# Proactive against reactive therapy for the prevention of lichen sclerosus exacerbation and progression of disease – a pragmatic, parallel group randomised controlled trial with embedded economic evaluation and process evaluation

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# SYNOPSIS

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| **Title** | Proactive against reactive therapy for the prevention of lichen sclerosus exacerbation and progression of disease – a pragmatic, parallel group randomised controlled trial with embedded economic evaluation and process evaluation |
| **Acronym** | PEARLS |
| **Short title** | ProactivE Against Reactive treatment for Lichen Sclerosus |
| **Chief Investigator** | Dr Rosalind Simpson |
| **Objectives** | **Aim:**<br>To compare the clinical and cost effectiveness of a twice weekly topical corticosteroid maintenance strategy (proactive therapy) with as required treatment (reactive therapy) in the management of vulval lichen sclerosus (LS).<br><br>**Primary Objectives:**<br>Compare the effectiveness of proactive versus reactive strategies for using topical corticosteroids on the number of flares within 12 months, in people aged ≥5 years with vulval lichen sclerosus (LS).<br><br>**Secondary objectives:**<br>1. Assess the effectiveness of proactive versus reactive use of topical corticosteroids (TCSs) over 24 months in reducing disease progression.<br>2. Assess the clinical effectiveness of proactive versus reactive strategies for the management of vulval LS for up to 24 months.<br>3. Assess the safety of using potent and superpotent TCSs in the vulval area over 24 months.<br>4. Assess the cost-effectiveness of the two treatment strategies.<br>5. Understand the acceptability of reactive and proactive long-term treatment strategies and the barriers and facilitators to continuing with prescribed treatment. |
| **Trial Configuration** | 2-arm, parallel-group, randomised, open label assessor-blinded, multicentre, superiority trial with an internal pilot phase. |

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| **Internal pilot** | The internal pilot phase will test the recruitment of sites and participants against agreed milestones. A formal review will take place 6 months after the first randomisation. |
| **Setting** | Primary care centres may act as participant identification centres (PICs), recruitment is via secondary care hospitals throughout the UK or specialist community hubs |
| **Sample size estimate** | Based on the likelihood ratio test statistic for comparison of two negative binomial rates, 320 participants for analysis are required to detect a relative reduction of 25% in number of flares, from an average of 4 flares per participant per year in the reactive therapy to 3 in the proactive therapy (absolute reduction of 1 flare per patient in a year), with 90% power, 1:1 allocation and a two-sided significance level of 0.05, using dispersion parameter value of 0.34 estimated from our survey data. To allow for ~20% non-collection of primary outcome data and treatment non-compliance, we plan to recruit 400 participants in total. |
| **Number of participants** | 400 |
| **Eligibility criteria** | **INCLUSION CRITERIA**<br>1. Clinical or biopsy confirmed diagnosis of vulval LS<br>2. Currently controlled disease (asymptomatic with minimal clinical evidence of active disease) at baseline<br>3. Age ≥5 years<br>4. Able to give consent/child assent plus parental consent<br><br>**EXCLUSION CRITERIA**<br>1. Previous vulval intraepithelial neoplasia (VIN) or vulval squamous cell carcinoma (SCC)<br>2. Contraindications to topical steroids<br>3. Concomitant use of other topical anti-inflammatory vulval treatments<br>4. Using systemic immunosuppressants (for any indication)<br>5. Using systemic treatment for LS<br>6. Patients with surgical alteration of vulval skin as part of gender reaffirming surgery, or patients not born with a vulva<br>7. Pregnant and breastfeeding women |
| **Description of interventions** | **Intervention:** Potent or superpotent TCS, used for two non-consecutive days per week, even in absence of symptoms ('proactive treatment') |

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| | **Control:** Treat flare as required with potent or superpotent TCS ('reactive treatment') daily until flare resolves (typically up to 7 days) |
| **Duration of trial** | Expected duration of the trial is 57 months from the start of set-up |
| **Randomisation and blinding** | Eligible patients who consent will be individually allocated in a 1:1 ratio to either proactive or reactive use of TCS. Treatment will be assigned randomly using a minimisation algorithm with a random element, balancing across groups on:<br>• recruitment site<br>• age at randomisation<br>- children – 5 to <12 years<br>- adolescent – 12 to <16 years<br>- adult – 16 to <45 years<br>- perimenopausal - 45 years & above<br>• time since last flare (≤6 months, >6 months)<br>• strength of TCS prescribed (potent or superpotent)<br>Allocation will be concealed using a web-based algorithm and held on a secure server, accessed via a secure website.<br><br>It is not possible to blind the participants, but independent examining clinicians will make assessments of disease activity and scarring at 12 and 24 months and will be blinded to treatment allocation. |
| **Outcome measures** | **PRIMARY OUTCOME**:<br>Number of flares over 12 months. Flare is defined as worsening of symptoms[1] requiring increased application of TCSs.<br><br>**SECONDARY OUTCOMES:**<br>**Clinical effectiveness**<br>• Progression of scarring assessed by blinded assessor at 12 and 24 months by comparing post randomisation assessment to baseline photographs (if patients consented), or assessed clinically if consent has not been given for photographs:<br>- Adults: scarring worsened (yes/no).<br>- Children and adolescents: failure of normal vulval development (clinical assessment) and/or evidence of scarring (yes/no) |

[1] *Symptoms of LS in women and girls include (but are not limited to) itching, burning, pain, painful sexual intercourse, pain on defecation.*

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| | • Vulval Architectural Severity Scale (VASS) at 12 and 24 months post randomisation.<br>• Time to first flare.<br>• Clinician global severity assessment of LS (5-point ordinal scale) at 3, 6, 12, 18 and 24 months. Plus assessed by blinded assessor at 12 and 24 months.<br>• Condition specific Quality of Life (QoL) at 3, 6, 12, 18 and 24 months using:<br>- Vulvar Quality Life Index (VQLI) (adults)<br>- Children's Dermatology Life Quality Index (CDLQI) (adolescents and children).<br>• Sexual function (adults only) using Female Sexual Function Index at 12 and 24 months.<br><br>**Safety**<br>• Adverse reactions e.g. stinging, skin thinning measured by patient reported symptoms and clinical examination from randomisation over 24 months.<br>• Development of vulval intraepithelial neoplasia or vulval squamous cell carcinoma at 24 months.<br><br>**Treatment acceptability and potential barriers/facilitators to treatment**<br>• Acceptability of treatment strategy at 12 and 24 months using a Likert scale.<br>• Adherence to treatment at 3, 6, 12, 18 and 24 months.<br>• Qualitative interview sub-study at 12 months.<br><br>**Cost-effectiveness**<br>• Generic utility instrument to measure QoL at 3, 6, 12, 18 and 24 months with EQ-5D-5L (adolescents and adults) and Child Health Utility Instrument - Nine dimensions (CHU-9) (children).<br>• Resource use including prescription, direct and indirect healthcare and out-of-pocket costs associated with vulval LS at 3, 6, 12, 18 and 24 months. |
| **Statistical methods** | Primary analysis will compare the number of flares per person-time between the treatment groups, with analysis according to the allocated treatment strategy regardless of adherence to the strategy (intention-to-treat). Negative binomial regression, adjusted for minimisation factors and incorporating exposure time (person-time), will be used to calculate the incident rate ratio and 95% confidence interval. Supplementary analyses for the primary outcomes will use |

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| | per-protocol or complier average causal effect (CACE) analysis to estimate the effect of the intervention among the participants who complied with their allocated intervention. Exploratory subgroup analyses for the primary outcome will be performed according to age at randomisation (children or adult), time since last flare, and strength of prescribed TCS (potent or superpotent), by including appropriate interaction terms in the primary model. Between-group comparison of secondary outcomes will be based on an appropriate regression model for the outcome (or appropriate non-parametric estimator), adjusted for the same variables as the primary analysis. A full statistical analysis plan will be developed and approved by the Trial Steering Committee (TSC) prior to database lock. |
| **Health economics** | Primary analysis undertaking a within-trial all-age cost effectiveness analysis estimating the incremental cost per flare averted from an NHS and Personal Social Services (PSS) perspective. Secondary cost utility analyses will be undertaken for those aged 12 and over, using the EQ-5D-5L to estimate Quality Adjusted Life Years (QALYs) and separately a cost utility analysis for those aged 11 years and under using the CHU-9D to estimate QALYs. Sensitivity analyses will be undertaken to explore the impact of missing data, a wider perspective, adherence and other uncertainties detailed in the health economic analysis plan. |

# ABBREVIATIONS

| | |
|---|---|
| **ACT** | Anatomical Therapeutic Chemical Classification |
| **ADR** | Adverse Drug Reaction |
| **AE** | Adverse Event |
| **CACE** | Complier Average Causal Effect |
| **CDLQI** | Children's Dermatology Life Quality Index |
| **CEA** | Cost Effectiveness Analysis |
| **CEAC** | Cost Effectiveness Acceptability Curve |
| **CF** | Informed Consent Form |
| **CGH** | Community Gynaecological Hub |
| **CHU-9D** | Child Health Utility Instrument - Nine dimensions |
| **CI** | Chief Investigator overall |
| **e-CRF** | Electronic/Case Report Form |
| **CUA** | Cost Utility Analysis |
| **DAP** | Data Analysis Plan |
| **DMC** | Data Monitoring Committee |
| **DMP** | Data Management Plan |
| **DSUR** | Development Safety Update Reports |
| **EOT** | End of Trial |
| **EQ-5D-5L** | EuroQol-5 Dimension 5 Level |
| **FTU** | Fingertip Unit |
| **GCP** | Good Clinical Practice |
| **GP** | General Practitioner |
| **ICER** | Incremental Cost Effectiveness Ratio |
| **IMP** | Investigational Medicinal Product |
| **ISF** | Investigator Site File |
| **QALY** | Quality-Adjusted Life Year |
| **LAG** | Lay Advisory Group |
| **LS** | Lichen Sclerosus |
| **MA** | Marketing Authorisation |
| **MHRA** | Medicines and Healthcare products Regulatory Agency |
| **MICE** | Multiple Imputation by Chained Equations |
| **MP** | Monitoring Plan |
| **NCTU** | Nottingham Clinical Trials Unit |
| **NHS** | National Health Service |
| **NIHR** | National Institute for Health Research |
| **P/GIS** | Parent / Guardian Information Sheet |
| **PI** | Principal Investigator at a local centre |
| **PIC** | Participant Identification Centre |
| **PIS** | Participant Information Sheet |
| **PPI** | Patient and Public Involvement |
| **PSS** | Personal Social Services |

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| **QALYs** | Quality-Adjusted Life Years |
| **QoL** | Quality of Life |
| **R&D** | Research and Development department |
| **RA** | Risk Assessment |
| **RCT** | Randomised Controlled Trial |
| **REC** | Research Ethics Committee |
| **SAE** | Serious Adverse Event |
| **SAP** | Statistical Analysis Plan |
| **SAR** | Serious Adverse Reaction |
| **SCC** | Squamous Cell Carcinoma |
| **SmPC** | Summary of product Characteristics |
| **SUSAR** | Suspected Unexpected Serious Adverse Reaction |
| **TCS** | Topical Corticosteroid |
| **TMG** | Trial Management Group |
| **TMF** | Trial Master File |
| **TSC** | Trial Steering Committee |
| **UK** | United Kingdom |
| **USM** | Urgent Safety Measure |
| **VASS** | Vulvar Architectural Severity Scale |
| **VIN** | Vulval Intraepithelial Neoplasia |
| **VQLI** | Vulvar Quality Life Index |

## DEFINITIONS

| | |
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| **EMIS & SystemOne** | Healthcare software, information technology and related services in the UK, electronic healthcare record system. |
| **REF** | Method used in pilot phase for data to be analysed rapidly using framework analysis (REF). |
| **QSR NVivo** | Qualitative data analysis software. |
| **Flare** | Worsening of symptoms requiring increased application of TCSs as reported by participants via two weekly reminders. |
| **Clinical or biopsy confirmed diagnosis of vulval LS** | Clinical diagnosis by an expert by findings of typical clinical features on examination, or by findings on histological examination when assessed by a histopathologist. The trial team will collect information at baseline on clinical vs histological diagnosis. |
| **Resolution of LS symptoms** | No more itching/discomfort (resolution of symptoms) as well as improvement of visual signs of flare (bruising under the skin, fissures, skin thickening) back to normal. |
| **End of flare** | Participant stops using their topical corticosteroids due to resolution of LS symptoms. |
| **Rescue TSC use** | Application once daily until symptoms and signs of active LS resolve (typically 7 days). |

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# 1 TRIAL BACKGROUND INFORMATION AND RATIONALE

## 1.1 Presentation and impact of Lichen Sclerosus

Vulval Lichen Sclerosus (LS) is a chronic inflammatory condition, with incidence peaks in childhood and post-menopause [1, 2]. Reported prevalence is up to 3%, affecting around 1 million women in the UK. Inflammation causes whitening of vulval tissue, bleeding under the skin, texture change and cuts. Patients report itching, pain (particularly during sex) and discomfort in daily activities [2]. Paediatric vulval LS accounts for up to 15% of cases [3-5]. In adults, inflammation leads to scarring which can narrow the vaginal entrance, bury the clitoris and resorb/fuse the labia minora. Untreated LS causes progressive loss of vulval architecture. Scarring may occur early in the disease [6, 7] and is irreversible without surgery [8]. LS persisting beyond puberty can prevent normal vulval anatomical development [4]. LS also occurs in males, but prevalence is believed to be less. LS is associated with risk of vulval intraepithelial neoplasia (VIN, a pre-malignant condition) and vulval squamous cell cancer (SCC, an invasive malignancy). Rates of vulval SCC with LS are 20 times higher than in the general population [9] with higher mortality than vulval SCC without LS [10].

The impact of LS is considerable due to the intimate and 'taboo' nature of the problem. LS affects psycho-social and sexual functioning and leads to embarrassment, isolation and relationship breakdown/difficulty in forming new relationships [11, 12]. A national survey of 325 women with a vulval health disorder reported that women with LS were twice as likely to have suffered with depression and over one-fifth had contemplated self-harm or suicide as a result of their condition [13].

## 1.2 Current management of LS

Treatment goals are to control symptoms, prevent scarring and reduce the risk of cancer. First-line therapy with a superpotent topical corticosteroid (TCS) applied daily for three months, combined with a soap substitute and barrier emollient to protect from irritants [14] achieves normalisation of skin colour/texture and resolution of symptoms in 70% patients [7]. However, LS is a relapsing-remitting condition and evidence to inform maintenance of remission/prevention of progression is poor. In many girls, the disease remits at puberty, but this cannot be assumed, and some studies describe a more chronic course where resolution does not always occur and continued treatment is necessary [15, 16]. A critically appraised topic has shown that 37% of girls have symptoms that persist past the first 3 months of treatment, 67% who were in remission recur after 1 year and 55% recur after 4 years [17].

It is important to note that LS can also affect boys and men, but there are differences in the management of male LS as circumcision is believed to be curative and long-term maintenance is usually not required. This protocol, therefore, is only in reference to women and girls with vulval LS.

## 1.3 Evidence for long term treatment of LS

Long term LS management strategies are not backed up by strong randomised controlled trial (RCT) evidence. UK guidelines are based on expert consensus [18], a few observational studies [14] and a small number of RCTs with, most assessed as low quality of evidence. A single armed, prospective study of patients with vulval LS in clinical and histological remission suggests 50% will

have relapsed after 16 months and 84% after 4 years [19]. UK guidelines state that there is no evidence for an optimal maintenance regimen [20] and European guidelines reiterate that 'maintenance' treatment is a matter of debate [21]. A recent commentary noted variation in ongoing management [22] and an Australasian consensus statement advises long term individualised proactive maintenance therapy [23].

### 1.4 Rationale of the trial

The trial will address two priorities from the 2018 Lichen Sclerosus Priority Setting Partnership [24]: a) What is the best way to prevent and manage anatomical changes caused by LS? b) Is it necessary to continue treatment for patients with LS who do not have any symptoms and/or signs of disease activity?

There are no robust long term RCTs to compare proactive against reactive TCS therapy for LS. An observational study [25] suggests symptoms and scarring are reduced by proactive therapy. Another small study (n=27) reports 60% of patients using only emollients will have a relapse compared with none using proactive TCS over one year [26].

Alternative topical treatment options are either unsuitable or ineffective [21, 23]. Topical calcineurin inhibitors pose theoretical increased risk of cancer due to their immunosuppressant effects on T cells. Topical retinoids are irritant to vulval skin, furthermore retinoids are teratogenic and therefore unsuitable for large proportion of LS sufferers. Topical testosterone has not been found to be effective. At present, there are no other known topical agents on the horizon for first line treatment of LS. As a result, TCS, which are inexpensive, effective and well understood, remain the mainstay of LS treatment. Optimising their usage and standardising advice given to patients is important.

The PEARLS Trial will compare reactive and proactive TCS maintenance strategies in a superiority trial of proactive over reactive treatment. The trial recruitment will be from primary and secondary care, including both women and girls ≥5 years of age with vulval LS. Due to differences in management and outcomes between male and female patients and reduced prevalence of LS in males, only female patients will be included. Paediatric patients are included, due to even greater paucity of evidence for this subset. There is a clear peak of incidence in girls aged four to six years old, which represents 7–15% of all vulvar lichen sclerosus cases [27]. The only published randomised control trial with paediatric patients enrolled only a handful of children and reported their data together with adult participants, making it impossible to draw any conclusions about the prepubertal patients [28]. Follow-up will be for 2 years to assess for scarring, with optional consent obtained for longer term outcomes and economic modelling (separate funding to be sought if appropriate).

### 1.5 Overall risk assessment of the trial

PEARLS is a pragmatic trial and trial participants in both intervention and comparator group will receive commonly prescribed topical corticosteroids (TCSs), which is tailored for the participant. The only difference between the treatment groups is the treatment regimen/strategy.
TCSs are licensed products. Their use for lichen sclerosus has been an established practice in healthcare. It is therefore considered that participants in the treatment group ('proactive' group)

are not at a higher risk than those in the comparator group ('reactive' group). Given that all TCSs are licenced treatments, used as off-label basis in routine practice for the same indication, the trial has been considered to be a phase IV trial and is consistent with risk type category A.
Although TCSs can be safely applied to the whole body in a single dose with minimal risk of adverse reactions, there is however a risk of adverse reactions following long-term use of topical corticosteroid on localised areas of skin (e.g. skin thinning, telangiectasia). These will be monitored during clinical examination at follow-up visits (or at an unscheduled trial visit, as necessary).
There is no additional risk identified in children with the use of TCSs. Adverse reactions used in the paediatric population will be monitored in the same way as in adults. Safety reporting procedure is described in section 11.

# 2 DETAILS OF INVESTIGATIONAL MEDICINAL PRODUCT(S) (IMP)

## 2.1 Description

Participants will be randomised to one of two treatment strategies:

**Intervention group:** Potent or superpotent topical corticosteroid (TCS) to be applied on two non-consecutive days per week even in the absence of symptoms (proactive).

**Comparator group:** Potent or superpotent topical corticosteroid (TCS) to be applied as required to treat a LS flare (reactive).

More details on the treatment strategies are described in Table 6. Intervention vs comparator group. Choice of TCS will be according to the patient's usual care and the trial will test TCS as a class defined by their Anatomical Therapeutic Chemical (ATC) classification numbers D07AC and D07AD (for potent and superpotent respectively). As this is a pragmatic trial, we will test the strategy of proactive vs reactive treatment using the potency of topical corticosteroid recommended by the treating clinician (potent or superpotent). There are several generic names available for these prescribed TCSs and all available brands and forms can be prescribed. The examples of the most commonly prescribed brands/products of the TCS class are listed below (for details see Table 1):

- Dermovate ointment - superpotent TCS
- Elocon® 0.1% w/w ointment - potent TCS

Table 1. Potent and superpotent TCSs description

| Name of exemplar product | International Non-Proprietary Name (INN) | Potency | Chemical name or CAS number | Formulation | Excipients | ATC code | Chemical and pharmacological properties | Manufacturer and MA (Marketing Authorisation) number |
|---|---|---|---|---|---|---|---|---|
| Dermovate ointment | Clobetasol 17-propionate 0.05375% w/w | Superpotent | 25122-46-7 | Ointment | Propylene glycol, Sorbitan sesquioleate, White soft paraffin. | D07AD01 | Pharmacotherapeutic group: Corticosteroids, very potent, dermatological preparations (group IV). Topical anti-inflammatory activity. The major effect on skin is a non-specific anti-inflammatory response, partially due to vasoconstriction and decrease in collagen synthesis. | Manufacturer: GlaxoSmithKline UK<br><br>MA number: PL 10949/0028 |
| Elocon® 0.1% w/w Ointment | Mometasone furoate 0.1% w/w | Potent | 83919-23-7 | Ointment | Hexylene glycol, Phosphoric acid, Propylene glycol stearate, White beeswax, White soft paraffin, Purified water. | D07AC13 | Pharmacotherapeutic group: Corticoids, potent (group III) Exhibits marked anti-inflammatory activity and marked anti-psoriatic activity in standard animal predictive models. | Organon Pharma (UK) Limited, UK<br><br>MA number: PL 00025/0578 |

## 2.2 Manufacture

The IMPs to be used in this trial will be manufactured by the MA holder as they are to be obtained from standard pharmacy stock.

## 2.3 Packaging and labelling

In accordance with the Medicines and Healthcare products Regulatory Agency (MHRA) risk-adapted approach to the management of clinical trials of investigational medicinal products, and the pragmatic nature of the trial, this trial will not require trial specific labelling [29]. This is considered a Type A trial, as all LS treatments being used in this trial are established treatments with well documented safety profiles. The TCSs used in the trial are "off the shelf" and are widely prescribed in standard care for patients with LS. Their use is already established practice for the treatment of LS and supported by published guidelines. This trial is merely exploring comparison of effects of different treatment strategies used in patients with LS. No new side effects are anticipated and the risk to patients is therefore low.

## 2.4 Storage, dispensing and return

IMPs will be stored in accordance with the standard conditions for these products whilst in the community pharmacies, and as per the instructions on the product when in the participant's home. Dispensing will be via community pharmacies as per current practice. Returns will not be made and products should be disposed of in accordance with the accompanying, standard, product instructions.

## 2.5 Placebo/comparator

No placebo is being used in this trial. The comparator is a strategy of reactive treatment to manage disease flares, as detailed in sections 2.1 and 8.

## 2.6 Known Side Effects

Known adverse reactions to TCSs include: infection, folliculitis, paraesthesia, burning sensation, contact dermatitis, skin hypopigmentation, hypertrichosis, skin striae, acneiform dermatitis, skin atrophy, pruritus and application site pain, according to the Summary of Product Characteristics (SmPC).

TCSs are used to treat a very wide range of inflammatory skin conditions, including common conditions such as eczema, psoriasis, vitiligo as well as LS. The risk of adverse effects for potent or superpotent TCSs (such as used in this trial) is modest, but it is widely acknowledged that the fear of adverse effects is usually disproportionately high, given the relative infrequency with which such adverse effects are observed. Despite the ubiquity of topical corticosteroids in dermatological therapeutic practice, there is surprisingly little evidence to quantify the risk of adverse effects accurately. Guidelines often suggest that potent/superpotent TCSs should be used only under close clinical supervision, particularly when used in children on anatomical sites where the skin is thinner and therefore more prone to adverse effects such as atrophy.

## 2.7 Reference Safety Information:

There are number of TCS products available on the market and all available brands and forms can be prescribed to participants. The safety information of two of the most commonly used TCSs, as listed in Table 1, are described in corresponding exemplar SmPCs and will act as the reference safety information for the trial:

- Superpotent TCS - Dermovate ointment - SmPC dated 16-Aug-2023, section 4.8
- Potent TCS - Elocon® 0.1% w/w Ointment - SmPC dated 20 April 2023, section 4.8

# 3 TRIAL OBJECTIVES AND PURPOSE

## 3.1 Purpose

To compare the clinical and cost effectiveness of a twice weekly topical corticosteroid maintenance strategy (proactive therapy) with as required treatment (reactive therapy) in the management of vulval LS.

## 3.2 Primary objectives

Compare the effectiveness of proactive versus reactive strategies for using topical corticosteroids on the number of flares within 12 months, in people aged ≥5 years with vulval LS.

## 3.3 Secondary objectives

1. Assess the effectiveness of proactive versus reactive use of TCSs over 24 months in reducing disease progression.
2. Assess the clinical effectiveness of proactive versus reactive strategies for the management of vulval LS for up to 24 months.
3. Assess the safety of using potent and superpotent TCSs in the vulval area over 24 months.
4. Assess the cost-effectiveness of the two treatment strategies.
5. Understand the acceptability of reactive and proactive long-term treatment strategies and the barriers and facilitators to continuing with prescribed treatment.

Trial objectives and outcome measures as mapped in Table 2.

*Table 2. Mapped objectives and outcome measures*

| Objective | Outcome Measure | Outcome Time Point | Method |
|---|---|---|---|
| **Primary objective** | | | |
| Compare the effectiveness of proactive versus reactive strategies for using topical corticosteroids on the number of flares within 12 months, in people aged ≥5 years with vulval Lichen Sclerosis | Number of flares | Over 12 months | Text/app/email reminders every two weeks for 12 months Participant reported |
| **Secondary objectives** | | | |
| 1. Assess the effectiveness of proactive versus reactive use of TCS over 24 months in reducing disease progression | Scarring | At 12 and 24 months | Clinical assessment comparing to baseline photographs, if consent given, or comparing to baseline clinical assessment diagram if consent for photographs not obtained. |
| | VASS | At 12 and 24 months | Clinical assessment |
| | Development of VIN or vulval SCC | Over 24 months | Clinical assessment/medical notes |
| 2. Assess the clinical effectiveness of proactive versus reactive strategies for the management of vulval Lichen Sclerosus for up to 24 months | Global clinical severity assessment | At 3, 6, 12, 18 and 24 months | Clinical assessment |
| | Sexual function | At 12 and 24 months | Participant reported |
| | Time to first flare | At 1st flare over 12 months | Text/app/email reminders every two weeks for 12 months Participant reported |

| Objective | Outcome Measure | Outcome Time Point | Method |
|---|---|---|---|
| | Condition specific QoL<br>CDLQI (adolescents and children) and VQLI (adults) | At 3, 6, 12, 18 and 24 months | Questionnaire<br>Participant reported |
| | Generic utility instrument measured by EQ-5D-5L (adolescents and adults) and CHU-9 (children) | At 3, 6, 12, 18 and 24 months | Questionnaire<br>Participant reported |
| 3. Assess the safety of using potent and superpotent TCSs in the vulval area over 24 months | Adverse events | For the duration of participation | Participant reported/clinical assessment/medical notes |
| 4. Assess the cost-effectiveness of the two treatment strategies. | Resource use | At 3, 6, 12, 18 and 24 months | Questionnaire<br>Participant reported |
| 5. Understand the acceptability of reactive and proactive long-term treatment strategies and the barriers and facilitators to continuing with prescribed treatment | Adherence to treatment | At 3, 6, 12, 18 and 24 months | Questionnaire<br>Participant reported |
| | Acceptability of treatment | At 12 24 months | Questionnaire<br>Participant reported |
| | Barriers and facilitators | At 12 months | Qualitative interviews |

# 4 TRIAL DESIGN

## 4.1 Trial configuration

PEARLS is a 2-arm, parallel-group, individually randomised, open label assessor-blinded, multicentre, superiority trial with an internal pilot phase.

## 4.2 Trial flowchart

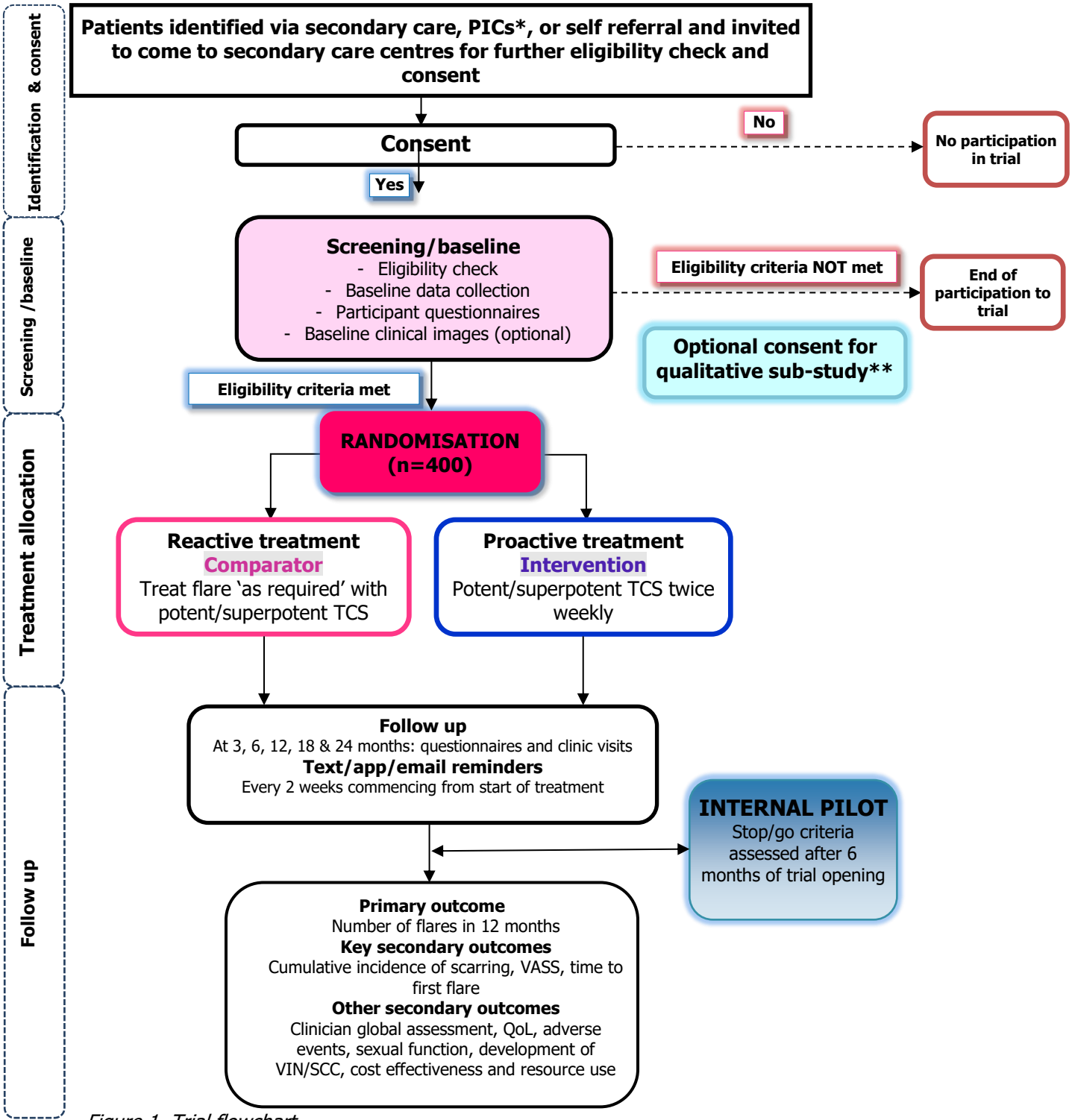



*Figure 1. Trial flowchart*

**For participant identification and screening pathways please refer to section 7.2*
***See details in section 13*

### 4.3 Primary endpoint

Number of flares over 12 months. Flare is defined as worsening of symptoms requiring increased application of TCSs as reported by participants via two weekly reminders.

### 4.4 Secondary endpoint

For the purposes of recording outcomes, age categories are divided into:

A. Children (5 - <12 years)
B. Adolescents (12 - <16 years)
C. Adults (16 years and over).

**Clinical effectiveness**

- Progression of scarring assessed by blinded assessor at 12 and 24 months by comparing post randomisation to baseline photographs (if participant consented), or assessed clinically if consent has not been given for photographs:
  - Adults: scarring worsened (yes/no)
  - Children and adolescents: failure of normal vulval development (clinical assessment) and/or evidence of scarring (yes/no).
- Vulvar Architectural Severity Scale at 12 and 24 months post randomisation (VASS) [30].
- Time to first flare.
- Global clinical severity assessment of LS (5-point ordinal scale) at 3, 6, 12, 18 & 24 months, plus assessed by blinded assessor at 12 and 24 months.
- Condition specific QoL at 3, 6, 12, 18 & 24 months using:
  - Vulvar Quality Life Index (VQLI) (adults) [31]
  - Children's Dermatology Life Quality Index (CDLQI) (adolescents and children) [32].
- Sexual function (adults only) using Female Sexual Function Index [33] at 12 & 24 Months.

**Safety**

- Development of vulval intraepithelial neoplasia or vulval squamous cell carcinoma at 24 months.
- Targeted adverse events e.g. stinging, skin thinning measured by patient reported symptoms and clinical examination from randomisation over 24 months.

**Treatment acceptability and potential barriers/facilitators to treatment**

- Acceptability of treatment strategy at 12 and 24 months using a Likert scale.
- Adherence to treatment at 3, 6, 12, 18 & 24 months.
- Qualitative interview sub-study at 12 months.

**Cost-effectiveness**

- Generic utility instrument to measure QoL at 3, 6, 12, 18 & 24 months with EQ-5D-5L (adolescents and adults) and CHU-9 (children).
- Resource use including prescription, direct and indirect healthcare and out-of-pocket costs associated with LS at 3, 6, 12, 18 and 24 months.

Table 3 below lists outcomes according to age bands.

*Table 3. Collection methods of outcome measures in age groups*

| Outcome | Children (5-<12 years) | Adolescents (12-<16 years) | Adults (16 and over) |
|---|---|---|---|
| **Flares (number and time to first flare)** | Text/email/app every 2 weeks to parent/guardian | Text/email/app every 2 weeks to patient/parent/guardian | Text/email/app every 2 weeks to patient |
| **Progression of scarring** | Photographs (at baseline, optional), VASS or clinical examination | Photographs (at baseline, optional), VASS or clinical examination | Photographs (at baseline, optional), VASS or clinical examination |
| **Global clinical severity** | Clinical assessment | Clinical assessment | Clinical assessment |
| **Condition specific QoL** | CDLQI | CDLQI | VQLI |
| **Generic utility instrument (health related QoL)** | CHU-9D | EQ-5D-5L | EQ-5D-5L |
| **Sexual function** | - | - | Female Sexual Function Index (FSFI) |
| **Acceptability to treatment** | Bespoke questions | Bespoke questions | Bespoke questions |
| **Adherence to treatment** | Bespoke questions | Bespoke questions | Bespoke questions |
| **Resource use (bespoke and healthcare)** | Bespoke questions | Bespoke questions | Bespoke questions |
| **VIN/vulval SCC** | Clinical assessment/medical notes | Clinical assessment/medical notes | Clinical assessment/medical notes |
| **Adverse effects of therapy** | Clinical assessment, medical notes/patient/parent/guardian reported | Clinical assessment, medical notes/patient/parent/guardian reported | Clinical assessment, medical notes/patient reported |

### 4.5 Safety endpoints

Given the low-risk nature of this trial, we will adopt a targeted approach to Adverse Event (AE) and Serious Adverse Event (SAE) reporting. All AE reporting is described in detail in section 11.

### 4.6 Stopping rules and discontinuation

Individual participants can withdraw from the trial at any time (see section 7*).* The trial may be discontinued partially or stopped entirely. The rules of the trial discontinuation are described in sections 7.8, 8.9 and 15.5.

# 5 RANDOMISATION AND BLINDING

Upon entry to the trial, participants will be individually allocated in a 1:1 ratio to either proactive or reactive use of TCS. The strategies of treatment will be assigned randomly using a minimisation algorithm with a random element, balancing across groups on:

- Recruitment by site
- Age at randomisation (prepubertal – 5 to <12 years, adolescent - 12 to <16 years, adult - 16 to <45 years, perimenopausal 45 years & above)
- Time since last flare (≤6 months, >6 months)
- Strength of study TCS (potent or superpotent)

The trial arm allocation will be concealed using a web-based algorithm and will be held on a secure server at the Nottingham Clinical Trial Unit (NCTU). The randomisation will be accessed via a secure website developed and maintained by NCTU. Unique usernames and passwords will be provided to those who are delegated the role of randomising participants using the web-based system. Randomisation can be performed by suitably trained site research staff assigned this task on the *Delegation of Responsibilities Log*, following confirmation of each individual participant's eligibility by a clinician.

## 5.1 Maintenance of randomisation codes and procedures for breaking code

The research staff randomising a participant won't be blinded to the allocation due to the nature of the treatment.

The outcomes to which an assessor will be blinded to treatment allocation will be scarring, assessed at 12 and 24 months. Global clinical severity will normally be reported by the site unblinded clinician at all time points but additionally it will be assessed by the blinded assessor at 12 and 24 months. The blinded assessor will be someone that is deemed by the PI as adequately qualified (and recorded on the delegation log) to examine and identify changes in participants with vulval LS. They will not be involved in any other trial activities. A blinded assessor will compare changes at 12 and 24 months against baseline photos or clinical assessment diagram. Where a blinded assessor is not available at the time of clinical assessment, assessment will be made subsequently by review either of the photos taken during the assessment or by comparison with the clinical diagram, and record findings. Revealing the treatment strategy allocation to the assessor should not be necessary as both involve topical steroids. However, in the unlikely scenario that assessors identify safety concerns, such as vulval cancer/pre-cancer, they will report to the site Principal Investigator (PI), who is unblinded, and who will inform NCTU as per the NCTU standard process.

The trial statisticians and Trial Steering Committee (TSC) members will be blinded to participant group allocations. An unblinded independent NCTU statistician will produce closed reports for the Data Monitoring Committee (DMC). No emergency unblinding processes are necessary. The Table 4 below describes which trial staff will be blinded/unblinded to the treatment allocation.

*Table 4. Blinding status of the PEARLS trial staff*

| | Blinding status | Comments |
|---|---|---|
| **Participant** | Not blinded | Not practical due to trial design |
| **Principal Investigator and other site staff** | Not blinded | Not practical due to trial design |
| **Clinical assessor at site** | Blinded assessor | Scarring and global clinical severity assessment at 12 and 24 months |
| | Unblinded assessor | Global clinical severity at all time points and development of VIN or vulval SCC at 24 months |
| **Chief Investigator** | Blinded | The Chief Investigator will remain blinded to treatment allocation with an exception of participants recruited at their site. |
| **Database Programmer** | Not blinded | The database programmer will be responsible for the management of the randomisation system and will have access to unblinded datasets within the trial database |
| **PEARLS Trial Management staff within NCTU** | Not blinded | PEARLS Trial Management staff within NCTU will have access to the unblinded datasets within the trial database including information on treatment regimen adherence |
| **Data Management** | Not blinded | Data management staff will have access to the unblinded datasets within the trial database to ensure data quality and undertake central monitoring activities |
| **Trial Statistician and Senior Trial Statistician** | Blinded | The trial and senior trial statistician will not have access to treatment allocations or data which has the potential to unblind until after the first database lock for the analysis |
| **Independent Statistician** | Not blinded | A statistician, independent to the trial team, will be responsible for the generation of closed reports for the Data Monitoring Committee (DMC) and other potentially unblinding data and will therefore be unblinded to trial treatments |

# 6 TRIAL MANAGEMENT

The trial will be managed from a central coordinating centre, the Nottingham Clinical Trials Unit (NCTU), University of Nottingham. The trial will be overseen by the TSC, DMC and Trial Management Group (TMG).

The Chief Investigator has overall responsibility for the trial and shall oversee all aspects of the trial management. The data custodian will be the Chief Investigator. Chief Investigator agrees to conduct the trial in compliance with the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

## 6.1 Trial Committees

The trial committee terms and references will be defined in TSC/DMC/TMG charters.

### 6.1.1 Trial Management group

The TMG will be responsible for oversight of the day-to-day management and for all aspects of the trial, including recruitment rate, budget management, safety reporting, protocol compliance and ensuring appropriate action is taken to safeguard trial participants and quality of the trial. Membership includes but is not limited to the CI, co-investigators, Trial Statisticians, Trial Manager and Data Manager. Other relevant members of the trial team will be invited to TMG meetings as required. The TMG members will meet regularly (approximately monthly) to ensure all practical details of the trial are progressing and working well.

### 6.1.2 Trial Steering Committee

The role of the TSC is to provide overall supervision for a project on behalf of the Sponsor and Funder and to ensure that the trial is conducted to the rigorous standards set out in the Department of Health's UK Policy Framework for Health and Social Care Research and the Guidelines for Good Clinical Practice. The remit of the TSC is to provide advice, focus on trial progress and adherence to trial protocol, patient rights, safety and well-being as well as considering new information and its relevance to the research question. The TSC will also ensure that all ethical and regulatory approvals are obtained and agree proposals for significant substantial protocol amendments.

The TSC will be composed of an Independent Chair, other independent members with clinical and research expertise, along with a lay member/Patient and Public Involvement (PPI) representative. The CI will also be a member of the TSC. National Institute for Health and Care Research (NIHR) and Sponsor Representatives may be invited to attend TSC meetings as observers, if required. The TSC will adopt a charter to define its terms of reference and operation. The TSC will meet on a regular basis as specified in the TSC charter, e.g. yearly or more regularly in response to significant changes to the trial and send reports and make recommendations to the TMG/Sponsor/Funder. The TSC members will be required to sign a 'conflict of interests declaration form'.

The TSC will consider and act, as appropriate, upon the recommendations of the DMC, and in accordance with the TSC Charter.

### 6.1.3 Data Monitoring Committee

Independence is a key characteristic of a DMC where the committee members are completely uninvolved in the running of the trial and thus cannot be unfairly influenced (either directly or indirectly) by people, or institutions, involved in the trial. The role of the DMC is to monitor outcome data, safety data and other trial data and make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue. The safety, rights and well-being of the trial participants will be considered paramount, alongside the validity of the trial data. The DMC will also consider data emerging from other related trials, provided by the Sponsor or Funder. The DMC will operate in accordance with a trial specific charter.

The DMC will consist of an Independent Chair, an Independent Clinician and an Independent Statistician. The DMC will meet on a regular basis as specified in the DMC charter, e.g. yearly, more regularly, or on an ad-hoc basis, when a meeting may be held in urgent instances in response to safety concerns. The DMC members will be required to sign a 'conflict of interests declaration form'. Following the meetings, the DMC will make recommendations to the TSC.

## Duration of the Trial and participant involvement

Participation duration: Participants will be followed up for a minimum of 24 months from the date of their randomisation.

Recruitment duration: The expected recruitment period to the trial is 18 months (first 6 months as pilot phase).

## 6.2 End of the Trial

The end of the trial will be the date of the final database hard lock. NCTU will notify the MHRA and REC that the trial has ended within 90 days of the end of trial. Should the trial be terminated early, NCTU will inform the MHRA and REC within 15 days of the end of trial. NCTU will provide them with a summary of the clinical trial report within 12 months of the end of trial.

# 7 SELECTION AND WITHDRAWAL OF PARTICIPANTS

## 7.1 Recruitment

For illustration of recruitment pathway please refer to the trial flowchart in section 4.2.

Recruitment of trial participants will be facilitated via different routes as described below in section Screening. Trial website, social media, PPI or PPI charity groups, Be Part of Research or online health communities will be utilised to share trial details. Short animation video will be available on these platforms.

## 7.2 Screening

### 7.2.1 Identification of potential participants at Participant Identification Centres (PICs)

PICs will be set up at GP surgeries to remove barriers to participation for those participants who would not normally attend hospital appointments for LS management. PICs, i.e. GP surgeries, will display information about the trial (e.g. posters or fliers in waiting rooms, clinical areas) to raise awareness in patients with LS and facilitate participant identification. As some patient-GP contact is still remote, this information may also be displayed online via practice website or social media groups.

PICs will conduct a search using a predefined strategy to produce a list of potential participants. The search will be done via Electronic Healthcare Record Systems, EMIS (formally known as Egton Medical Information Systems) or SystemOne and reviewed by a General Practitioner (GP) or other members of the clinical care team, to ensure that no patients have been included inappropriately and to confirm potential eligibility of patients. These patients and/or their parents or guardians will then be approached by the PICs by different methods, used at GP surgeries, including text message, email or invitation letter. Patients will be provided with the PIS, and instructions on how to express their interest in the trial and give their permission to be contacted by the secondary care site to arrange a screening visit (eligibility check). The agreement to be contacted will be tracked on the trial database. The secondary care site, which is in the catchment area of the PICs, will phone the patient to perform basic eligibility checks (e.g. symptom free, willing to travel) and ascertain their willingness to participate.

### 7.2.2 Identification of potential participants and screening at secondary care sites

Potential participants will also be identified at the secondary care centres, i.e. hospital standard vulval clinics or community hubs (such as gynaecology or dermatology centres), where staff are experienced in the management of vulval skin disorders. The information about the trial will be displayed in the relevant clinical areas at hospitals or community hubs.

At the secondary care centres, patients will be identified and approached by their clinical care team, where possible in advance of their next appointment, however they may also be identified while attending routine clinic appointments and will be offered the opportunity to meet the site team investigator or a research nurse for further information.

Following the identification of patients by the clinical care team, an invitation letter (which will include appropriate instructions how to express interest in the trial), along with the PIS, will be provided to the patient. Once the patient has expressed interest, and agreed to be contacted, a site team member will get in touch (usually by phone or face-to-face at the patient's clinic appointment) to perform basic eligibility checks (e.g. symptom free, willing to travel) and willingness to participate. Participants' contact details of those who do not consent for us to retain them, will be deleted at the end of the trial.

### 7.2.3 Self referrals

Potential patients, who have been diagnosed with LS and found the trial details via the routes described in 7.1 above, may be able to self-refer. They will be able to get in touch with the study team directly or log their interest to be contacted by a central research team or a team at a secondary care site. Patients who self-refer will be pre-screened and provided with a PIS, if appropriate, and a suitable secondary care site will arrange a screening visit (eligibility check).

Screening for eligibility criteria

Once patients (identified through either PICs, self-referral or secondary care centres) confirm their expression of interest, they will be invited by site team to their first, screening/baseline visit. At this visit, the trial will be discussed in more detail and, if agreed, informed consent will be taken.

Following informed consent (section 7.9), eligibility will be confirmed by a site investigator, a medically qualified doctor, and baseline data will be collected. A physical investigation will be conducted to confirm diagnosis. Patients will be asked to confirm that they are symptom-free. Other eligibility criteria will be confirmed from medical notes or discussion. If the patient meets all eligibility criteria, they will be randomised to the trial treatment at which point the participant trial unique number will be allocated.

Those who do not meet the trial eligibility criteria, or do not wish to participate in the trial, not be randomised and will be excluded from the trial.

## 7.3 Participant identification and screening logs

The site team at the trial centres will maintain a list of potentially eligible participants who were identified through self-referrals, PICs or secondary care centres and were approached to discuss the trial. The sites will upload anonymised data (totals) from the logs on monthly basis on the trial database.

The trial central coordinating team, at the NCTU, may request the identification and screening logs from the sites, for monitoring purposes. The sites will redact any personal identifiable information from the logs prior to sending to the NCTU.

## 7.4 Eligibility criteria

### 7.4.1 Inclusion criteria

1. Clinical or biopsy confirmed diagnosis of vulval LS
2. Currently controlled disease (asymptomatic with minimal clinical evidence of active disease) at baseline
3. Age ≥5 years
4. Able to give consent/child assent plus parental consent

### 7.4.2 Exclusion criteria

1. Previous vulval intraepithelial neoplasia (VIN) or vulval squamous cell carcinoma (SCC)
2. Contraindications to topical steroids
3. Concomitant use of other topical anti-inflammatory vulval treatments
4. Using systemic immunosuppressants (for any indication)
5. Using systemic treatment for LS
6. Patients with surgical alteration of vulval skin as part of gender reaffirming surgery, or patients not born with a vulva
7. Pregnant and breastfeeding women

The trial inclusion criteria are designed to mimic usual practice. LS is a clinical diagnosis and biopsy is only performed if there is a poor response to first-line treatment, diagnostic doubt or concern of pre-malignancy/malignancy. Those patients who are asymptomatic and with minimal evidence of active disease at baseline are considered to be well-controlled. Girls aged 5 or older will be included as there is paucity of evidence for LS management in paediatric patients.

By definition, anyone with previous vulval intraepithelial neoplasia, or vulval cancer, have complicated LS, are not eligible for the trial. If there is sensitivity to topical corticosteroids entering the trial might worsen this. Finally, other anti-inflammatory agents, topical or systemic, would act as a confounder, and patients on these treatments are more likely to have complicated disease.

In accordance with the Clinical Trial Facilitation Group "recommendations related to contraception and pregnancy testing in trials", given that the trial IMPs are all licensed products, participants of child-bearing potential can be included in the trial providing an acceptable effective method of contraception is used until treatment discontinuation. 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. Participants will be advised of the importance of these requirements before entry into the trial. The trial IMPs are licensed products which are routinely prescribed to pregnant women therefore a pregnancy test will not be required before entry to the trial, but the participant should contact their GP and seek further direction if pregnancy should subsequently be confirmed.

Disease progression will be assessed, monitored and analysed based on characteristic anatomical features of the vulva. For this reason, patients who were born with a vulva (which has not been altered as part of gender affirming surgery) can be considered to be included in the trial.

### 7.5 Expected duration of participant participation

Trial participation for individual participants will last for 24 months.

### 7.6 Removal of participants from therapy or assessments

Everyone conducting or taking part in this trial should follow the PeRSEVERE guiding principles [34] for clinical trial research:

1. Everyone running or taking part in the trial should be aware that participants may choose to change, reduce or stop their participation after they agree to join the trial.
2. The nature and extent of participation changes should be the participant's decision to make, within the limits of what is possible for the trial. Their decision should be informed and freely-given.
3. Everyone running or taking part in the trial should be aware that collecting as much as possible of the trial's planned data can help the trial reach a clear and reliable conclusion.
4. Loss of contact between a participant and researchers should not be considered the same as a participant saying that they want to stop the trial participation.
5. The trial data collection should continue until the trial participant explicitly tells researchers that they want it to stop.
6. Data collected for the trial up to the point the trial participant stops providing data should be used in the trial analysis, and kept with the other trial data until the trial is over.
7. Stopping participation early does not affect participants' right to receive the trial-related information later on, if they want to receive it or if it could be important for them to have.

Participants who become pregnant during the course of the trial will be withdrawn from the trial and should contact their GP for further direction regarding the pregnancy, and their managing clinician for advice on managing LS during pregnancy. The occurrence of pregnancy will be captured at site via the trial *Pregnancy Notification Form* on the trial database.

### 7.7 Withdrawal from the trial

Prior to obtaining informed consent, participants will be informed that entry into the trial is entirely voluntary and that their treatment and care will not be compromised by their decision. It will also be explained that they can withdraw at any time.

The trial site staff must inform NCTU of all withdrawals. If site staff are made aware of a participant's withdrawal of consent for any trial activities, the PI or delegate should record this in the electronic case report form (e-CRF) as soon as possible (and within 24 hours) to ensure the correct procedures are followed by NCTU and the site team.

Stopping participation early does not affect participants' right to receive trial-related information when it becomes available (should they wish to receive). Participants will be asked their reason(s) for withdrawal but are not obliged to provide these. In the event of participant withdrawal, it will be explained that the data collected from them so far will be retained and will

still be used in the analysis of the trial. The data will not be erased as it should be possible to recreate a participant's participation up to their point of any withdrawal. Participants can withdraw from clinic visits, questionnaires, treatment or from all procedures completely. Different level of withdrawal and data collection according to withdrawal levels are summarised in Table 5.

*Table 5. Use of data according to withdrawal type*

| Withdrawal type | Withdrawal procedure | Use of data |
|---|---|---|
| Discontinue from ALL trial procedures and data collection (complete withdrawal) | Site will complete relevant e-CRF and inform NCTU as soon as possible.<br>ALL clinic visits, data collection and treatment will stop from the date of withdrawal onwards.<br>Participants will stop participation in the trial completely and will continue with their routine care, if needed.<br>Results of the trial and updates may be communicated with the participant if they consented and still wish to receive updates. | Any data collected prior to participant withdrawal will be retained and used. Data from the date of withdrawal onwards will not be collected. |
| Discontinue from trial treatment | Site will complete relevant e-CRF and inform NCTU.<br>Participants will cease the trial treatment and will continue with their routine care, if needed. | Any data collected prior to participant withdrawal will be retained and used.<br>From the date of withdrawal onwards, only following data will be collected:<br>- Number of flares<br>- Time to first flare<br>- Clinical photographs (if consented), VASS and clinical examination<br>- Development of VIN or vulval SCC<br>- Global clinical severity assessment<br>- Vulval development and scarring (in adolescents and children)<br>- Sexual function (adults only)<br>- Condition specific QoL - CDLQI for children and VQLI for adults<br>- Generic utility instrument (health related) – CHU-9D for children and EQ-5D-5L for adolescents/adults<br>- Adverse events<br>- Resource use<br>- Concomitant medication |
| Discontinue from clinic visits | Site will complete relevant e-CRFs and inform NCTU. | Any data collected prior to participant withdrawal will be retained and used. |

| | | |
|---|---|---|
| | Any participant that requests to discontinue from clinic visits will be marked on the trial database so that next visits will not be populated. Clinic visits will stop from the date of withdrawal onwards but the data can be collected from medical notes and from the trial questionnaire. | From the date of discontinuation onwards only following data will be collected:<br>- Number of flares<br>- Time to first flare<br>- Development of VIN or vulval SCC<br>- Sexual function (adults only)<br>- Condition specific QoL - CDLQI for children and VQLI for adults<br>- Generic utility instrument (health related) – CHU-9D for children and EQ-5D-5L for adolescents/adults<br>- Adverse events<br>- Resource use<br>- Acceptability of treatment<br>- Adherence to treatment<br>- Concomitant medication |
| Discontinue follow-up questionnaires | Site will complete relevant e-CRFs and inform NCTU.<br>Upon participant request to discontinue from trial questionnaires will be marked as withdrawn from questionnaire collection on the trial database and no further contact will be made with the participant for the purpose of obtaining questionnaire follow-up data.<br>Clinic visits and data collection from medical notes will continue. | Any data collected prior to participant withdrawal will be retained and used.<br>From the date of discontinuation onwards only following data will be collected:<br>- Number of flares<br>- Time to first flare<br>- Clinical photographs (if consented), VASS and examination<br>- Development of VIN or vulval SCC<br>- Global clinical severity assessment<br>- Vulval development and scarring (in adolescents and children)<br>- Adverse events<br>- Concomitant medication |

| | | |
|---|---|---|
| Discontinue from two weekly notifications | Site will complete relevant e-CRF and inform NCTU as soon as possible.<br>The trial treatment and ALL follow up data collection, apart from two weekly data collection, will continue | Any data collected prior to participant withdrawal will be retained and used.<br>From the date of withdrawal onwards, only following data will be collected:<br>- Clinical photographs (if consented), VASS and clinical examination<br>- Development of VIN or vulval SCC<br>- Global clinical severity assessment<br>- Vulval development and scarring (in adolescents and children)<br>- Sexual function (adults only)<br>- Condition specific QoL - CDLQI for children and VQLI for adults<br>- Generic utility instrument (health related) – CHU-9D for children and EQ-5D-5L for adolescents/adults<br>- Adverse events<br>- Resource use<br>- Concomitant medication |

The site team should make every effort to keep their contact with the trial participants, within the scope of this protocol, to collect as much as possible data that can help to answer the research question.

### 7.8 Discontinuation and withdrawal following randomisation

Participants who withdraw after randomisation will not be replaced. In addition, if any significant new information becomes available regarding the treatment they received in the trial, it may be necessary to contact them in the future.

Participants can also opt to discontinue their allocated intervention or receive an alternative treatment, but still continue in the trial for follow-up measures. A record of participants who do not receive allocated treatment regimen, along with the actual treatment regimen they received and the reason for not receiving the allocated treatment, will be kept for analysis purposes. Participants will be asked to continue to provide follow up data in the event that they wish to withdraw from receiving the trial treatment.

### 7.9 Informed consent

All participants will provide written informed consent. The PIS will be provided to patients in advance to their appointments, where possible, to ensure that they have sufficient time to consider their participation to the trial. At their screening/baseline visit, the Investigator (or a delegate) will explain the details of the trial and answer any questions that the patient may have concerning the trial. During the discussion, if needed, the usual hospital interpreter and translator services will be available to help with the understanding of the trial, discuss the participant information sheets, and consent forms. However, the consent forms and information sheets will not be available printed in other languages. The Informed Consent Form (ICF) will be signed and dated by the participant before they enter the trial and countersigned by the Investigator (or a delegate).

Where the participant is a child, under age 16, an appropriate age range Participant Information Sheet will be provided. Parental or legal guardian consent must be obtained, however, in addition to parent/guardian consent, assent will be obtained for all children. The assent will be formally captured (signed) for those 12 years and older. In the event of any conflict between the parent and child, the child WILL NOT enter the study. Once a participant reaches the age of legal consent, adult PIS and a specific re-consent form will be used to re-consent.

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 given to the participant, one will be kept by the Investigator (who will then upload the copy on the trial database), and a third will be retained in the patient's hospital records. Completed ICF will be uploaded on the trial database for monitoring purposes.

Any subsequent amendment to the prevailing protocol, which might affect a participation in the trial, continuing consent will be obtained using an amended consent form which will be signed by the participant.

In this trial participants will be followed up for 2 years to assess for scarring. An optional consent will be obtained for longer term outcomes and economic modelling to allow potential future follow

up through efficient means (such as routine data) as part of a separately funded study, e.g. to investigate malignancy rates and other long-term effects in relation to maintenance regimens (separate funding to be sought if appropriate).

# 8 TRIAL TREATMENT AND REGIMEN

Trial participants will be allocated to either 'Proactive' or 'Reactive' treatment arm. In the 'Proactive' arm, participants will be prescribed their TCS by their treating physician twice a week for 24 months, regardless of presence of LS symptoms. In the 'Reactive' arm, participants will be allocated to use their TCS only when LS symptoms (or increase in visual signs) are present (please refer to table below for more details). The choice of TCS will be at the discretion of the treating physician. Repeat prescriptions will be obtained by participants as per the usual care.

*Table 6. Intervention vs comparator group*

| **Treatment group** | **Proactive**<br>**Intervention group** | **Reactive**<br>**Comparator group** |
|---|---|---|
| Treatment name | Superpotent or potent topical corticosteroid | Superpotent or potent topical corticosteroid |
| Formulation | Cream/ointment | Cream/ointment |
| Dosage | 1 application twice-weekly on two non-consecutive days in the absence of symptoms.<br>If symptoms flare, apply once a day until symptoms resolve. | Only use during flare.<br>Apply once a day until symptoms resolve. |
| Route of administration | Topical (application of a thin layer on affected area) | Topical (application of a thin layer on affected area) |
| Sourcing | Provided directly as per usual care | Provided directly as per usual care |
| Packaging and labelling | Topical steroid will be provided and labelled as per usual care prescription, and as required for each patient | Topical steroid will be provided and labelled as per usual care prescription, and as required for each patient |

Topical dosage of TCSs for both trial groups will be recommended in Fingertip Units (FTU) depending upon area affected by LS (typically 0.5-1 FTU). FTU is the amount of topical steroid (ointment or cream) that is applied along an adult's fingertip to the first crease in the finger. One FTU is sufficient to treat an area of skin twice the size of the flat of an adult's hand with the fingers together (i.e. a 'handprint'). FTU is also used to treat an area of skin on a child. Participants in the 'Proactive' arm will use the recommended amount of their TCS twice per week on a scheduled time of the day. Participants in the 'Reactive' arm will use the recommended amount of their TCS but only when required. If participants are identified to have a flare (regardless of their group allocation) they will be instructed to use the recommended amount once a day until their symptoms subside up to one month. The treating physician will advise on the dosage for adults or children.

All participants will have received advice, as part of clinical care, on a good vulval hygiene routine including avoidance of irritants and the use of emollient as a soap substitute and barrier/moisturiser. The choice of emollient will be usual medical practice for that recruiting site. If, in the proactive arm, a participant forgets to apply their treatment, they should use their ointment/cream as soon as they remember it, provided there is a gap of at least 24 hours between the doses.

## 8.1 Study visits

This section describes study visits. Each visit will take place face-to-face, in clinics. More detailed information about assessments is summarised in Table 7.

**Baseline**

Visit **1**

(at baseline)

- Informed consent
- Eligibility check and confirmation
- Contact details
- Collection of baseline data:
    - Concomitant medication (relevant to condition) and relevant medical history
    - Demographic information
    - Clinician global severity assessment
    - Scarring assessment (VASS, clinical examination)
    - Vulval development and scarring (in adolescents and children)
    - Condition specific QoL (VQLI or CDQLI)
    - Health related QoL assessed by EQ-5D-5L in adolescents/adults and CHU-9D in children
    - Bespoke resource use questionnaire and healthcare questionnaire
- Clinical photographs, or clinical diagram if consent for photographs not taken
- Randomisation

Clinical photographs

Photographs will be taken at baseline for patients who consent to this, to assess scarring. Photographs will not be a mandatory requirement as some patients are hesitant due to the intimate nature of LS. Parents of children with LS are less likely to consent to photographs. Photographs taken up to 1 month prior to baseline appointment can be accepted, if the patient had no active disease during this period. If a photograph is not taken, clinicians will be asked to document a detailed clinical diagram (using a predefined schematic diagram) for comparison. Images taken at the baseline will remain in participant's medical notes and will not be sent to NCTU. Subsequent clinical examinations will assess changes against the baseline photo/diagram. Blinded assessments of scarring (or failure of normal anatomical development as appropriate) will be assessed at 12 and 24 months comparing to baseline clinical photographs.

**Follow up between clinic visits**

Number of flares (primary outcome) and time to first flare (secondary outcome) will be captured throughout the first 12 months of the study. The primary outcome will be collected every two weeks via text/email/app (as per participant preference). An automated text message/email/app notification prompt will be sent to remind participants to complete their data entry with reminders for those who have not completed. The data collected via these methods will be linked to a web-browser page which is a direct interface to the trial database, REDCap. For the small proportion of patients who do not have a smartphone or computer, a member of the research team will telephone call to collect the information.

Visit **2**
(at 3 months)

- EQ-5D-5L in adolescents/adults and CHU-9D in children
- Condition specific Quality of Life will be assessed via VLQI or CDLQI
- Clinical global severity assessment – assessed by treating clinician
- Vulval development and scarring (in adolescents and children)
- Concomitant medication (relevant to condition)
- Bespoke resource use questionnaire and healthcare questionnaire
- Adherence to treatment
- Change or cessation of therapy
- Adverse events

Visit **3**
(at 6 months)

- EQ-5D-5L in adolescents/adults and CHU-9D in children
- Condition specific Quality of Life will be assessed via VLQI or CDLQI
- Clinical global severity assessment – assessed by treating clinician
- Vulval development and scarring (in adolescents and children)
- Concomitant medication (relevant to condition)
- Bespoke resource use questionnaire and healthcare questionnaire
- Adherence to treatment
- Change or cessation of therapy
- Adverse events

Visit **4**
(at 12 months)

- EQ-5D-5L in adolescents/adults and CHU-9D in children
- Condition specific Quality of Life will be assessed via VLQI or CDLQI
- Clinical global severity assessment - assessed by treating clinician and blinded assessor
- Vulval development and scarring (in adolescents and children)
- Concomitant medication (relevant to condition)
- Bespoke resource use questionnaire and healthcare questionnaire
- Adherence to treatment
- Change or cessation of therapy
- Adverse events
- Scarring (VASS and examination) – by blinded assessor
- Acceptability of treatment
- Sexual function using Female Sexual Function Index (in adults only)

Visit **5**
(at 18 months)

- EQ-5D-5L in adults and CHU-9D in children
- Condition specific Quality of Life will be assessed via VLQI or CDLQI
- Clinical global severity assessment – assessed by treating clinician

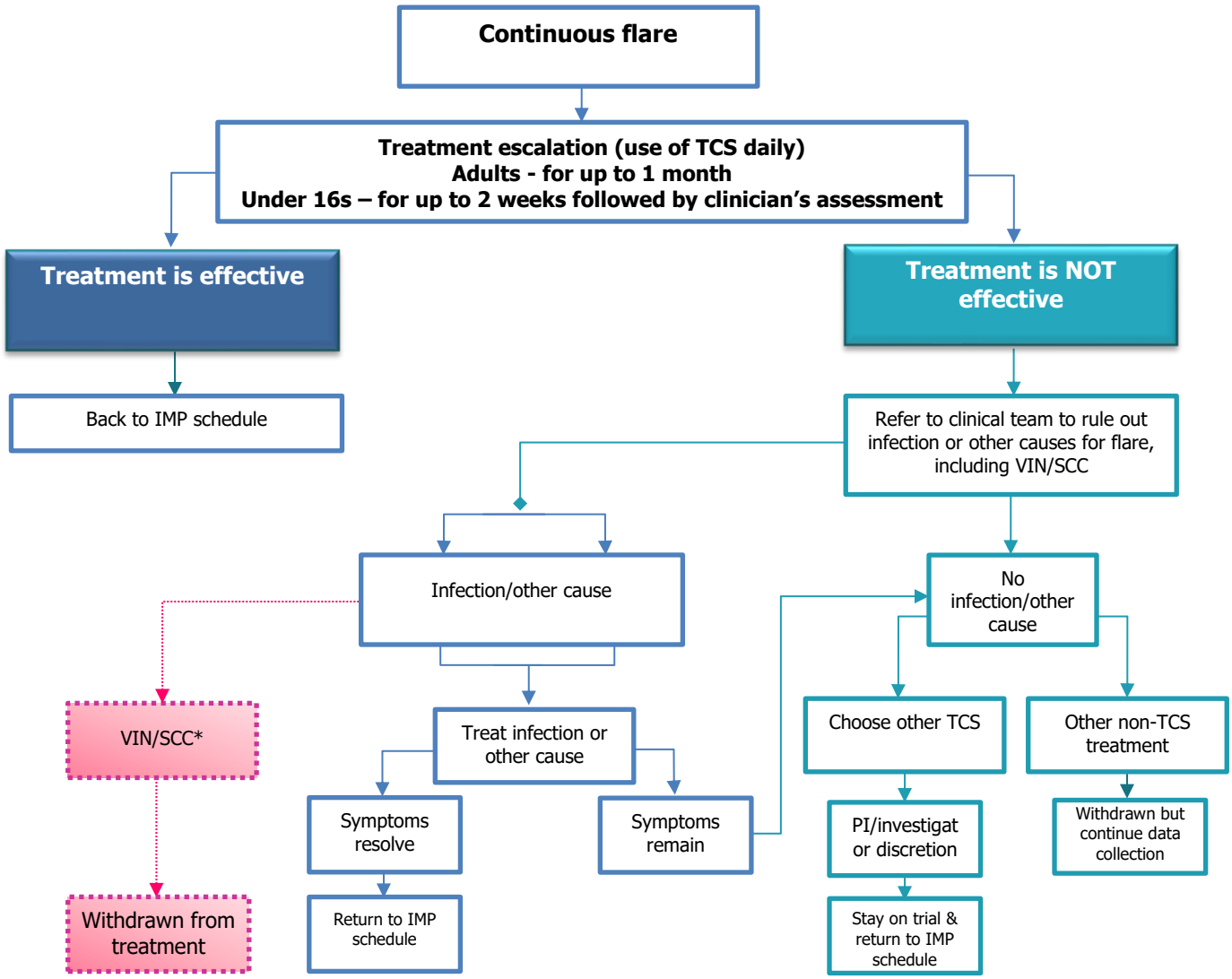
- Vulval development and scarring (in adolescents and children)
- Concomitant medication (relevant to condition)
- Bespoke resource use questionnaire and healthcare questionnaire
- Adherence to treatment
- Change or cessation of therapy
- Adverse events

Visit **6**
(at 24 months)

- EQ-5D-5L in adolescents/adults and CHU-9D in children
- Condition specific Quality of Life will be assessed via VLQI or CDLQI
- Clinical global severity – assessed by treating clinician and blinded assessor
- Vulval development and scarring (in adolescents and children)
- Concomitant medication (relevant to condition)
- Bespoke resource use questionnaire and healthcare questionnaire
- Adherence to treatment
- Change or cessation of therapy
- Adverse events
- Scarring (VASS and examination) – by blinded assessor
- Acceptability of treatment
- Sexual function using Female Sexual Function Index (in adults only)
- VIN or vulval SCC assessment

## 8.2 Concomitant and Rescue Medications and Treatments

Concomitant medication (on entry and during their participation), relevant to the condition, will be documented in the Electronic Case Report Form (e-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. In the event of flaring symptoms, the Investigator may use an escalation of treatment algorithm (plan) as described in the figure below:




**Refer to urgent assessment according to local protocols.*

*Figure 2. Recommended rescue treatment algorithm*

All concomitant medications present at screening/baseline and which do not interfere with the assessments should, where possible, be kept constant from screening/baseline throughout the study.

## 8.3 Compliance

Adherence (compliance) to the allocated treatment regimens will be assessed using a bespoke questionnaire at 3, 6, 12, 18 and 24 months.

## 8.4 Accountability for drugs

Participants will be given prescriptions to obtain their allocated treatment at either hospital or community pharmacies (depending upon which is usual practice at the individual sites) in the same way as their routine medication. Therefore, there will be no drug dispensing and accountability in this trial.

## 8.5 Management of study drug overdose

The risk of overdose of the TCS is very low. TCS can be safely applied to the whole body in a single dose with minimal risk of adverse reactions. There is however a risk of adverse reactions following long-term use of topical corticosteroid to localised areas of skin (e.g. skin thinning, telangiectasia) and these will be monitored during clinical examination at follow-up visits (or at an unscheduled trial visit, as necessary).

## 8.6 Urgent Safety Measures

An Urgent Safety Measure (USM) procedure will be initiated if any research participant is identified as being at risk of harm in relation to their involvement in a research project. Urgent action, which deviates from the approved protocol, is required to manage the event and protect the participant. If any urgent safety measures are taken the CI shall immediately and, in any event, no later than 3 days from the date the measures are taken, give verbal and written notice to the MHRA, the relevant REC and the sponsor, of the measures taken and the circumstances giving rise to those measures. The sponsor must then follow-up with notification in writing within three days of the action being taken. The notification should be in the form of a substantial amendment and should describe the event, the measures taken and justification for the measures taken.

USMs which originate from MHRA will be communicated expeditiously with sites by the PEARLS central trial office.

## 8.7 Trial assessments*

*Table 7. Data collection timepoints*

| Trial assessment | Source | | Timepoint and visit number | | | | |
|---|---|---|---|---|---|---|---|
| | | Screening/baseline Visit 1 | 3 month Visit 2 | 6 month Visit 3 | 12 month Visit 4 | 18 month Visit 5 | 24 month Visit 6 |
| Confirmation of eligibility | Medical notes/clinician/participant | X | | | | | |
| Consent | Participant | X | | | | | |
| Randomisation | Participant | X | | | | | |
| Medical history | Participant/medical notes | X | | | | | |
| Demographic information | Participant/medical notes | X | | | | | |
| Concomitant medication (relevant to condition only) | Participant | X | X | X | X | X | X |
| Number of flares and time to 1st flare | Participant | Starting 2 weeks from randomisation, every 2 weeks for 12 months | | | | | |
| Progression of scarring via photograph (optional), VASS and examination | Clinician | X** | | | X€¥ | | X€¥ |
| Vulval development and scarring (adolescents and children) | X | X | X | X | X | X | X |
| Clinical global severity assessment | Clinician | X | X | X | Xμ | X | Xμ |
| Condition specific Quality of Life (VQLI or CDLQI) | Participant | X | X | X | X | X | X |
| Health related quality of life (generic utility instrument) (EQ-5D-5L in adolescents/adults or CHU-9D in children) | Participant | X | X | X | X | X | X |
| Sexual function using Female Sexual Function Index (adults only) | Participant | | | | X | | X |
| Acceptability of treatment | Participant | | | | X | | X |
| Adherence to treatment | Participant | | X | X | X | X | X |
| Resource use (bespoke and healthcare) | Participant | X | X | X | X | X | X |
| VIN or vulval SCC | Clinician | | | | | | X |
| Adverse effects of therapy | Participant, Clinician | | X | X | X | X | X |
| Change/cessation of therapy | Participant | | X | X | X | X | X |

** Definition of age groups for purpose of assessments is described in **section 4.4***

*** Assessed by photographs (if consented) or clinical assessment diagram*

*€ Clinical assessment comparing to baseline photographs (if consent given for photographs) or to baseline clinical assessment diagram if consent for photographs not obtained*

*¥ At 12 and 24 months assessed by blinded assessor*

*μ At 12 and 24 months assessed by treating clinician and blinded assessor*

## 8.8 Protocol Deviations and Violations

A protocol deviation can be defined as a move away from described procedures in the treatment regimen e.g. a missed dose, study visit missed or taking place later than planned leading to data collections being at time-points differing to the rest of the study population. Because PEARLS is a pragmatic trial, and the assessment windows are selected to mirror the clinical practice, delayed assessments will only be reportable routinely to the TMG/TSC but will not constitute towards protocol violations which will need to be reported immediately to the sponsor.

A protocol violation is a variation in practice from the protocol which will need to be assessed for their impact on safety of the trial participant and of the data integrity, because they:

a. Reduce the quality or completeness of data (e.g. not using backups for database)
b. Impact trial participant's safety, rights or welfare (e.g. randomising patient without prior consent or without fulfilling eligibility criteria, disclosing participants identifiable information to third parties without consent)

Protocol violations may on occasions lead to the protocol being altered via a substantial amendment or a trial participant being excluded from the trial.

Protocol deviations (apart from those deviated from assessment windows) and ALL violations must be reported immediately to the PEARLS Trial Office.

The CI will notify the Sponsor if a protocol or non-protocol violation has an impact, or a potential to have an impact, on participant safety or integrity of the trial data. The Sponsor will advise on appropriate measures to address the occurrence which may include reporting of a serious GCP, protocol, GDPR etc breach, internal audit of the trial and seeking counsel of the trial committees.

## 8.9 Criteria for terminating trial

The trial recruitment will be assessed following the internal pilot phase (see section 8.10) to determine the feasibility of recruitment according to agreed progression criteria. The review will be undertaken by the TMG and TSC and if recruitment figures meet the red or amber categories, see Table 8, additional strategies will be put in place to attempt to improve these. The Sponsor also reserves the right to discontinue the 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 TSC and the funder as appropriate in making this decision. As such, on the recommendation of the TSC, the sponsor (in collaboration with the TMG) may stop the trial if emerging evidence of efficacy or major safety concerns arise, or if there are significant concerns regarding trial conduct. There should be proof beyond reasonable doubt for overall efficacy or major safety concerns (internal or external evidence) for the TSC and TMG to recommend the trial is stopped.

## 8.10 Internal pilot

The trial will have an internal pilot phase that will test the recruitment of sites and participants against agreed milestones, and a formal review will take place 6 months after the first

randomisation. At the end of the internal pilot, we project to recruit a minimum of 74 participants. *Table 8* below denotes the progression criteria, along with actions that will be undertaken for each category.

*Table 8 progression criteria for pilot study*

| **Progression criteria** | **Red** | **Amber** | **Green** |
|---|---|---|---|
| Recruitment rate/site/month | <1 | 1 - 2.3 | ≥2.4 |
| Number of sites opened | <3 | 3 – 4 | 5 - 8 |
| Total number of participants | <40 | 40 – 73 | ≥74 |
| Action | Consider stopping the trial* | Improvement required | Continue, no action needed |

**Utilise information from qualitative sub-study to identify barriers to recruitment; liaise with Trial Steering Committee and sites to strengthen recruitment strategy via relevant publicity and understanding any issues at local sites.*

# 9 DATA MANAGEMENT PLAN

Full details about data management will be provided in the *Data Management Plan (DMP)* which will be finalised prior to commencement of recruitment.

## 9.1 General

Data handling, validation specifications, source data verification, data storage and protection steps along with other data related procedures will be detailed in the trial DMP.

## 9.2 Data Capture and Data Queries

All trial data will be entered onto the electronic Case Report Forms (e-CRFs) in the trial specific database (REDCap, a secure web platform for building and managing online databases), developed and locally hosted by NCTU. Participants will be identified on the database with their unique trial number and initials.

The trial data collected at clinic visits will be entered directly on the database by site staff. Where access to the online database system is not available, paper worksheets can be used to collate data, which will then be transcribed onto the trial database. The site staff who have access to the trial database will have a designated data entry role on the trial Delegation and Responsibilities Log. Entry to the database will be password protected. PIs signature on e-CRFs will be collected via the database.

Fortnightly text messages/emails/app notifications will be sent to participants for a year to collect information about number of flares and time to first flare. Text messages will be sent to either parent/guardian or adolescent, depending on their preference. The data that will be used will be initial response received, i.e. if a child response to the questionnaire first that would be the data analysed and vice versa. Participants responding via text and email will be sent a link and those using the app will enter responses directly in response to notifications. Entered responses will be automatically uploaded onto the trial database, REDCap.

Normal route of collection of questionnaire data will be via app or web, where participants will enter their answers directly, but if preferred, the central management team at NCTU will post paper questionnaire booklets to the participant's address along with the FREEPOST envelope. Completed questionnaires will be received at NCTU where the answers will be transcribed onto the database.

The access to the database will be controlled with unique log-in usernames and passwords for each member of the research team. The staff will be trained on completion of e-CRFs and data entry on the electronic system. E-CRF completion guidelines will be provided to the sites. The CI will be given access to the trial database and will be able to sign off the expectedness and causality of SAEs electronically, where relevant. PIs at sites will ensure that the e-CRFs have been completed correctly and that the data is accurate. This will be evidenced by the signature of the site's Principal Investigator on the e-CRF.

## 9.3 Description of Data Entry Validation

The database used for the purposes of this trial will be Redcap®. Access to the database will be restricted and secure. The trial database will have built-in validation steps to alert or restrict non-sensical and ambiguous data entry. Any missing and ambiguous data will be queried with the site via e-CRFs. Sites should respond to the data queries in a timely manner, ideally within 2 weeks of the query being raised. All access and data transactions will be logged on the database via a full audit trail.

## 9.4 Data Cleaning and Database Lock

Participant's e-CRF data will be reviewed as soon as they are confirmed with validation rules, missing data have been obtained and all data passed through validation checks (i.e. there are no data queries outstanding). At the end of the trial, prior to the data analysis, the data will be validated, and the trial database will be locked to prevent amendment to the data collected. The rules of the data validation and soft/hard database locks are described in the *Data Management Plan* as part of the internal quality management process.

## 9.5 Monitoring

Details of trial monitoring will be described in detail in the trial *Monitoring Plan*.

Central monitoring will be carried out on a regular basis based on the trial *Monitoring Plan* and *Risk Assessment* following a risk assessment and as documented in the PEARLS Trial *Monitoring Plan*, whilst onsite monitoring may be triggered, for example by poor data return, poor data quality, lower/higher than expected SAE reporting rates, or excessive number of participant withdrawals or deviations. If an on-site monitoring visit is required, NCTU will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. NCTU will be in regular contact with each site's research team to check on progress and address any queries that they may have. Central monitoring will include regular checks for incoming e-CRF data for adherence with the protocol, data consistency, missing data and timing. Sites will be asked for missing data or clarification of inconsistencies or discrepancies.

Investigators will allow NCTU trial/monitoring staff access to source documents as requested. Sites will be requested to provide copies of signed ICFs and other documentation for in-house review for central monitoring for all participants.

# 10 STATISTICAL CONSIDERATIONS

## 10.1 Sample size and justification

Using data from a subset of 211 women with LS surveyed in preparation for the funding application for this trial who would be broadly eligible, the mean (SD) number of flares in this group was estimated to be 4.0 (2.8) per year. The data showed evidence of overdispersion (variance larger than the mean) hence a negative binomial regression would be appropriate for the data. Assuming an event rate of 4 flares per patient per year, a sample size of 320 would be required to detect a relative reduction of 25% in number of flares in the intervention group to 3 flares per patient per year (absolute reduction of 1 flare per patient in a year), with 90% power, 1:1 allocation and a two-sided significance level of 0.05, using dispersion parameter value of 0.34 estimated from the survey data. A relative reduction in number of symptom flares by 25% is considered meaningful by patients and clinicians since eligible patients have controlled LS so even a small reduction in number of flares would be meaningful to them. Loss to follow-up is expected to be around 5-10% [35-38]. Inflating the sample size by 20% to account for both non-collection of primary outcome data and treatment non-compliance, PEARLS aims to randomise 400 participants.

## 10.2 Analysis of outcome measures

The reporting of the trial will be in accordance with CONSORT guidelines. A full statistical analysis plan (SAP) will be developed and agreed with the Trial Steering Committee (TSC) prior to database lock.

Appropriate descriptive statistics for the demographic and clinical outcome measures at baseline will be used to assess balance between the randomised arms at baseline. Descriptive statistics appropriate for the outcome will also be presented for all outcomes at all collected time points by treatment arm.

Primary analysis will compare the average number of flares per person-time between the treatment groups, with analysis according to the allocated treatment strategy regardless of adherence to the strategy (intention-to-treat). Negative binomial regression, adjusted for minimisation factors and incorporating exposure time (person-time), will be used to calculate the incident rate ratio and 95% confidence interval. Supplementary analyses for the primary outcomes will use per-protocol or complier average causal effect (CACE) analysis if possible to estimate the effect of the intervention among the participants who would comply with their allocated intervention. Subgroup analyses for the primary outcome will be performed according to age at randomisation (children or adult), time since last flare, and strength of prescribed TCS (potent or superpotent), by including appropriate interaction terms in the primary model, however, results will be regarded as exploratory as the trial is not powered to detect interactions. Any additional sub-groups to be explored will be pre-specified in the SAP.

Between-group comparison of secondary outcomes will be based on an appropriate regression model for the outcome (or appropriate non-parametric estimator), adjusted for the same variables as the primary analysis.

### 10.3 Planned interim analysis

There is no planned formal interim statistical analysis of treatment effectiveness. However, an integral internal pilot phase will allow a feasibility assessment, examining recruitment, and retention. As part of continuous oversight, the DMC will be provided with confidential reports by trial arm, containing information on recruitment, protocol compliance, safety, and interim assessments of outcomes (between-group estimates of differences in efficacy and/or safety outcomes), as agreed.

### 10.4 Timing for final analyses

Final analyses will be performed once the database has been locked.

### 10.5 Planned subgroup analyses

Subgroup analyses for the primary outcomes will be performed according to age at randomisation (children (<16 years) or adults (≥16)), time since last flare (≤6 months, >6 months), and strength of study TCS (potent or superpotent) by including appropriate interaction terms in the regression models. The trial is not powered to detect any interactions hence the subgroup analyses will be treated as exploratory.

### 10.6 Assessment of safety

Analysis of safety data will be presented descriptively using frequency counts and percentages in each allocated group.

### 10.7 Procedures for missing, unused and spurious data

Analysis of the primary outcomes will be via intention to treat with data from all participants included in the analysis. Every effort will be made to follow up all participants up to the primary endpoint, however, as missing data is inevitable, we will employ statistical techniques for handling missing data for the primary outcomes. The primary negative binomial regression model will account for exposure time (person-time). Should there be other predictors of missingness not adjusted for in the primary model, a sensitivity analysis for effect of missing data will use multiple imputation, based on multivariate imputation by chained equations (MICE), under the missing at random assumption. At least 20 imputations will be performed, and the results combined using Rubin's rule.

### 10.8 Definition of populations analysed

For the primary analysis, all randomised participants who receive at least one dose of the study medication, will be analysed according to allocated treatment group regardless of adherence to the allocated treatment. This will be supplemented by analysing only the participants who would comply with their allocated intervention. Full definition and cut-off for compliance will be specified in the SAP.

For the secondary outcomes, participants will be analysed according to allocated treatment group regardless of adherence to the allocated treatment.

For the safety outcomes, all randomised participants who receive at least one dose of the study medication will be analysed according to:

- treatment received.

- allocated treatment group regardless of adherence to the allocated treatment.

# 11 ADVERSE EVENTS

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 includes:

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 trial.
4. Continuous persistent disease or symptoms present at baseline that worsen following the start of the trial.

The interventions being evaluated in this trial are treatments that are widely available within the NHS and used in standard care for lichen sclerosus. Given the well-known safety profile of the interventions, we will adopt a targeted approach to AE reporting.

Reporting and follow-up of these targeted participant and investigator-reported complications associated with the intervention delivery will be recorded in trial e-CRFs in a structured format and do not need to be reported to the Research Ethics Committee (REC).

An AE does not include:

1. Medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion); but the condition that leads to the procedure is an AE.
2. Pre-existing disease or conditions present or detected at the start of the trial 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.

Although all AEs should be recorded in the medical notes, in accordance with GCP, only those AEs which are directly referred to in the e-CRF will be collected for this trial. However, where any AE event meets the criteria of an SAE (see section 11.2), it will require reporting on a SAE form by the PI or delegate.

## 11.1 Reference Safety Information:

The known side effects are events that do not require expedited reporting (providing they do not meet the criteria of an SAE), but will be collated on the e-CRFs, have been taken from the exemplar

Summary of Product Characteristics, sections 4.8 of Dermovate ointment and Elocon ointment, and are detailed in this protocol section 11.4.

### 11.2 Serious Adverse Event (SAE)

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

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.

All reportable SAEs, must be assessed for causality by the PI or delegate.

### 11.3 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 trial IMP is assessed by the PI or Medical Monitor 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.

### 11.4 Reporting of adverse events

Targeted adverse events will be recorded and closely monitored until resolution, stabilisation, or until it has been shown that the trial medication or treatment is not the cause.

In the PEARLS trial these targeted AEs are:

- Progression of scarring
- Pre-cancerous changes to the anatomy
- Infection (thrush and superficial bacterial infection)
- Hypersensitivity, generalised rash
- Cushing's syndrome
- Local skin burning/skin pain and pruritus
- Allergic/contact dermatitis, erythema, rash, urticaria, local atrophic changes in the skin such as thinning, skin wrinkling, skin dryness, striae and dilatation of the superficial blood vessels (telangiectasias) may be caused by prolonged and intensive treatment with highly active corticosteroid preparations, particularly when occlusive dressings are used or when skin folds are involved.

Sites should report these events via e-CRFs.

### 11.5 Reporting of Serious Adverse Events

Participants will be asked to contact the study site immediately in the event of any serious adverse event. Research sites will be asked to contact NCTU immediately (within 24 hours) upon becoming aware of any serious adverse event as described in section 11.2.

Following identification of an SAE, sites will email completed (or partially completed) SAE Form to central coordinating team at the NCTU within 24 hours of becoming aware of the SAE. The investigator (or delegate) must complete, date and sign an SAE form.

Sites will report an SAE by emailing the central coordinating team at the NCTU using a specific SAE mailbox, ms-nctu-sae@exmail.nottingham.ac.uk. On receipt of the SAE, the central coordinating team will allocate the SAE a unique reference number, which will then be forwarded to the site as a proof of receipt within 1 working day. If confirmation is not received within 1 working day, the site should contact the NCTU office. The SAE reference number will be quoted on all correspondence and follow up reports regarding the SAE and filed with the actual SAE in the Site File and Trial Master File (TMF).

When an SAE form is completed someone other than Investigator, the Investigator will countersign the original SAE form to confirm agreement with the causality and seriousness assessments. The form should then be returned to NCTU and a copy kept in the Investigator Site File (ISF). The investigator should also report SAEs to their own Trust according to the local practice.

At the NCTU, SAEs on receipt will be reviewed independently by the Chief Investigator, who will be responsible to confirm the seriousness and causality assessment. If the causal relationship is either possibly, probably or definitely related with the trial IMP, this will be regarded as Serious Adverse Reaction (SAR). This SAR will be assessed by the CI for expectedness. If the SAR is unexpected (not defined in the RSI, see section 4.8 of the reference SmPC), it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

Non-expedited Serious Adverse Events:
Certain events, although they are, by definition classed, as Serious Adverse Events, are expected and will not require expedited reporting since a clinical assessment of expectedness is not required, but are still expected to be recorded in the clinical notes. In the context of this trial, this could be either:

- Adverse reaction from TCS use, requiring cessation of TCS;
- Active LS not controlled by rescue therapy, requiring escalation of therapy (either stepping up of TCS potency or moving to second-line immunosuppression);
- Suspicion of development of pre cancer/cancer of the vulva, requiring urgent action as per the recruiting sites usual process for investigating suspected malignancy.

All serious adverse events will be recorded and reported to the MHRA and REC as part of the annual Development Safety Update Reports (DSUR). SUSARs will be reported within the statutory timeframes to the MHRA and REC as stated below. The Sponsor shall ultimately be responsible for adverse event reporting.

### 11.6 Notification of pregnancy

If a pregnancy occurs in a participant who is in either arm of the trial, they will be withdrawn from the trial and should follow the direction of their GP regarding the pregnancy. Due to the low risk associated with the trial medications, no trial related adverse events in the mother or child are expected, therefore pregnancies and outcomes in withdrawn trial participants will not be actively monitored. However, all serious adverse events will be recorded and reported to the MHRA and REC as part of the annual DSUR. SUSARs will be reported within the statutory timeframes to the MHRA and REC as stated below. The Sponsor shall ultimately be responsible for adverse event reporting.

Current advice from the UK Tetralogy Information Service with regards to topical corticosteroids in pregnancy is that *'treatment should not be withheld if these products are indicated at any stage in pregnancy*. European Guidelines (2023) [39] state that *'there is no objection to occasional use of TCS in genital LS (e.g. once or twice a week), however, potent TCS (e.g. mometasone furoate) are preferred to very potent TCS (clobetasol propionate) during pregnancy*.' The British Association of

Dermatologists Guidelines (2018) [14] state '*topical steroids can be safely continued during pregnancy and in the postdelivery period, if needed.'*

### 11.7 Urgent Safety Measures

Definition of Urgent Safety Measures and reporting is described on section 8.6.

### 11.8 SUSARs

A serious adverse event that is either sudden in its onset (anaphylaxis), 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.

**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 ICSR Submissions.
- Shall inform the REC using the reporting form found on the HRA 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

### 11.9 Trial Treatment Related SAEs

A serious adverse event that is unexpected in its severity and seriousness *and* deemed directly related to or suspected to be related to the trial treatment but not the IMPs shall be reported to the ethics committee that gave a favourable opinion as stated below.

**The event shall be reported immediately of knowledge of its occurrence to the Chief Investigator.**

**The Chief Investigator will:**

- Assess the event for seriousness, expectedness and relatedness to the trial treatment.
- Take appropriate medical action, which may include halting the trial and inform the Sponsor of such action.

- If the event is deemed related to the trial treatment shall inform the REC using the reporting form found on the Health Research Authority 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 REC.
- Make any amendments as required to the trial protocol and inform the REC as required.

### 11.10 Participant removal from the study due to adverse events

Any participant who experiences an adverse event may be withdrawn from the study at the discretion of the Investigator.

# 12 HEALTH ECONOMIC EVALUATION

There is a scarcity of economic evidence to help inform decisions about the efficient management and treatment of LS. This economic evaluation will therefore be important not only in providing evidence on value for money of the specific interventions evaluated but also on providing evidence around the range of costs incurred by people with LS and the validity of utility instruments for this condition.

An incremental cost analysis will be conducted from an NHS and Personal Social Services (PSS) perspective in the primary analysis capturing the intervention resource use and wider health resource use related to LS (including any related to adverse effects) throughout the trial period. In addition to an NHS and PSS perspective, but presented separately, an estimate of out-of-pocket and time costs of managing LS for participants and parents/guardians (where appropriate) will be recorded. Intervention costs will be recorded during the trial through e-CRFs and wider health care resource costs associated with LS will be estimated using resource use data captured in participant questionnaires at baseline, 3, 6, 12, 18 and 24 months. Resource use will be valued using published unit costs or participant reported estimates for a common recent price year.

We will undertake a cost effectiveness analysis as the primary analysis because it will enable us to analyse all participants together, irrespective of age. Using the primary outcome measure we will estimate the incremental cost per flare averted. However, it will mean decision makers will need to make a value judgement about the acceptable value of the cost per flare averted. The use of available generic utility instruments in LS is under-researched such that it is unclear how well they capture the health-related quality of life aspects of people living with LS. Research to explore the measurement properties of the EQ-5D and CHU-9D in this patient group would be useful and therefore, as a secondary analysis we will conduct two cost-utility analyses estimating incremental cost per quality-adjusted life years (QALY) based on age to reflect the utility instrument used. Utility will be measured at baseline, 3, 6, 12, 18 and 24 months using the EQ-5D -5L [40, 41] (for adults and children aged 12 years or over) and CHU -9D [42-44] (for children aged 5 -11 years, where for participants aged 5-6 years old the CHU-9D will be completed by parental proxy, but for all other ages will be self-completed) questionnaires, which will be used to estimate the quality-adjusted life years over the study period using linear interpolation and area under the curve analysis

with and without baseline adjustment [45]. Separate cost utility analyses will be presented for those aged 12 years and over, using the EQ-5D-5L to estimate QALYs and for those aged under 12 years using the CHU-9D (where participants complete the same utility instrument throughout the study based on their age at baseline). The rationale for using the EQ-5D-5L is based upon the EUROQOL EQ-5D-Y user guide (https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-Y_User_Guide_v1.0_2014.pdf), which states that although the EQ-5D-Y "is generally recommended" the adult version might be possible in older children. Using just the one version of the EQ-5D will enable consistency, the EQ-5D-Y also does not currently have a UK valuation set. The CHU-9D was chosen over the EQ-5D-Y because a UK valuation set exists for it. The EQ-5D will be analysed in line with recommendations at the time of analysis [46].

Where appropriate (i.e. in the absence of either intervention dominating) the incremental cost effectiveness of proactive maintenance therapy compared to reactive treatment will be estimated by dividing the difference in costs by the difference in outcomes (number of flares in the cost effectiveness analysis and QALYs in the secondary cost-utility analysis) using a regression based approach such as seemingly unrelated regression analysis if assumptions hold and using multiple imputation methods to take account of missing data. Decision uncertainty will be presented via Cost-Effectiveness Acceptability Curves (CEACs) based on non-parametric bootstrapping of cost and effect pairs [47, 48]. We will write a detailed health economics analysis plan, in advance of database lock that will be reviewed by other study team members and another health economist, to include a section on planned sensitivity analyses. Sensitivity analyses will be undertaken to explore key uncertainties around important parameters in the economic evaluation. This might include, for instance, the impact of missing data and how this is handled in the analysis, using recommended methods [49], should missing data be found to be an issue; the impact of taking a wider perspective beyond the NHS and PSS taken in the primary analysis; and the impact of adherence to treatment on cost-effectiveness. These sensitivity analyses will be presented in a way that aids understanding about the interpretation of cost-effectiveness results.

Given the paucity of evidence for reactive and proactive treatment and the longer-term outcomes for people with LS we do not propose to undertake longer term cost-effectiveness modelling as part of this trial but this is something that would be worth considering in future when the results of this study are known and when longer term data around the impact of maintenance regimes on malignancy rates becomes available. This within-trial economic evaluation will provide robust trial evidence to inform longer term modelling in due course and decision makers about the likely short-term (two year) cost-effectiveness of interventions for LS, in particular about whether proactive or reactive treatment offers greater value for money.

# 13 QUALITATIVE SUB-STUDY

The nested qualitative sub-study has the following aims:

- Identify ways to optimise recruitment, outcome completion, and other trial processes (pilot phase)

- Explore participants' experiences of and adherence to the two treatment regimens to inform interpretation of trial results and future implementation (main trial phase)

### 13.1 Pilot phase

In the pilot phase of the trial, we will carry out remote interviews with patients (or parents/guardians of paediatric patients) who enter or decline the study (n=18-20) and staff involved in recruitment (n=8-10).

Approximately 15 staff meetings (e.g. site initiation visits, training) will be observed using an observation template to identify issues with recruitment related to e.g. equipoise, inclusion/exclusion criteria, or treatment pathways.

Observations and interviews will be analysed rapidly using framework analysis. This will enable rapid feedback to the team and implementation of any potential improvements.

### 13.2 Main trial phase

In the second phase of the qualitative sub-study we will explore participants' experiences of, and adherence to, the two treatment regimens. This will include the values and experiences that inform their perceptions of acceptability, as well as contextual factors that may be important in implementation.

We will aim to interview 10-12 participants from each trial group, who consent to take part in the sub-study, following their completion of the primary outcome. This time point has been chosen so that participants can reflect back over their experience in the trial and give their thoughts on how they will manage their LS beyond the trial. These interviews may take place remotely or face-to-face depending on mutual preference.

### 13.3 Recruitment and consent

Trial participants: At the time of entering the trial, all participants will be asked if they consent to be approached about a qualitative interview in the main consent form. The details of those who agree to be approached will be shared securely with the qualitative researcher.
Decliners: those who decline will be asked, gently and sensitively by recruiting staff if they would be willing to speak to a researcher about their reasons for not taking part. They will be assured that this is unrelated to their care, and that the interview is not intended to persuade them to take part but to help us document and understand reasons that people do not want to take part in the trial. The details of those who agree to be approached will be shared securely with the qualitative researcher.

Staff: all staff involved in the trial will be informed about the nested qualitative sub-study, including meeting observations and interviews. Staff involved in recruitment will be contacted directly by the researcher, with details retrieved from the study paperwork.

All potential participants will be approached directly by the qualitative researcher from University of Bristol, via telephone or email initially. They will be provided with verbal and written information about the interview before they decide whether to participate. If they agree, a date

will be agreed for the interview at a later date. Interviews will take place over the telephone or using MS Teams. The qualitative researcher will be the interviewer.

For all interviews, consent will be obtained verbally before the interview commences. Participants will be sent the relevant information sheet and consent statements in advance and invited to ask any questions. Before starting the recorder, the interviewer will recap the main points in the information sheet including consent, withdrawing, and pseudonymisation. After starting the recorder, the researcher will read out the statements and ask the participant to confirm verbally they agree. Consent will be considered a process continuing throughout the interview, and the interviewer will endeavour to ensure participants feel comfortable answering the questions during and at the end of the interview.

All communication with participants will be limited to the duration of their participation in the trial. Participants may also optionally consent to their contact details being retained beyond the duration of their participation in the trial, in order to be updated about the outcomes of the research or informed of future research.

### 13.4 Sampling

The chosen sample size is based on our previous experience and expectation that the interviews with this population are likely to generate a large volume of rich qualitative data [50].

Trial participants: Participants recruited in the pilot phase will be purposively sampled to achieve variation in age, ethnicity, and study site (n=10-12). In addition, for the main study interviews they will be sampled by trial arm and primary outcome (number of flares in the 12-month period) (n=20-25).

Decliners: It is likely that all participants who decline the trial but agree to an interview will be sampled for an interview, as the pool may be small. However, if the pool is large, participants will be purposively sampled using study site. We are aiming for 8-10 participants in this group.

Staff: Staff will be sampled to achieve variation in terms of role and study site.
We are aiming for 8-10 participants in this group.

### 13.5 Data collection

Interviews will take place remotely using telephone or video conferencing software (MS Teams) according to the participant's preference. Main study interviews may take place in person if mutually convenient for researcher and participant. Interviews will be audio- or video-recorded (MS Teams video-recordings will be converted to audio files). A flexible topic guide will be used to guide the conversation. Verbal consent will be agreed and recorded at the start of the interview.
An observation template will be used to observe meetings and other training opportunities.

### 13.6 Data analysis

Pilot phase: All data will be analysed rapidly using framework analysis. A template will be developed for the analysis. A sample of interviews/observations will be analysed by a second researcher. Findings will be fed back to the trial team regularly in order to share knowledge and implement any potential improvements rapidly.

Main trial phase: Interviews will be transcribed verbatim by an approved supplier with a confidentiality agreement in place and added to the qualitative data analysis software (QSR NVivo) for reflexive thematic analysis. This will involve data familiarisation, initial coding, interrogating the relationships between the codes and building an interpretation to a set of themes [38, 51].

### 13.7 Data storage and management

The researcher will store information about the participants in a password-protected database on the University of Nottingham server. Any identifiable data will be removed from the transcripts and a pseudonym added. A key to link the pseudonyms with the patients will be kept securely and destroyed once data collection and analysis is completed.

Video recordings (e.g. from MS Teams interviews) will be converted to encrypted audio files as soon as possible and the video destroyed. Demographic details of those who decline trial participation will not be collected. Therefore, we will use site as a characteristic to purposively sample.

No identifiable data will be documented from the pilot phase observations.

# 14 ETHICAL AND REGULATORY ASPECTS

## 14.1 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), the respective National Health Service (NHS) or other healthcare provider's Research & Development (R&D) department, and the Health Research Authority (HRA) if required. 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 and GP 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 UK Department of Health Policy Framework for Health and Social Care, 2017.

## 14.2 Informed consent and participant information

The process for obtaining participant informed consent or assent and parent / guardian informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. Informed consent procedure is detailed in section 0.

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).

## 14.3 Records

### 14.3.1 Drug accountability

Trial participants will obtain their prescribed TCS by the Investigator at site, who is a clinician, to be obtained from community pharmacies the same way they obtain their normal drugs. Therefore, there will be no pharmacies and drug accountability at the sites. E-CRFs, however, will collect information on how many prescriptions participants have received during the trial.

### 14.3.2 Case Report Forms

Each participant will be assigned a trial identity code number, allocated at randomisation if appropriate, for use on other trial documents and the electronic database. The documents and the database will also collect and store their initials and date of birth. Participant contact details will be entered and stored on a separate part of the trial database, to ensure identifiable data security.

Participant contact details may also be used by the trial team to send out trial related documentations such as questionnaires and other trial related correspondence, as well as text messages. The database will have in-built validation to ensure that the identifiers used all match with the allocated participant ID number.

The identifiers used will be robust and able to prevent miss-assignment of data in databases. The database will have in-built checks to ensure that the identifiers used all match with the allocated study number. The identifiers will also allow sufficient identification to prove that a person exists, matches the consent obtained (so the identifiers used must be listed on the trial recruitment log) and allows identification of the participant when chasing data queries with participating remote sites.

E-CRFs or paper worksheets, which are used to collate and record clinical trial data and are an integral part of the trial and subsequent reports. The worksheets, therefore, must be legible and complete. All paper worksheets (if applicable) where possible, shall be completed using black ink. Errors shall be striked through but not obliterated by using correction fluid and the correction inserted, initialled and dated.

The trial data will be collated on paper worksheets and then transcribed onto the electronic e-CRFs on the trial database. Paper worksheets will be completed with ink. If errors were made, they will be corrected by strike through the error, initialled and dated.

E-CRFs will be treated as confidential documents and held securely in accordance with current regulations. They will be restricted to personnel approved by the CI or PI and recorded on the delegation log. The trial database will be on a secure server of University of Nottingham. The e-CRF will only collect the minimum required information for the purposes of the trial. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities. NCTU trial management team will have access to full dataset including identifiable information, however, trial statisticians access will be limited to pseudo-anonymised data.

The CI and local PI (or their delegate) will sign a declaration to ensure accuracy of data recorded in the e-CRFs. The PI 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.

### 14.3.3 Source documents

Source documents provide evidence for the existence of the participant and permit verification of the data collected. Source documents shall be filed at the Investigator site and may include but are not limited to, consent forms, current medical records, laboratory results and pharmacy records. A e-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.

### 14.3.4 Direct access to source data / documents

The -CRFs 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).

## 14.4 Data protection

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent. The researchers conducting the qualitative study meet the same data protection requirements for the audio and video recordings in terms of encryption, back up, secure controlled access etc. Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act, 2018. The e-CRFs will only collect the minimum required information for the purposes of the trial. Paper worksheets 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. Electronic data will be backed up every 24 hours to both local and remote media in encrypted format. 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. Participants may optionally consent for their data to be looked at for up to 15 years. This will allow NCTU to conduct a separately funded research study to collect further data such as investigating malignancy rates and other long-term effects in relation to maintenance regimens. The data may be obtained from either the participants themselves or NHS centralised records, GP notes and other current & future NHS bodies. Participants' identifiable information such as their /their parent/guardian (where appropriate) names, initials, addresses and contact details, participant's date of birth and NHS number will be kept centrally at the NCTU and will be deleted upon participants' withdrawal of consent or at the end of the future research study, whichever is earlier.

# 15 QUALITY ASSURANCE & AUDIT

## 15.1 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 with both public liability insurance and clinical trials insurance in respect of claims made by research subjects.

## 15.2 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.

## 15.3 Trial data

A risk assessment will determine trial specific risks and mitigations through central and on-site monitoring. E-CRF completion and its monitoring will be documented and conducted in accordance with the trial IMP. Trial data and the TMF will be made available for inspection by the regulatory authority as required.

**Data sharing**

Individual participant medical information, obtained as a result of this trial, is considered confidential and disclosure to third parties is prohibited with the exceptions noted in this protocol.

Any personal data will be held in a secure database using encryption, with restricted password protected access. Only appropriate members of the participating site team and NCTU research team will have access to these data.

Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in computer files.

Anonymised participant data may be shared with researchers external to the trial research team in accordance with the NCTU's data sharing procedure. All requests for data should be sent to the Nottingham Clinical Trials Unit.

### 15.4 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 a minimum of 7 years following the first publication. 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.

### 15.5 Discontinuation of the trial by 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 TSC and DMC as appropriate in making this decision.

### 15.6 Statement and 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.

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.

# 16 PUBLICATION AND DISSEMINATION POLICY

At the end of the trial and analysis we will publish the HTA report in the NIHR Journal. The results of clinical outcomes and health economic results will also be published in relevant high-impact journals. We will present the results at relevant academic conferences. Infographics and patient story video(s) may be shared on social media.

The trial will involve the Lay Advisory Group (LAG), co-applicants and panel members, as well as relevant patient organisations to develop a dissemination strategy and materials that convey the findings in meaningful ways to patients. Due to the sensitivity of the nature of LS, a range of strategies for dissemination is important so that patients can access information in the way that they choose, so that it can be accessed discretely if necessary.

# 17 USER AND PUBLIC INVOLVEMENT

PPI co-applicants will be members of the ongoing Trial Management Group, which will have remote meetings. Their involvement will be facilitated by the PPI lead. Face-to-face meetings will be arranged at the study initiation and during results reveal. PPI co-applicants will be given training and the opportunity to attend a conference where the results will be shared. We will also recruit two public members with lived experience of LS to the Trial Steering Committee. Public members will be reimbursed for their time.

The PPI lead will coordinate PPI activities, e.g. convening Lay Advisory Group (LAG) meetings, arrange trainings, supporting PPI contributors, and ensuring involvement of diverse and underserved groups.

Development and design of trial procedures will seek to include underserved groups. People from ethnic minorities have generally been less represented in LS research to date, although LS itself is an under-researched condition. LS is a sensitive topic which may influence how willing certain communities are to engage in the research. The discussions will be held with the LAG on how to make it acceptable and appealing to different communities, and to ensure that the study is accessible to those who lack sufficient digital competence/confidence, or access to a smartphone/computer.

Public contributors will also be involved in designing routes to dissemination for the trial outcomes, as well as reaching out to other stakeholders such as charities and special interest groups.
We will inform all participants of the trial results, unless they opt out of communications. The trial will seek to include public contributors as co-authors on outputs of this research. The social media such as Twitter and Instagram will be utilised for publicity, and the results of the study will be shared to the online support group and the social media awareness pages run by our co-applicants, which have a very wide reach.

# 18 STUDY FINANCES

## 18.1 Funding source

This study is funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Ref: NIHR135121.

## 18.2 Participant stipends and payments

Participants who consented to enter the qualitative study, will be gifted a £10 shopping voucher. Adult participants in the main trial will be compensated for travel (on presentation of receipts) if their research appointment is outside of their routine care appointments and £5 high-street voucher, inconvenience allowance, will be provided after successful completion of each research visit.

# 19 SIGNATURE PAGES

## 19.1 Signatures to protocol:

**Chief Investigator:** (name) Rosalind Simpson

Signature Rosalind Simpson (Sep 15, 2024 10:47 GMT+2) Date (dd-mmm-yyyy): Sep 15, 2024

**Trial Statistician**: (name) Reuben Ogollah

Signature: R Ogollah (Sep 15, 2024 22:15 GMT+1) Date (dd-mmm-yyyy): Sep 15, 2024

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