/day for 1 week, then 5mg/day for 1 week then stop)

Research arm 1: Oral hydroxychloroquine (up to 200mg twice daily) PLUS topical clobetasol propionate 0.05%% in the same regimen as in the control group. The exact dose will be decided by the treating physician according to clinical requirement. Oral hydroxychloroquine should be used as per usual practice following national guidelines including appropriate safety monitoring.

Research arm 2: Oral methotrexate (starting at 5mg weekly titrated upwards over 3-4 months to a ceiling dose of 25mg weekly) PLUS topical clobetasol propionate 0.05% in the same regimen as in the control group. Oral methotrexate should be used as per usual practice following national guidelines including appropriate safety monitoring.

Research arm 3: Oral mycophenolate mofetil (starting at 500mg OD titrated upwards over 3-4 months to a ceiling dose of 3g/day) PLUS topical clobetasol propionate 0.05% in the same regimen as in the control group. Oral mycophenolate mofetil should be used as per usual practice following national guidelines including appropriate safety monitoring.

All participants will receive an emollient to be used as soap substitute and moisturiser. The choice of emollient will be usual medical practice for that recruiting site.

Investigational products

Clobetasol propionate 0.05%

Clobetasol propionate 0.05% will be used by all of the treatment groups. Clobetasol propionate 0.05% is available by the topical route only. It is available in proprietary and non-proprietary form and it is also available as a cream or an ointment. It is a highly active corticosteroid with topical anti-inflammatory activity. The major effect of clobetasol propionate 0.05% on skin is a non-specific anti-inflammatory response, partially due to vasoconstriction and decrease in collagen synthesis.

Prednisolone

Prednisolone is a highly potent glucocorticoid steroid which has an anti-inflammatory effect.

Prednisolone will be taken by the control group only (standard care) as a short course for the first four weeks of treatment. It is available by the oral route and is available in non-proprietary form. The 5mg tablet strength will be required for this study, as participants will be treated with 20mg reducing by 5mg per week over 4 week. Any brand may be prescribed and dispensed. Oral prednisolone should be used as per usual practice following national guidelines; use of bone protection and gastro protection is not prohibited by this study.

Hydroxychloroquine sulfate (HCQ)

Hydroxychloroquine is available as 200mg, a dose of up to 200mg twice daily will be used for this study.

Any brand may be prescribed and dispensed. Oral hydroxychloroquine should be used as per usual practice following national guidelines including appropriate safety monitoring.

Hydroxychloroquine has several pharmacological actions which may be involved in its clinical effects, but the role of each action is not known. These include interaction with sulphydryl groups, interference with enzyme activity, DNA binding, stabilisation of lysosomal membranes, inhibition of prostaglandin formation, possible interference with interleukin 1 production from monocytes and inhibition of neutrophil superoxide release.

Methotrexate (MTX)

Methotrexate is available by the oral, intramuscular or subcutaneous routes. The oral route will be the method of administration for the purposes of this study. It is available as 2.5mg and 10mg tablets, the 2.5mg strength will be used for this study (which is standard practice within dermatology). Methotrexate is taken on a once weekly basis.

Any brand may be prescribed and dispensed for the study. Oral methotrexate should be used as per usual practice following national guidelines; use of folic acid is not prohibited by this study.

Methotrexate is a folate antagonist and its major site of action is the enzyme dihydrofolate reductase. Its main effect is inhibition of DNA synthesis but it also acts directly both on RNA and protein synthesis.

Mycophenolate mofetil (MMF)

Mycophenolate mofetil is available by the oral route. It is available in non-proprietary form (Myfenax) in 250mg and 500mg tablets. It is also marketed as ‘Cellcept®’ (Roche) which is also available in 250mg and 500mg tablets. Both 250mg and 500mg strengths will be required for this study as the dose is gradually titrated to the maximum tolerated amount that is therapeutic for the participant. If a participant is intolerant to the tablet form of mycophenolate mofetil the prescriber may consider prescribing an oral suspension. Oral suspension is only produced by Cellcept® and is available in 1g/5ml strength only.

Any brand may be prescribed and dispensed for the study. Oral mycophenolate mofetil should be used as per usual practice following national guidelines including appropriate safety monitoring.

Mycophenolate mofetil is an ester of mycophenolic acid. Mycophenolic acid is a potent, selective, uncompetitive and reversible inhibitor of inosine guanosine nucleotide synthesis without incorporation into DNA. T and B lymphocytes are dependent for their proliferation on *de novo* synthesis of purines. Mycophenolic acid (and therefore mycophenolate mofetil) therefore has potent cytostatic effects on lymphocytes (but not on other cells which are not critically dependent upon the synthesis of purines).

Packaging and labelling

This is an open-label trial. All of the IMPs will be prescribed as normal by the treating clinician and will be dispensed from the participant's usual pharmacy with labelling in accordance with the dispensed medicines regulations.

Storage, dispensing and return

Each IMP will be stored as per local pharmacy protocols and in accordance with the relevant summary of product characteristics (SmPC). They will be dispensed from the participant's usual pharmacy without any changes from usual practice. In the event of treatment change or discontinuation, participants will be advised to return any unused medication to their local pharmacy for destruction. There will not be any accountability for returned IMP as they are being used in accordance with standard clinical practice.

Placebo

No placebo is planned for use in this study as it is an open-labelled trial.

Known Side Effects

The reference safety information for the IMPs can be found in the relevant SmPC. The dispensed medicines will also have a participant information leaflet included, which will provide a summary of known side effects.

Specifically the following is noted:

-Participants receiving immunosuppressive therapy are at increased risk of malignancies, particularly of the skin, and some of the investigational medicinal products may induce photosensitivity. Therefore, exposure to sunlight and ultra violet (UV) light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

- For patients taking mycophenolate mofetil treatment should be discontinued if neutropenia develops (absolute neutrophil count < 1.3 x 10^^{3}).

As the investigational medications have been used as part of routine clinical practice for years it is not anticipated that they will have any additional side-effects in the ELPV population.

TRIAL OBJECTIVES AND PURPOSE

Purpose

To identify interventions that are effective in improving disease control in patients with erosive lichen planus affecting the vulva (ELPV).

Primary Objective

To assess whether adjunctive systemic therapies are better than topical treatment (in conjunction with a short course of oral corticosteroids) in treating patients with ELPV that is refractory to standard first-line topical therapy. The trial will be powered to assess whether each of the three agents are more effective than the control treatment, it will not be powered to assess which of the three is the most effective., because it would be too difficult to recruit the required number of participants to perform this analysis.

Secondary Objectives

To assess the tolerability of the systemic therapies in patients with ELPV.

TRIAL / STUDY DESIGN

Trial / Study Configuration

This is a pragmatic, multi-centre, open-label, randomised controlled trial centrally managed by Centre of Evidence Based Dermatology, University of Nottingham.

Primary outcome measure

The proportion of patients achieving treatment success at 6 months. Treatment should be classed as successful if both Patient Global Assessment and Investigator Global Assessment are met:

- **Patient Global Assessment** of disease severity of 0 or 1 on a 4-point scale
- **Assessment** of improvement from baseline judged by **Blinded assessment** of clinical images

Patient Global Assessment and Investigator Assessment are not standardised. These assessments have been derived from two patient focus group sessions and after carrying out a systematic review for all outcome measures used for vulval disease and after discussion with the British Society for the Study of Vulval Disease (BSSVD).

Secondary outcome measure

- **Reduction in soreness** throughout the 6 month treatment period compared with baseline using a ten-point scale.

- **Global assessment of disease** assessed by:

  Patient Global Assessment at baseline, 3, 6 and 12 months

  Investigator Assessment by treating clinician at baseline, 3 and 6 months

  Assessment by blinded assessor using clinical images at baseline and 6 months

- **Assessment of severity of other oral and vaginal sites if affected –** Investigator assessment by physician at baseline, 3 and 6 months.

- **Psychological assessment** using the Hospital Anxiety and Depression Scale at baseline, 6 and 12 months.

- **Assessment of sexual function** at baseline, 6 and 12 months**.**

- Impact on **health-related quality of life** –using a dermatology specific tool 'Skindex-29' [22] and a general utility measure, the 'Short Form 36'[23] at baseline, 6 and 12 months.

- Days of topical steroid use (as a surrogate marker of control in each of the groups) as documented in patient diary.

- **Overall treatment satisfaction** assessed by
    - overall satisfaction
    - number of patients continuing treatment post the primary endpoint

- **Economic considerations**: Average cost of intervention in each treatment group per participant based on prescribed medication.

The secondary outcome measures are not standardised. These assessments have been derived from two patient focus group sessions and after carrying out a systematic review for all outcome measures used for vulval disease and after discussion with the British Society for the Study of Vulval Disease (BSSVD).

Safety endpoints

All of the investigational medications are familiar to Dermatology and have been used as part of routine clinical practice for years. It is not anticipated that these agents will have any greater side-effects in this population.

Safety endpoints will be adverse events (AEs) reported during the study, and discontinuation of medications due to AEs.

Adverse reactions to study medications – adverse events will be collected if they are considered secondary to the study drug. All serious events will be collected and causality subsequently assigned.

Stopping rules and discontinuation

An individual participant will stop treatment (but continue follow up) if:

- they have poor ongoing control of disease despite good adherence to the treatment regimen and optimising topical clobetasol propionate 0.05% use and the clinician feels it is unethical to continue; or

- side effects indicate that the participant should not carry on with the designated treatment regimen. Please note - Specifically for patients taking mycophenolate mofetil if

neutropenia develops (absolute neutrophil count < 1.3 x 10^3) treatment should be discontinued.

If participants stop the study treatment they will continue to be followed up.

Participants may stop the trial early either at their own request or at the Investigator's discretion (for example due to severe secondary infection, pregnancy and development of malignancy). If possible data will continue to be collected. The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they stop the trial, data collected to date cannot be erased and will still be used in the final analysis.

Participants who are randomised but are subsequently found to be ineligible will be replaced and will not be included in the intention to treat analysis. Participants who are randomised but choose not to start their medication (i.e. change their mind re: participation) will be followed up and will be included in the intention to treat analysis.

The trial may be stopped by the TSC on the advice of the DMC.

RANDOMISATION AND BLINDING

Randomisation codes will be generated by computer using minimization with a random element of 80% and held by the Nottingham Clinical Trials Unit (NCTU). This will ensure allocation concealment. Randomisation will be based on minimisation criteria on recruiting centre and disease severity (moderate or severe). The randomisation sequence will be concealed until interventions are all assigned and recruitment, data collection, and data cleaning are complete.

Randomisation will be used for allocation to study groups but as this is an open-label RCT treatments will not be blinded to the researcher, patient participant or local pharmacist.

The trial statistician and assessor of clinical images taken at baseline and at 6 months will both be blinded.

The reason for designing an open-label trial is that because of the widely differing treatment regimes, complete participant blinding will be prohibitively expensive and impractical as each participant would need to take multiple tablets every day. Furthermore, it was felt that with so many different regimens and the potential side effects of some of the treatments it could be potentially dangerous to blind the participant and investigator to the intervention.

Although it is an open-label trial, the participants will be randomised to receive one of the four interventions and therefore a large proportion of biases that could be introduced through a non-randomised open trial will be removed.

Maintenance of randomisation codes and procedures for breaking code

Not applicable for this open-label RCT.

TRIAL MANAGEMENT

The Chief Investigator Professor Kim Thomas has overall responsibility for the study, shall oversee all study management and will be the data custodian. Dr Ruth Murphy will be the medical expert, and will provide clinical expertise.

The trial will be co-ordinated from the Centre of Evidence Based Dermatology by the Trial Manager (Dr R Simpson) who is a Doctoral Research Fellow.

The trial will be overseen by a trial steering committee (TSC), which will include an independent chair and two other independent members, along with the Chief Investigators, the Lead Clinician and other members as appropriate. The Trial Management Group (TMG) will comprise the Chief Investigators, the Co-Investigators, two lay persons, a methodologist from the MRC Clinical Trials Unit, a statistician from the MRC Clinical Trials Unit and a member of the UK Dermatology Clinical Trials Network. The TMG will meet monthly although this may change to reflect the requirements of the trial as it progresses.

A Data Monitoring Committee (DMC) will also be involved with this study. All members will be independent of the participants and study team. This committee will meet one to two times a year and will oversee all ethical and safety issues.

Schedule of meetings

The Trial Management Group will meet monthly during the set up and recruitment phases of the trial and quarterly thereon. Additional Trial Management Group meetings will be held if considered necessary.

The Trial Steering Committee will meet prior to the start of the trial and then annually thereon.

The Data Monitoring Committee will meet six months after the first participant has been recruited and annually thereon, although additional meetings will be held if considered necessary having reviewed the interim data.

DURATION OF THE TRIAL / STUDY AND PARTICIPANT INVOLVEMENT

The overall duration of trial is expected to be 24 months.

The recruitment period is anticipated to begin in July 2014 and to last for 12 months. If the number of participants entering the trial is low, then recruitment may be extended.
Each participant will participate in the trial for 12 months (treatment period: 6 months, follow-up phone call 12 months after randomisation, her participation will commence upon signing the consent form.

End of the Trial

The end of the trial will be the last contact with the last participant.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

Up to 96 participants will be recruited from secondary care clinics. All participants will be females as the condition under investigation is a female genital dermatosis. We will aim to recruit up to a maximum of 96 participants into the trial in order to have a clinically relevant outcome.

The initial approach will either be during the clinic, or from the participant's usual care team via post to participants identified from existing confidential participant lists.

If a participant is believed to be eligible a PIS will then be provided and any questions answered by the investigator or their designated nominee.

If needed, the usual hospital interpreter and translator services will be available to assist with discussion of the trial and the participant information sheets as consent forms will not be available printed in other languages.

It will be explained to the potential participant that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time but attempts will be made to avoid this occurrence. In the event of their withdrawal it will be explained that their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate.

Inclusion/Exclusion criteria

Inclusion criteria

- Clinical diagnosis of erosive lichen planus affecting the vulval region (ELPV);
- Histological examination of vulval tissue that excludes malignant/pre-malignant disease; biopsy to be repeated if clinically indicated prior to consideration of systemic therapy
- Inadequate control despite first-line therapy with clobetasol propionate 0.05%;
- Disease severity of moderate-severe on Investigator Global Assessment
- Microbiological swabs negative, or result that is not clinically relevant, at study entry;
- Willing and capable of giving informed consent;
- Willing to have clinical images taken;
- Female aged 18 years or over (there is no upper age limit);
- Use of effective contraceptive methods in females of childbearing age for the duration of treatment.
- For participants receiving methotrexate to use effective contraceptive methods until 6 months after the end of treatment.

  NB - Acceptable contraceptive methods include: established use of oral, injected or implanted hormonal methods; placement of an intrauterine device (IUD) or intrauterine system (IUS); condom or occlusive cap (diaphragm or cervical/vault caps) with spermicide; true abstinence (when this is in line with the preferred and usual lifestyle of the participant); or vasectomised partner.

Exclusion criteria

- Cases of lichen sclerosus/lichen planus overlap;
- Received one or more of the trial drugs within the last one month (excluding clobetasol propionate 0.05%);
- Previous/current diagnosis of malignant disease (skin or internal);
- History of or current diagnosis of pre-malignant vulval skin or cervical disease;
- Receiving concurrent medications (as listed in the BNF) that would preclude the use of any of the trial medications in normal practice;

- History of clinically significant renal or liver impairment or other pre-existing medical conditions that would preclude the use of any of the trial medications in normal practice;

- Administration of a live vaccine (BCG, Measles, Mumps, Rubella, Yellow Fever, Oral Polio, Oral Typhoid) within the last 2 weeks;

- Pregnancy (to be confirmed by testing) or breast-feeding;
- Known sensitivity to any of the trial medications.

Expected duration of participant participation

Study participants will be participating in the study for 12 months.

Informed consent

All participants will provide written informed consent. The Consent Form will be signed and dated by the participant before they enter the trial. The Investigator will explain the details of the trial and provide a Participant Information Sheet (PIS), ensuring that the participant has sufficient time to consider participating or not. The Investigator will answer any questions that the participant has concerning study participation.

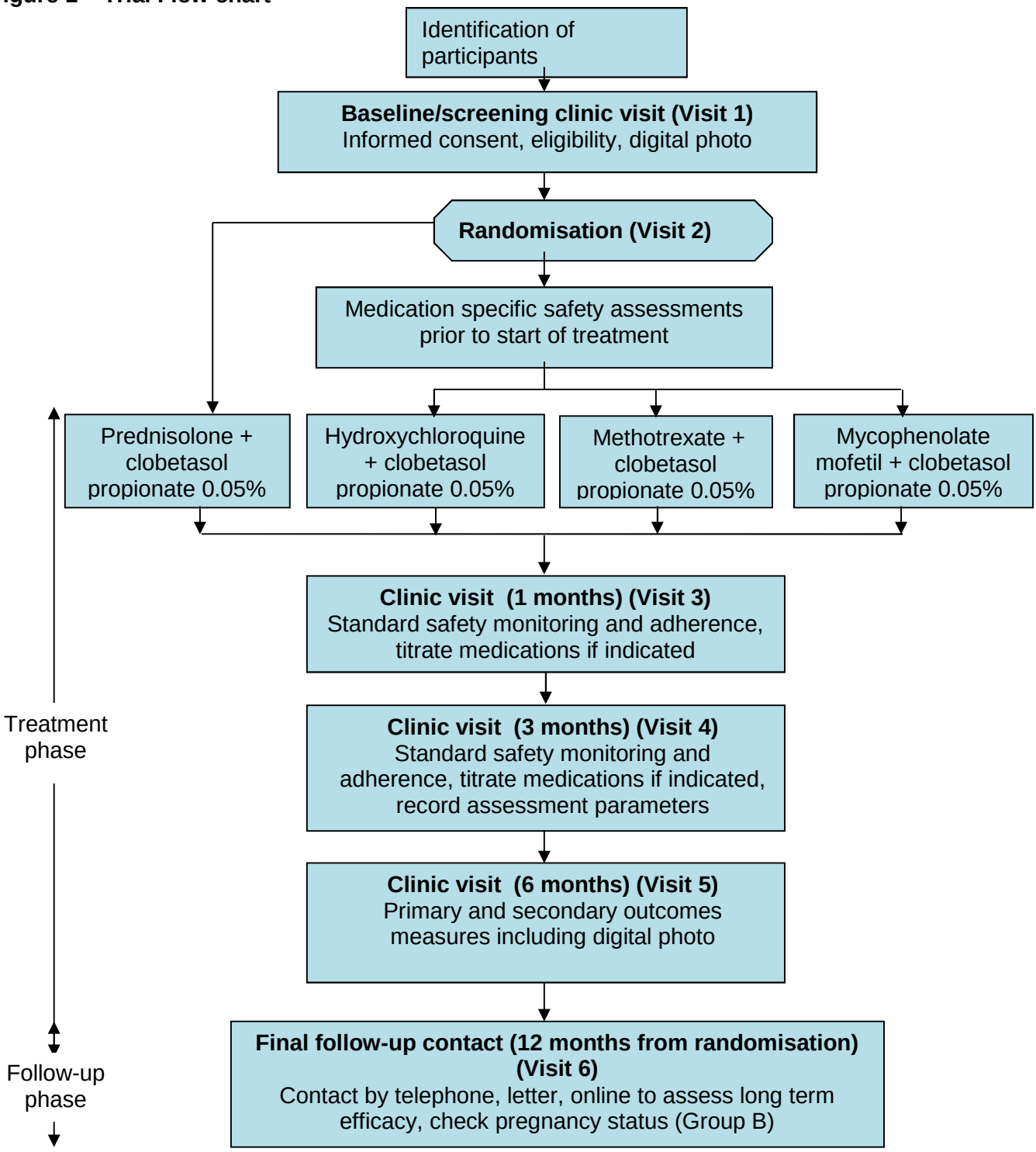
Informed consent will be collected from each participant before they undergo any interventions (including physical examination and history taking) related to the study. One copy of this will be kept by the participant, one will be kept by the Investigator, and a third will be retained in the participant's hospital records.

Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the trial, continuing consent will be obtained using an amended Consent form which will be signed by the participant.

TRIAL / STUDY TREATMENT AND REGIMEN

This is a pragmatic, multi-centre, open-label, randomised controlled trial. The study is an open-label trial.

Figure 1 – Trial Flow chart



- N.B. There are Interim Visits for Group C participants for monitoring purposes (see below)

Pre-screening

Participants with ELPV will be identified by participant's usual care teams through the outpatient clinic and databases held by the recruiting centres.

Participants with ELPV will be under the care of the PI, or a delegate, at the individual recruiting centres. Identified participants will be provided with a hELP Trial PIS at their outpatient clinic appointment or by post prior to their next appointment.

If the participant has received clobetasol propionate 0.05% for 3 months or more at any time during the management of their ELPV and still has moderate or severe disease as judged by Investigator Global Assessment, the following should be checked:

- That a biopsy of vulval tissue has been performed at some point in the patient's history which excludes malignant/premalignant disease(It may be clinically indicated to repeat the biopsy if unusual clinical features are present for example if the diagnosis was in doubt before commencing immunosuppressive therapy due to the risk of malignant transformation. This will be a decision made by the clinician on a case by case basis as part of normal care);
- That microbiological swabs are negative; or show a result that is not clinically significant (as infection can worsen disease severity). Swabs would only be repeated if there was a clinical need to do so as part of normal care.

Eligible participants will be provided with a full PIS (including standardised BAD wording about the interventions and a screening visit appointment will be made. The screening visit may be on the same day as pre-screening depending upon individual circumstances.

If the above criteria (i.e. biopsy and swabs) are not satisfied the necessary tests should be carried out and the participant reviewed with the results before being given a screening appointment.

Baseline visit (Study visit 1)

It may be possible to combine the baseline and safety screening visits (visits I and 2) for participants who have already had the relevant screening investigations done within the past month (this could be the case for participants under long-term care who were already been considered for systemic therapy) or those randomised to the control group, who do not need any safety screening investigations.

In some cases it may be considered clinically appropriate to commence treatment immediately and this will be at the discretion of the treating clinician provided they feel they have all of the relevant information to safely commence therapy and the participant has had enough time to consider their participation in the trial.

If at baseline there is any diagnostic uncertainty or if the patient has not had previous histological examination of vulval tissue, a biopsy to be taken from the edge of the lesion should be arranged according to normal practice to exclude neoplasia or premalignant disease.

Procedures to be carried out at baseline:

- Informed consent
- Confirmation of eligibility criteria.

- Pregnancy test for women of child bearing potential
- Assessment of patient and clinician reported outcome measures
    - Pain/soreness using a visual analogue scale.
    - Patient Global Assessment at baseline
    - Investigator Assessment by treating clinician at baseline
    - Investigator assessment by physician of other oral and vaginal sites
    - Hospital Anxiety and Depression Scale
    - Assessment of sexual function
    - 'Skindex-29' [22] and 'Short Form 36'[23]
- Digital images to be taken. Digital images do not necessarily need to be taken by medical photography as it is just looking for overall improvement rather than detailed improvement such as grade of erythema.

Safety Screening Visit and randomisation (Visit 2)

Once eligibility is confirmed participants will be randomised, when treatment allocation is known relevant safety screening investigations should be performed. These will be standard care safety monitoring investigations specific to the treatment allocation as recommended through national guidance.

Start of treatment

Participants will be randomised to one of four treatment groups as outlined in Table 2.

Table 2 – Table of treatment groups

Trial treatment arm	Dose summary
Control group: Clobetasol propionate 0.05% ointment alone plus initial reducing course of oral prednisolone	Clobetasol propionate 0.05% once daily for one month followed by alternate day application for one month then twice weekly application. Increase to daily during times of flare and then gradually reduce as before. A course of oral prednisolone starting at 20mg OD for 1 week then reduce by 5mg/week until stop. Oral prednisolone should be used as per usual practice following national guidelines; use of bone protection and gastro protection is not prohibited by this study.
Group A: Hydroxychloroquine plus clobetasol propionate 0.05% ointment	Hydroxychloroquine 400mg p.o. daily. May be reduced to 200mg daily depending upon clinical response. **Maximum dose 6.5mg/kg/d.**

	Oral hydroxychloroquine should be used as per usual practice following national guidelines including and appropriate safety monitoring. Clobetasol propionate 0.05% ointment to be used as in control group.
Group B: Methotrexate plus clobetasol propionate 0.05% ointment	Methotrexate starting dose 5-10mg p.o. weekly, increase by 2.5-5mg every 2 weeks until disease stabilised. **Maximum dose 25mg weekly.** Oral methotrexate should be used as per usual practice following national guidelines including and appropriate safety monitoring; use of folic acid is not prohibited by this study. Clobetasol propionate 0.05% ointment to be used as in control group.
Group C: Mycophenolate mofetil plus clobetasol propionate 0.05% ointment	Mycophenolate mofetil starting dose 500mg p.o. daily for the first week, 500mg twice daily for the second week then increase by 500mg each week until maximum dose reached. **Maximum dose 3g daily** (in divided doses). Oral Mycophenolate mofetil should be used as per usual practice following national guidelines including and appropriate safety monitoring. Clobetasol propionate 0.05% ointment to be used as in control group. In accordance with mycophenolate mofetil SmPC participants should have complete blood counts weekly during the first month, twice monthly for the second and third months of treatment, then monthly.

Interim Visits Group C Participants

- Weekly FBC, in accordance with mycophenolate mofetil SmPC (for month 1 of treatment).
- Blood tests to be performed either in secondary care or at GPs as per usual practice
- For participants taking mycophenolate mofetil treatment should be discontinuation if neutropenia develops (absolute neutrophil count < 1.3 x 10^^{3}).

1 month clinic visit (Study visit 3)

Outcomes will not be formally assessed at this stage.

Procedures to be carried out during this 1 month clinic visit are:

- Samples taken as required for standard care safety monitoring according to the national guidelines for each specific treatment.

- In accordance with mycophenolate mofetil SmPC participants should have complete blood counts weekly during the first month, twice monthly for the second and third months of treatment, then monthly.
- Pregnancy test for women of child bearing potential who are sexually active.
- Check treatment adherence.
- Document current dosage of therapy and adjust treatment dose as required;
- Check adverse events.

Interim Visits Group C Participants

- Fortnightly FBC, in accordance with mycophenolate mofetil SmPC (for months 2 & 3 of treatment).
- Blood tests to be performed either in secondary care or at GPs as per usual practice
- For participants taking mycophenolate mofetil treatment should be discontinuation if neutropenia develops (absolute neutrophil count < 1.3 x 10^^{3}).

3 month clinic visit (Study visit 4)

The purpose of this visit will be to perform an interim assessment of response and side effects, to assess tolerance and adjust trial medication dosage as necessary. This is normal follow up practice when these therapies are commenced in standard care.

Procedures to be carried out during this 3 month clinic visit are:

- Samples taken as required for standard care safety monitoring according to the national guidelines for each specific treatment.
- Pregnancy test for women of child bearing potential who are sexually active.
- Check treatment adherence.
- Document current dosage of therapy and adjust treatment dose as required;
- Check adverse events.
- Assess patient and clinician reported outcome measures

Interim Visits Group C Participants

- Monthly FBC, in accordance with mycophenolate mofetil SmPC (for months 4-6 of treatment).
- Blood tests to be performed either in secondary care or at GPs as per usual practice
- For participants taking mycophenolate mofetil treatment should be discontinuation if neutropenia develops (absolute neutrophil count < 1.3 x 10^^{3}).

6 month clinic visit (Study visit 5)

During this visit the clinician and participant should make a pragmatic decision about ongoing treatment. If adequate control or disease tolerability are considerably improved, the medication should be continued for as long as is clinically indicated, as per local guidelines.

Medication should be stopped at this visit if they have poor ongoing control of disease despite good adherence to the treatment regimen or if the side effects indicate that the participant should not carry on with the designated treatment. This will be a pragmatic decision by the treating physician according to local guidelines; there will be no study specific guidelines as this is a pragmatic study.

Procedures to be carried out during this 6 month clinic visit are:

- Samples taken as required for standard care safety monitoring according to the national guidelines for each specific treatment.
- Pregnancy test for women of child bearing potential who are sexually active.
- For those women who are receiving Methotrexate use of effective contraception for a further 6 months must be reinforced
- Check treatment adherence.
- Document current dosage of therapy and adjust treatment dose as required;
- Check adverse events.
- Assess patient and clinician reported outcome measures
- Repeat digital photograph to be taken. Digital images do not necessarily need to be taken by medical photography as it is just looking for overall improvement rather than detailed improvement such as grade of erythema.

12 month follow-up

This will be done by telephone, email or letter. Its purpose will be to assess long term use and efficacy.

Procedures to be carried out during this 12 month follow up are:

- Assess patient reported outcome measures
- Assess current medication use
- For those women who are receiving Methotrexate check pregnancy status and record result

Table 3 - Summary table of assessments

Assessment	0 months			1 month	3 months	6 months	12 months[7]
	Screening/ eligibility	Baseline/randomisation	Start of treatment				
Informed consent		✓					
Eligibility checks	✓						
Medical history	✓	✓					✓
Demographics		✓					
Randomisation		✓					
Standard safety monitoring [1]		✓		✓	✓	✓	
Pregnancy test [2]			✓	✓	✓	✓	Check status
Prescription given [3]			✓	✓	✓	✓	
Treatment log [4]			✓	✓	✓	✓	
Digital images [5]		✓				✓	
Pain/Soreness VAS [6]		✓			✓	✓	
Patient Global Assessment (PGA) [6]		✓			✓	✓	✓
Investigator assessment of vulva		✓			✓	✓	
Investigator assessment of other sites		✓			✓	✓	
Anxiety and depression scale score [6]		✓				✓	
Assessment of sexual function [6]		✓				✓	
Skindex 29 [6]		✓				✓	
SF36 [6]		✓				✓	
Patient diary [6]		✓		✓	✓	✓	
Adverse Events				✓	✓	✓	
Issue vouchers		✓			✓	✓	

[1] Please note specifically in accordance with mycophenolate mofetil SmPC participants should have complete blood counts weekly during the first month, twice monthly for the second and third months of treatment, then monthly. Recommended monitoring investigations are in section 12 of the CRF files

[2] For women of child bearing potential who are sexually active

[3] Recommended dosing schedule is in section 13 of the CRF files

[4] Treatment log is in section 1 of the CRF files

[5] Images ideally to be taken by medical photography (images at baseline and 6 months MUST be by same mode), analysis by blinded assessor at coordinating centre

[6] Assessment completed by the participant

[7] Assessment to be carried out by telephone, letter or email

Ongoing monitoring investigations

All participants

As part of usual practice biopsy should be repeated during the trial if the clinical appearance of the vulva changes and there is suspicion of premalignant/malignant change.

Control group:

As part of usual practice no ongoing monitoring investigations are required.

Active interventions:

As part of usual practice participants receiving hydroxychloroquine, methotrexate or mycophenolate mofetil require monitoring investigations. Monitoring of these should follow national recommendations from the BSR/BHPR guideline for disease-modifying anti-rheumatic drug therapy in consultation with the British Association of Dermatologists [24] and the individual medication SmPCs .

Concomitant and Rescue Medications and Treatments

All medications being continued by a participant on entry to the study and all medication given in addition to the study treatment during the study will be documented on the CRF (using generic name and trade name as appropriate) and also in the participant's medical records. Any changes to these treatments and dosage will be documented.
All concomitant medications present at baseline and which do not interfere with the assessments should, where possible, be kept constant from screening throughout the study.

Non-permitted concomitant treatment and medications:

Participants will **not be entered** into the intervention phase if randomisation could potentially result in the combinations documented in Table 5.

Table 5: Contraindicated medications for HELP Trial

Trial medication	Contraindicated medications
Hydroxychloroquine	Amiodarone Artemether (anti-malarial) Droperidol Histamine Laronidase Lemefantrine (antimalarial) Mefloquine Moxifloxacin Quinine
Methotrexate	Acitretin Clozapine Live vaccines

Mycophenolate mofetil	Live vaccines

Concomitant treatment and medications to be used with caution due to possibility of interaction:

A list of medications which should be used **with caution** in conjunction with the trial medications are listed in the individual SmPCs. Medications to be taken with caution in conjunction with the trial medications should not prevent a patient from entering the trial if eligibility criteria are met and the clinician is happy that systemic therapy is indicated. Participants should continue to take their medications for other conditions as normal.

Rescue therapy

If the trial treatments appear to be ineffective, in the first instance compliance with study medications should be checked and concomitant complications (e.g. infection and malignancy) should be ruled out. The frequency of topical clobetasol propionate 0.05% should then be increased to once daily, if not already. If no improvement in disease control is seen within one month, the clinician and the participant should decide whether to carry on with the trial treatment, or whether different therapy e.g. oral corticosteroids are required. If this is decided to be the case then the participant will be classified as a treatment failure and will be withdrawn from the treatment (although they will continue to be followed up where possible) .

Compliance

This is a pragmatic study that seeks to reflect current practice as far as possible (regardless of whether or not the drugs have been taken appropriately). ELPV is a painful and debilitating condition, making it more likely that participants will comply with treatment.

Adherence will be assessed by the managing physician and through self-assessment as reported by the participants at outpatient visits. Acceptable adherence is defined as a participant taking their medication as instructed and partaking in the necessary monitoring investigations.

Accountability for drugs & placebos

As this is a pragmatic open label study using prescriptions as normal from local pharmacies local policies and guidelines should be followed for prescription, dispensing and disposal of drugs.

Management of study drug overdose

Specific management of overdose is addressed in the SmPCs for the individual medications.

Criteria for terminating the study

Stopping the trial as a whole may be as a result of a formal interim analysis and based on overwhelming evidence of efficacy/inefficacy of any of the drugs, major safety concerns, new information, or issues with trial conduct (e.g. poor recruitment, loss of resources).

Stopping the trial at one centre will reflect unacceptable performance in recruitment or non-compliance with protocol.

Disposal of unused trial medications

As this is an open label trial with the prescription and dispensing of unchanged medications, any unused medications from the study should be returned as per local protocol.

STATISTICS

Methods

The Trial Steering Committee will approve the final statistical analysis plan and will also approve any amendments. Any deviations from the plan will be documented and justified in the final report.

The trial statistician will analyse the results based on treatment code using a statistical analysis plan finalised prior to revealing the coded allocation sequence. Only after the analysis is complete will the actual treatment arms corresponding to the treatment codes be revealed.

For the primary efficacy variable, the absolute difference in the proportion of treatment successes will be calculated for each experimental arm compared to the control. A 95% confidence interval will be presented for each treatment effect. As this is a multi-arm trial, the probability of finding a false positive result (familywise error rate) is increased. Therefore an analysis adjusting for multiple comparisons will also be presented, controlling the maximum familywise error rate at 5%.

All analyses will be conducted on the intention-to-treat population and will adjust for the minimisation variables.

Sample size and justification

Assuming a control success rate of 10% for the primary outcome, 17 patients per arm are required to detect a 40% absolute increase in the proportion of treatment successes (see page 16 for definition) in an experimental arm, with 80% power at the two-sided 5% significance level and using a 1:1:1:1 allocation ratio. The target difference between the groups is based upon data collected from patients and clinicians and is the minimally important clinical difference required to make taking one of the investigational medicinal products worthwhile.

To account for a loss-to-follow-up rate of 10% a total of 76 patients are required. To control the familywise error rate (probability of any type I error) at the 5% level and maintain the power of each pairwise comparison at 80%, 96 patients will be required

As this is the first RCT for ELPV and the recruitment window is limited to 12 months we will take a staged approach to recruitment. After six months, or the recruitment of 40 participants (whichever comes first) we will assess whether with the time and resources remaining the target of 76 or 96 patients (as per the sample size calculation for a definitive trial) can be achieved. If so, we will continue with recruitment.

Assessment of efficacy

All binary outcomes (primary outcome, secondary outcome number 8 listed on, page 16) will be analysed using an absolute difference in proportions. The change in continuous outcomes (secondary outcomes 1-7 listed on page 16) between baseline and follow-up will be compared between treatment arms using an absolute difference in means.

Assessment of safety

One of the secondary endpoints will be cessation of medication due to adverse events. As this study is designed to reflect normal practice, adverse events are most likely to be detected in one of three ways:

Patient-reported side effects at the time of their clinic consultation;

The managing clinician detecting abnormalities in monitoring blood tests;

The participant contacting the managing clinician in between clinic appointments to state any problems.

Adverse events will be collected if they are considered secondary to the study drug. All *serious* events will be collected regardless of whether seen as secondary and causality subsequently assigned.

Procedures for missing, unused and spurious data

If clinical images are missing at the primary endpoint, alternative data in the form of an Investigator Global Assessment by the treating clinician will still be available. The last recorded investigator global assessment will be used in place of the clinical image.

Procedures will be specified in the statistical analysis plan.

Definition of populations analysed

The populations whose data will be analysed are:

Safety set: All randomised participants who receive at least one dose of the study drug.

Full Analysis (eligible cohort) set: All participants who are randomised and continue to be eligible (after the post-randomisation eligibility assessments) to their allocated trial arm regardless of whether they commence the study medication, or not. All primary and secondary outcome measures will be performed on the full analysis set.

Per protocol set: All participants in the Full Analysis set who are deemed to have no major protocol violations that could interfere with the objectives of the study. Only the primary outcome measure will be completed on the per protocol set.

Efficacy will be assessed on both the full analysis set and the per protocol set. Safety summaries will be performed on the safety set. If more than one experimental arm is found to be better than the control group, an exploratory analysis will be performed to compare the experimental arms against each other. However, this will have limited power and the results will need to be interpreted appropriately.

ADVERSE EVENTS

Definitions

An adverse event is any unfavourable and unintended sign, symptom, syndrome or illness that develops or worsens during the period of observation in the study.
An AE does include a / an:

1. exacerbation of a pre-existing illness.

2. increase in frequency or intensity of a pre-existing episodic event or condition.

3. condition detected or diagnosed after medicinal product administration even though it may have been present prior to the start of the study.

4. continuous persistent disease or symptoms present at baseline that worsen following the start of the study.

5. side effect of the medication as described by the SMPC of the trial medications.

Known side effects and adverse events are detailed in the individual SmPCs

An AE does not include a / an:

1. medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that lead to the procedure is an AE.

2. pre-existing disease or conditions present or detected at the start of the study that did not worsen.

3. situations where an untoward medical occurrence has not occurred (e.g., hospitalisations for cosmetic elective surgery, social and / or convenience admissions).

4. disease or disorder being studied or sign or symptom associated with the disease or disorder unless more severe than expected for the participant's condition.

5. overdose of concurrent medication without any signs or symptoms.

A Serious Adverse Event (SAE) is any adverse event occurring following study mandated procedures, having received the IMP or placebo that results in any of the following outcomes:

1. Death

2. A life-threatening adverse event

3. Inpatient hospitalisation or prolongation of existing hospitalisation

4. A disability / incapacity

5. A congenital anomaly in the offspring of a participant

Important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

All adverse events will be assessed for seriousness, expectedness and causality:

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

Causality

Not related or improbable: a clinical event including laboratory test abnormality with temporal relationship to trial treatment administration which makes a causal relationship incompatible or for which other drugs, chemicals or disease provide a plausible explanation**.** This will be counted as "unrelated" for notification purposes.

Possible: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, but which could also be explained by other drugs, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Probable: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and is unlikely to be due to other drugs, chemicals or concurrent disease. This will be counted as "related" for notification purposes.

Definite: a clinical event, including laboratory test abnormality, with temporal relationship to trial treatment administration which makes a causal relationship a reasonable possibility, and which can definitely not be attributed to other causes. This will be counted as "related" for notification purposes.

An AE whose causal relationship to the study IMP is assessed by the Chief Investigator as "possible", "probable", or "definite" is an Adverse Drug Reaction.

With regard to the criteria above, medical and scientific judgment shall be used in deciding whether prompt reporting is appropriate in that situation.

Reporting of adverse events

Participants will be asked to contact the study site immediately in the event of any serious adverse event. All adverse events will be recorded and closely monitored until resolution, stabilisation, or until it has been shown that the study medication or treatment is not the cause. The Chief Investigator (delegated responsibility by the Sponsor) shall be informed immediately (within 24 hours) of any serious adverse events and shall determine seriousness and causality in conjunction with any treating medical practitioners. This process will be performed in parallel with the trial medical expert.
In the event of a pregnancy occurring in a trial participant monitoring shall occur during the pregnancy and after delivery to ascertain any trial related adverse events in the mother or the offspring.

All serious adverse events will be recorded and reported to the MHRA and REC as part of the annual reports. SUSARs will be reported within the statutory timeframes to the MHRA and REC as stated below. The Chief Investigator shall be responsible for all adverse event reporting.

SUSARs

A serious adverse event that is either sudden in its onset, unexpected in its severity and seriousness or not a known side effect of the IMP *and* related or suspected to be related to the IMP is classed as Suspected Unexpected Serious Adverse Reaction and requires expedited reporting as per the clinical trials regulations.

All serious adverse events that fall or are suspected to fall within these criteria shall be treated as a SUSAR until deemed otherwise.

The event shall be reported immediately (within 24 hours) of knowledge of its occurrence to the Chief Investigator who will subsequently inform the Data Monitoring Committee within 24 hours.

The Chief Investigator will:

- Assess the event for seriousness, expectedness and relatedness to the study IMP
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action
- If the event is deemed a SUSAR, shall, within seven days, enter the required data on the MHRA's eSUSAR web site.
- Shall inform the REC using the reporting form found on the NRES web page within 7 days of knowledge of the event
- Shall, within a further eight days send any follow-up information and reports to the MHRA and REC.
- Make any amendments as required to the study protocol and inform the ethics and regulatory authorities as required

Participant removal from the study due to adverse events

Any participant who experiences an adverse event may stop the study medication at the discretion of the Investigator although every attempt will be made to maintain follow up and to collect subsequent data.

ETHICAL AND REGULATORY ASPECTS

Ethics Committee and regulatory Approvals

The trial will not be initiated before the protocol, informed consent forms and participant and GP information sheets have received approval / favourable opinion from the Medicines and Healthcare products Regulatory Agency (MHRA), Research Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) department. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the MHRA, R&D and REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, in accordance with the Medicines for Human Use Regulations, Statutory Instrument 2004, 1031 and its subsequent amendments and the Department of Health Research Governance Framework for Health and Social care, 2005.

Informed Consent and Participant Information

The process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant or other legally authorised representative shall both sign and date the Consent Form before the person can participate in the study.

The participant will receive a copy of the signed and dated forms and the original will be retained in the Trial Master File. A second copy will be filed in the participant's medical notes and a signed and dated note made in the notes that informed consent was obtained for the trial.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be done before informed consent has been obtained.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the Informed Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

RECORDS

Drug accountability

Drug supplies will be kept in a secure, limited access storage area under the storage conditions specified by Pharmacy.

Case Report Forms

Each participant will be assigned a trial identity code number, allocated at randomisation, for use on CRFs other trial documents and the electronic database. The documents and database will also use their initials (of first and last names separated by a hyphen or a middle name initial when available) and date of birth (dd/mm/yy).

CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Participant Trial Number (the Trial Recruitment Log), to permit identification of all participants enrolled in the trial in accordance with regulatory requirements and for follow-up as required.

CRFs shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log.'

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.

The Chief or local Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

Source documents

Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, current medical records, laboratory results and pharmacy records. A CRF may also completely serve as its own source data. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

Direct access to source data / documents

The CRF and all source documents, including progress notes and copies of laboratory and medical test results shall made be available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities (MHRA).

DATA PROTECTION

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 1998. The CRF will only collect the minimum required information for the purposes of the trial. CRFs will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method).
Information about the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff, research participants and research protocols with both public liability insurance and clinical trials insurance. These policies include provision for indemnity in the event of a successful litigious claim for proven non-negligent harm.

TRIAL CONDUCT

Trial conduct will be subject to systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; CVs of trial staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); adverse event recording and reporting; drug accountability, pharmacy records and equipment calibration logs.
The Trial Manager, or where required, a nominated designee of the Sponsor, shall carry out a site systems audit at least yearly and an audit report shall be made to the Trial Steering Committee.

TRIAL DATA

Monitoring of trial data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Trial Manager, or where required, a nominated designee of the Sponsor, shall carry out monitoring of trial data as an ongoing activity.

Entries on CRFs will be verified by inspection against the source data. A sample of CRFs (10% or as per the trial risk assessment) will be checked on a regular basis for verification of all entries made. In addition the subsequent capture of the data on the trial database will be checked. Where corrections are required these will carry a full audit trail and justification.

Trial data and evidence of monitoring and systems audits will be made available for inspection by the regulatory authority as required.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Code of Research Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.
The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all trial databases and associated meta-data encryption codes.

DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee and Data Monitoring Committee as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above. Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare. If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

We will also ask participants if we can keep their contact details on file so that they may be contacted about future research.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

We will ensure that results are disseminated appropriately to the multiple specialties that manage ELPV. These primarily include dermatologists but also gynaecologists, genitourinary physicians and specialist nurses. The optimal way to reach these groups, in addition to publications in peer reviewed journals, will be through the British and International Societies for the Study of Vulval Disease (BSSVD and ISSVD). These multidisciplinary groups each hold a biennial conference at which we would present our findings. We would also aim to present at the British Association of Dermatologists (BAD) Annual meeting.

We hope that ultimately results from the definitive trial will stimulate further research into ELPV. Findings from ours and other research studies can then be combined to develop evidence based guidelines for treating ELPV which is urgently needed.

We would further collaborate with the BAD to update their PIL on Lichen Planus as the current version does not cover the erosive subtype. Other groups that our team has links include:

The UK Dermatology Clinical Trials Network

The UK Lichen Planus Society (UKLP)

NHS Choices

Nottinghamshire Collaboration for Leadership in Applied Health Research and Care (CLAHRC)

We will liaise with these groups to produce patient-oriented information that can be accessed through their online resources and can be generated into PILs for use in the clinic environment. In this way patients who have been directly involved in the research can benefit from their contribution. The UK DCTN and Centre of Evidence Based Dermatology (where this project is being co-ordinated) have a reputation for producing research newsletter updates and keeping their trial websites up to date. We will follow this lead and do the same for our project, hence keeping members of the public informed.

It should be stressed that participants will not be identified in any publications.

USER AND PUBLIC INVOLVEMENT

This study was originally prioritised through engagement with patient and clinician societies – the UK Lichen Planus Society and the British Society for the Study of Vulval Disease. Clinicians have continued to be consulted about the optimum and most clinically relevant trial design.

Service users have also commented on the design and conduct of this study as part of our initial feasibility work. Two focus group discussions (involving six patients) and one structured interview have been conducted. The results of these discussions were used to inform certain aspects of study design, outcomes measures (outcome measures were determined following these discussions) and comments were made as to the clarity of the participant information sheets.

One patient, who was involved in the structured interview, has acted as a patient representative for the trial and has contributed to Trial Development Group meetings. Another patient, who has a skin condition that affects the genital area (although not ELPV) has also been involved. This patient sits on the Patient Panel for the Centre of Evidence Based Dermatology and is experienced in performing lay reviews and being involved in this sort of work.

Furthermore, a patient who was part of the focus group is involved as a member of the trial steering committee.

STUDY FINANCES

Funding source

This study is funded by the National Institute for Health Research (NIHR Doctoral Research Fellowship awarded to Dr Rosalind Simpson, grant ref NIHR-DRF-2012-05-166).

Participant stipends and payments

Participants will not be paid to participate in the trial. However, an allowance of £10 in high street vouchers will be offered following the visits at baseline, month 3 and month 6. This allowance is intended to cover expenses / inconvenience for the participants.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: (name)_____

Signature:_____

Date: _____

Trial Statistician: (name)_____

Signature:_____

Date: _____

REFERENCES

1. Neumann, R., C.J. Dutt, and C.S. Foster, *Immunohistopathologic features and therapy of conjunctival lichen planus.* Am J Ophthalmol, 1993. **115**(4): p. 494-500.

2. Abraham, S.C., et al., *Esophageal lichen planus: case report and review of the literature.* Am J Surg Pathol, 2000. **24**(12): p. 1678-82.

3. Eisen, D., *The evaluation of cutaneous, genital, scalp, nail, esophageal, and ocular involvement in patients with oral lichen planus.* Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 1999. **88**(4): p. 431-6.

4. Cooper, S.M., et al., *The association of lichen sclerosus and erosive lichen planus of the vulva with autoimmune disease: a case-control study.* Arch Dermatol, 2008. **144**(11): p. 1432-5.

5. Danielsson, K., et al., *Autoantibodies and decreased expression of the transcription factor ELF-3 together with increased chemokine pathways support an autoimmune phenotype and altered differentiation in lichen planus located in oral mucosa.* J Eur Acad Dermatol Venereol, 2012.

6. Cooper, S.M., et al., *Erosive lichen planus of the vulva: weak circulating basement membrane zone antibodies are present.* Clin Exp Dermatol, 2005. **30**(5): p. 551-6.

7. Simpson, R.C. and R. Murphy, *Considerations for Disease Impact and Outcome Measures in Vulvar Disease.* J Low Genit Tract Dis, 2012.

8. Simpson, R.C. and R. Murphy, *Is vulval erosive lichen planus a premalignant condition?* Arch Dermatol, 2012. **148**(11): p. 1314-6.

9. Lewis, F.M. and C.I. Harrington, *Squamous cell carcinoma arising in vulval lichen planus.* British Journal of Dermatology, 1994. **131**(5): p. 703-5.

10. Cooper, S.M. and F. Wojnarowska, *Influence of treatment of erosive lichen planus of the vulva on its prognosis.* Archives of Dermatology, 2006. **142**(3): p. 289-94.

11. McPherson, T. and S. Cooper, *Vulval lichen sclerosus and lichen planus.* Dermatologic Therapy, 2010. **23**(5): p. 523-32.

12. Bradford, J. and G. Fischer, *Management of vulvovaginal lichen planus: a new approach.* J Low Genit Tract Dis, 2013. **17**(1): p. 28-32.

13. Lawton, S. and S. Littlewood, *Vulval Skin Conditions: Disease Activity and Quality of Life.* J Low Genit Tract Dis, 2013. **17**(2): p. 117-24.

14. Simpson, R.C., et al., *Diagnostic Criteria for Erosive Lichen Planus Affecting the Vulva: An international electronic-Delphi Consensus Exercise.* Br J Dermatol, 2013.

15. Cheng, S., et al., *Interventions for erosive lichen planus affecting mucosal sites.* Cochrane Database Syst Rev, 2012. **2**: p. CD008092.

16. Simpson, R.C., et al., *Real-life experience of managing vulval erosive lichen planus: a case-based review and U.K. multicentre case note audit.* Br J Dermatol, 2012. **167**(1): p. 85-91.

17. Simpson, R.C., K.T. Thomas, and R. Murphy, *Vulval Erosive Lichen Planus: A qualitative investigation of UK clinician views and principles of management.* Br J Dermatol, 2013(In press).

18. Lewis, F.M., M. Shah, and C.I. Harrington, *Vulval involvement in lichen planus: a study of 37 women.* British Journal of Dermatology, 1996. **135**(1): p. 89-91.

19. Helgesen, A.L., et al., *Vaginal involvement in genital erosive lichen planus.* Acta Obstet Gynecol Scand, 2010. **89**(7): p. 966-70.

20. Cribier, B., C. Frances, and O. Chosidow, *Treatment of lichen planus. An evidence-based medicine analysis of efficacy.* Arch Dermatol, 1998. **134**(12): p. 1521-30.

21. Simpson, R.C., K.S. Thomas, and R. Murphy, *Outcome measures for vulval skin conditions: A systematic review of randomised controlled trials.* Br J Dermatol, 2013.

22. Ponte, M., et al., *Effects of vulvodynia on quality of life.* J Am Acad Dermatol, 2009. **60**(1): p. 70-6.

23. Brazier, J.E., et al., *Validating the SF-36 health survey questionnaire: new outcome measure for primary care.* BMJ, 1992. **305**(6846): p. 160-4.

24. Chakravarty, K., et al., *BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists.* Rheumatology (Oxford), 2008. **47**(6): p. 924-5.