# Establishing Effective Diagnostic Criteria for Lichen Sclerosus: A Diagnostic Test Accuracy Study (SHELLS)

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| **Short title:** | Establishing Effective Diagnostic Criteria for Lichen Sclerosus |
| **Acronym:** | *SHELLS* |
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## SYNOPSIS

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| Title | Establishing Effective Diagnostic Criteria for Vulval Lichen Sclerosus: A diagnostic test accuracy study |
| Acronym | SHELLS |
| Short title | Diagnostic Criteria for Vulval Lichen Sclerosus |
| Chief Investigator | Dr Rosalind Simpson |
| Objectives | **Primary objective:**<br>To test and validate expert-agreed diagnostic criteria (from previous electronic-Delphi consensus study) to establish the best predictors for vulval lichen sclerosus and subsequently develop a diagnostic tool.<br><br>**Secondary objective:**<br>To develop training resources/manual to support the use of a future diagnostic tool. |
| Study Configuration | Multi-centre, cohort cross-sectional diagnostic test accuracy study. |
| Setting | Secondary care specialist outpatient clinics and community specialist hubs. Potential involvement of international sites. |
| Sample size estimate | A sample size of 370 people (185 people with the outcome LS and 185 non-LS) is needed to target a confidence interval of 0.45-0.55 for the overall outcome proportion of 0.5 and to target a mean absolute error of 0.062 between observed and true outcome probabilities based on up to nine predictor variables.<br><br>The final recruitment figure of 407 participants includes a 10% increase for missing data |
| Number of participants | 407 participants will be recruited to the study. |
| Eligibility criteria | Inclusion criteria:<br>• Adults (≥18 years of age)<br>• Female<br>• New presentation to a specialist clinic (secondary care or community hub) with a vulval skin complaint<br>Exclusion criteria:<br>• Inability to provide informed consent<br>• Patients with surgical alteration of vulval skin as part of gender reaffirming surgery, or patients not born with a vulva<br>• More than 2 weeks since initial consultation in specialist clinic |

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| Description of interventions | This is an observational study. There are 17 Delphi-agreed LS diagnostic criteria being tested in this study.<br><br>Patients will have one study visit lasting approximately 30 minutes. The study visit will include 2 clinical examinations for diagnostic assessment. At one centre (Nottingham), there will be a potential third assessment for testing of the inter-observer variability of the diagnostic criteria.<br><br>The reference standard diagnostic assessment will be undertaken by the patients' managing clinicians.<br><br>A trained blinded assessor will examine the patient to record the presence or absence of the Delphi-agreed diagnostic criteria.<br><br>Information will also be collected from the patient including, age, ethnicity, post code (for socioeconomic status), patient rating of the condition on the day of assessment, physician global assessment of severity, symptom duration, diagnosis of LS prior to clinic appointment, previous diagnosis of a vulval condition, treatments received, treatment duration, whether on active treatment at the time of recruitment, treatment length, and clinical assessment of 'early' or 'late' stage LS.<br><br>Clinical photographs will be taken in line with usual care and participants can opt out of these being used for research purposes if they wish.<br><br>Skin biopsy will be taken in line with usual care. Histological diagnosis will be recorded if patients have undergone a biopsy. |
| Duration of study | Study duration: 24 months.<br><br>Participant duration: Participants will be involved in a single appointment that will last approximately 30 minutes. |
| Methods of analysis | Descriptive analysis will be used to summarise the study population including age, gender, ethnicity, disease severity and stage, disease duration and treatment(s).<br><br>There will be a 2-stage analysis plan.<br><br>**Stage 1: Developing a diagnostic prediction model**<br><br>i. Refining the diagnostic prediction model: Multivariable backward logistic regression model with exit criteria.<br><br>ii. Quantifying the performance of the diagnostic prediction model: A calibration plot will assess how well predictions agree with the observed data. Smoothed calibration curves will be plotted using a loess smoother. All data for model development will be included for use in internal-external cross validation across centres (alongside bootstrapping). Discrimination will be measured using the C statistic. |

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| | iii. Clinical utility: Thresholds on the calibration plot will be based on clinical utility i.e. what defines high risk and trade-offs between benefits and harms, defined by patients and doctors.<br><br>**Stage 2: Model validation**<br><br>Internal validation to (i) obtain an unbiased estimate of the developed model's predictive performance, and (ii) adjust the developed model for optimisation). Bootstrapping and uniform shrinkage techniques will be used for analysis.<br><br>Inter-observer variability in the assessment of the diagnostic criteria will be calculated using the Kappa statistic. |

## ABBREVIATIONS

| | |
|---|---|
| CI | Chief Investigator overall |
| CRF | Case Report Form |
| GCP | Good Clinical Practice |
| HRA | Health Research Authority |
| NCTU | Nottingham Clinical Trials Unit |
| NHS | National Health Service |
| NIHR | National Institute of Health and Care Research |
| LS | Lichen Sclerosus |
| PI | Principal Investigator at a local centre |
| PIS | Participant Information Sheet |
| REC | Research Ethics Committee |
| REDCap | Research Electronic Data Capture |
| R&D | Research and Development department |
| UoN | University of Nottingham |

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# 1 STUDY BACKGROUND INFORMATION AND RATIONALE

## 1.1 Presentation of Lichen Sclerosus

Disorders affecting the female genital (vulval) area are common and frequently affect physical, psychological and psychosexual wellbeing.[1-4]

In particular, lichen sclerosus (LS) is the most common inflammatory vulval skin condition.[5] The overall prevalence of vulval LS has been reported to be up to 3% in postmenopausal women.[6] The actual prevalence in the general population may well be higher, as up to 30% of affected women are estimated to be asymptomatic (or have minimal symptoms); LS can therefore go unrecognised.[7-9] Symptoms of itching and discomfort can affect activities of daily living, for example, sitting, walking and going to the toilet. If not treated, LS can cause irreversible sticking together (scarring) of the vulval skin in both symptomatic and non-symptomatic patients. These changes further impact on normal daily activity and quality of life. Typical presentation includes symptoms of itch, discomfort, vulval splitting and painful sexual intercourse. Clinical features in early LS can be subtle with minimal inflammation (redness), pallor (whitening), and oedema (swelling) of tissues. As the disease progresses, characteristic bruising, splitting, and skin thinning are seen. Scarring with loss of normal anatomy occurs in established LS. Negative impact can lead to self-harm or suicidal thoughts.[2,3,10]

LS is mainly diagnosed clinically. It has two peaks of clinical presentation in pre-pubertal girls and post-menopausal women.[11] In girls, it may be misdiagnosed for child abuse which is devastating for families. Scarring caused by untreated LS is irreversible and can prevent normal daily function such as passing urine, and in adults, sexual activity. LS is a major cause of vulval cancer,[12,13] increasing the risk of cancer of the vulva in women and this can happen early in the disease process. Vulval squamous cell carcinoma cases have increased by 17% since the 1990s.[14] The risk of developing vulval squamous cell carcinoma is 3-5% in those affected with LS, which is a 20-fold risk of vulval cancer compared to the general female population.[15] This is thought to occur more frequently in those who have neglected, or inadequately treated LS.

## 1.2 Management and diagnosis of LS

In the UK, multiple specialities manage vulval skin conditions including dermatology, gynaecology, sexual health and primary care. Pathways of care are not well developed and not all UK regions have specialist vulval services. Teaching of vulval disease in undergraduate and postgraduate medicine is limited, leading to lack of awareness amongst the wider medical community. Delay in diagnosis[4] and unsatisfactory clinical experience[16] are often experienced by patients with LS. Patient involvement into this research development highlighted that misdiagnosis from non-specialists, ill-defined care pathways and social stigma/embarrassment preventing people seeking help are ongoing issues.

The use of biopsy to diagnose LS is controversial, and confirmatory biopsy is not necessary when typical clinical features are present.[17] Histological findings can be varied and non-specific, even in clinically evident LS.[18] This is likely due to sampling error; it is important to biopsy the correct area to give the greatest chance of typical histological features. UK guidelines state that biopsy is indicated if there are atypical features or diagnostic uncertainty; it is essential if there is suspicion of neoplastic change.[17] Biopsy is not a routine procedure in primary care and should only be performed when necessary in secondary care by an experienced operator to minimise false-negative results.

First-line treatment with a super potent topical steroid, in conjunction with simple vulval hygiene measures, brings disease remission in 70% of adult females over a 3-month period.[11,19] Therefore, early recognition and treatment is important as most patients respond well and progression of disease can be slowed or even halted.

### 1.3 Study rationale

Whilst LS can be treated, it is often difficult to diagnose, especially for non-specialists. There are no specific checklists to guide doctors in what they should be looking for. This means that LS often goes under-recognised and undertreated, with community diagnosis being delayed, preventing the initiation of early effective therapy.[20] Patients often self-diagnose thrush and obtain over the counter treatments. Misdiagnosis is also common when patients present to primary care/non-specialists. To aid early diagnosis, patients, primary care providers and health professionals not experienced in this field need a simple method of recognising vulval LS. Effective diagnosis will lead to earlier treatment and when needed, timely referral to specialist care. This will reduce complications such as scarring, anatomical changes and progression to vulval cancer.

A four-round electronic-Delphi consensus study has been undertaken by the University of Nottingham with international expert stakeholders to agree the most important clinical diagnostic criteria for LS (Establishing diagnostic criteria for vulval lichen sclerosus (SHELLS): an international electronic-Delphi consensus study).[21] The study was approved by the University of Nottingham's Faculty of Medicine & Health Sciences Research Ethics Committee (FMHS 39-0722).

A total of five diagnostic features reached consensus as 'critical' and 12 were rated 'important but not critical'.

The aim of this diagnostic test accuracy study (SHELLS) is to test the Delphi criteria agreed as 'critical', and/or 'important but not critical', in the clinical setting, and subsequently develop a diagnostic tool which will support the diagnosis of LS. The diagnostic tool will be available for use by a range of health professionals (not only skin specialists) to diagnose LS as well as to help patients self-diagnose in the community.

## 2. STUDY OBJECTIVES AND PURPOSE

## 2. 1 Purpose:

To develop and validate a diagnostic criteria model for vulval LS which can be used by health professionals and patients.

### 2.2 Primary objective

To test and validate expert-agreed diagnostic criteria (from previous electronic-Delphi consensus study) to establish the best predictors for vulval LS and subsequently develop a diagnostic tool.

### 2.3 Secondary objective

To develop training resources/manual to support the use of a future diagnostic tool.

# 3. STUDY DESIGN

## 3.1 Study configuration

Multi-centre, cohort cross-sectional diagnostic test accuracy study.

## 3.2 Setting

Research centres will comprise of UK specialist outpatient clinics in secondary and tertiary care as well as community specialist hubs. This setting is a feasible environment in which the reference standard (dermatologist's diagnosis, see below) can be obtained and the sample size recruited within the time and resources available. We anticipate that 50-60% of new patients referred to the vulval clinic will have LS.

There is potential for including international centres in this study, although it is anticipated that the majority will be in the UK.

## 3.3 Index and reference tests

### 3.3.1 Index test

The international electronic-Delphi exercise involving expert health professionals and patients (see section 1.3 for further detail) has identified a list of 17 diagnostic features which were agreed to be 'critical', or 'important but not critical' in the diagnosis of LS. The SHELLS diagnostic test accuracy study is using this list of 17 diagnostic features as the index test.

A diagnostic criteria assessment looking for the presence or absence of these 17 diagnostic features, using experience and clinical judgement, will be performed by an assessor blinded to the reference standard (specialist's diagnosis – see section 3.3.2).

List of diagnostic features to be assessed as part of the index test:

Critical:

- Changes in the anatomy of the genital area
- Response to topical corticosteroids
- Whiteness
- Itch
- Burying of the clitoral area

Important but not critical:

- Absence of vaginal involvement
- Fissuring
- Crinkly skin
- Bruising/bleeding under the skin
- Fissuring at the back entrance to the vagina
- Pain/soreness unrelated to sexual activity
- Pain/soreness related to sexual activity
- Skin thickening
- Loss of skin stretchiness

- Erosions
- Irritation
- Perianal fissure

### 3.3.2 Reference standard

Specialist's diagnosis as recorded in the participant's medical record. The diagnosis is a clinical diagnosis and may include, but does not require, a skin biopsy. This diagnosis is undertaken as part of the patient's usual care.

### 3.4 Study flow

This is a cohort cross-sectional study, including consecutive new patients presenting with a vulval skin complaint to a specialist outpatient clinic (see under 'Setting' – section 3.2 for types of clinic). The patient flow through the study is depicted in Figure 1.

## 4 STUDY MANAGEMENT

The Chief Investigator has overall responsibility for the study and shall oversee all study management.

The data custodian will be the Chief Investigator.

This study will be managed from the Centre of Evidence Based Dermatology at the University of Nottingham by Dr Rosalind Simpson, Associate Professor and Consultant Dermatologist as part of her NIHR Advanced Fellowship. Dr Simpson will be supported by Professor Kim Thomas (Co-Director of the Centre of Evidence Based Dermatology), Professor Jane Daniels (Professor of Clinical Trials) and Dr Sonia Gran (study statistician). A Research Assistant will be supporting Dr Simpson with the running and coordination of the study. There will be regular meetings to ensure adequate progress and address any rising issues. These are likely to be monthly to begin with but may decrease in frequency once the study is smoothly up and running.

Research data management & collection will be supported through the University of Nottingham's Clinical Database Support Service and their locally hosted/managed REDCap platform.

A Research Assistant will support the co-ordination of the multicentre study in terms of obtaining relevant approvals, site initiation, data management and overall administration. In addition, Nottingham Clinical Trials Unit (NCTU) will supervise the Research Assistant with regards to these aspects.

A study management group including patients, clinical experts, methodologists and an independent advisor will oversee the research. This group will meet at least quarterly.

### 4.1 Duration of the study and participant involvement

Study Duration: The study will last for approximately 24 months overall, with the possibility for extension if participant recruitment is slow. Participant enrolment will begin once HRA and REC approvals have been obtained and all site approvals are in place.

Participant Duration: Participants will be involved at the point of consent to the study until the diagnostic criteria assessments have been completed. Participants will have one study visit that will last approximately 30 minutes. There will be no follow up appointments related to the study.

### 4.2 End of the Study

The end of the study will be the last study visit of the last participant.

# 5 SELECTION AND WITHDRAWAL OF PARTICIPANTS

### 5.1 Recruitment

- Potential participants will be consecutive new patients referred with a vulval skin complaint to a specialist outpatient clinic (types of clinic are detailed in section 3.2).
- They will be identified from clinic lists by the usual care team.
- The study participant information sheet (PIS) will be sent in advance of their outpatient appointment via letter of invitation, or text message with a link to the PIS (depending upon site specific processes for contacting patients).
- Interested patients will complete an online expression of interest form following which the local site research team will contact the patient to answer any questions and discuss potential participation. They can also contact the local site research team via telephone if preferable to the patient (i.e patient doesn't want to click on the link or QR code in the PIS).
- Following discussion with the local site research team, if willing to participate, the patient can complete consent online in advance of their appointment. If not completed in advance, they can complete consent at the time of their face-to-face scheduled clinic appointment.
- On attendance at the face-to-face outpatient appointment:
    - Those **who have already consented** to participate in the study will have consent confirmed by a member of the research team. They will undergo their usual consultation (history and examination) plus a second examination by a blinded trained assessor. Participants who are from the Nottingham centre may also receive a third examination. This is to assess whether two different professionals using the diagnostic criteria agree on the same diagnosis. A member of the research team will collect additional information and enter this onto the CRFs.
    - Those **who have not yet consented** will be given the opportunity to discuss their participation further with a member of the research team. If willing, they will complete online/paper consent and they will go on to have their usual consultation plus a second examination by a blinded trained assessor. Participants who are from the Nottingham centre may also receive a third examination. This is to assess whether two different professionals using the diagnostic criteria agree on the same diagnosis. A member of the research team will collect additional information and enter this onto the CRFs.
    - Examinations by both the managing clinician **and** the blinded assessor must be completed for inclusion in the study.
    - If needed, hospital interpreter and translator services will be available to assist with the discussion of the study, the participant information sheets and consent forms. The consent forms and information sheets however will not be available in other languages.
    - Those who do not consent will have their usual clinical consultation. They will be made aware that their care will not be affected by their decision to decline participation in the study.

- Those who are unsure and request more time to consider the study will have their usual clinical consultation. If at a later stage they decide to participate, they will provide consent online and the research team will invite them to attend a research visit where information to complete CRFs will be collected in addition to an examination by a blinded assessor. In this situation, participation will only be possible if patients can return for a research appointment **within two weeks of the initial consultation at the specialist clinic.**

Those who do not receive information prior to their scheduled outpatient consultation will be approached on the day by their usual care team to provide information and invite for discussion with the research team regarding the study.

Posters and flyers will also be visible in outpatient clinics for patients to view which detail links and a QR code for further study information.

### 5.2 Eligibility Criteria

#### 5.2.1 Inclusion criteria

- Female
- ≥18 years of age
- New presentation to a specialist clinic (secondary care or community hub) with a vulval skin complaint

#### 5.2.2 Exclusion criteria

- Inability to provide informed consent
- Patients with surgical alteration of vulval skin as part of gender reaffirming surgery, or patients not born with a vulva
- More than 2 weeks since initial consultation from managing clinician

### 5.3 Expected duration of participant participation

Study participants participate in the study for approximately 30 minutes at a single study visit.

### 5.4 Participant withdrawal

Participants may be withdrawn from the study either at their own request or at the discretion of the Investigator. The participants will be made aware that this will not affect their future care. Participants will be made aware (via the PIS and consent form) that should they withdraw, the data collected to date cannot be erased and may still be used in the final analysis.

Participant data will be collected during the study visit when the diagnostic criteria assessment takes place. In the event that the participant withdraws from the study, all data collected by that point will be recorded in the CRF and where possible, the reason for withdrawal will be documented.

### 5.5 Informed consent

Informed consent will be obtained in accordance with the Research Ethics Committee guidance and Good Clinical Practice. Participant information will be developed involving patient representatives to ensure it is clear and easily understood. Potential participants will be allowed sufficient time to consider their participation. Same day research appointments will be available, but if patients request additional time to consider their involvement this will also be possible. The PIS will also cover what happens if a patient wishes to withdraw from the study.

All participants will provide written or digital informed consent. The Informed Consent Form will be signed and dated by the participant before entering the study. The Investigator or their nominee will explain the details of the trial and provide a PIS (either in advance of, or at the time of the outpatient clinic visit), ensuring that the participant has sufficient time to consider participating. The Investigator or their nominee will answer any questions that the participant has concerning study participation. As the study is low risk due to being non-interventional, we believe there will be sufficient time to consider participation for those who receive the PIS on the same day as their outpatient visit. This has the added benefit of being more convenient than coming back for another visit. However, potential participants will be given the opportunity to return on another occasion, within the next two weeks, if they wish (Figure 1).

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

Clinical photographs will be taken as part of normal medical care. Participants will be asked specifically for consent to use the photographs for research purposes for development of a training manual which will be used at a later stage alongside the diagnostic tool to support its use.

Informed consent will be obtained from each participant before they undergo physical examination and have information collected for the study. Consent will primarily be completed online, but where a paper version is completed, this will be scanned and uploaded to REDCap. The participant will be provided a copy of this and it will be recorded in the medical record that consent for the study has been obtained.

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

## 6. REGIMEN

### 6.1 Patient pathway – Assessments

- Participants will receive a clinical assessment from their usual managing clinician as part of their usual outpatient appointment. This will involve a physical examination and routine clinical questions.
- A blinded assessor (for example, Trainee, Clinical Fellow, Specialist Nurse) will then examine the patient and record clinical diagnostic features on the CRF. A third assessor who is also blinded may also examine the patient at the Nottingham site. Participants can opt out of examination by two different professionals if they wish, but to participate in SHELLS they must agree to at least one additional examination.
- The blinded assessor will be asked to examine the patient without speaking to the managing clinician. The managing clinician will ensure that the clinical notes are closed

and unable to be viewed by the blinded assessor as they come in the room, and REDCap (Research Electronic Data Capture) will disable access to the clinician diagnosis by the blinded assessor. The patient will be advised not to give any information to the blinded assessor/s other than specific questions that are asked in relation to the research.

- The blinded assessment will ideally take place immediately after the managing clinician has examined the patient. This will prevent disruption of flow to patients coming through the clinic and it will prevent patients from having to get undressed twice.
- However, we acknowledge that flexibility is required and each site may need to adapt their own flow for how the clinical assessments are performed, ensuring blinding of the additional assessor/s.

- Information collected by the research team (not the blinded assessor) for each participant will include:
  - Age
  - Ethnicity
  - Post code (for socioeconomic status)
  - Participant rating of the condition on the day of assessment
  - Physician global assessment of disease severity (assessed and recorded by managing clinician)
  - Symptom duration
  - Diagnosis of LS prior to clinic appointment
  - Previous diagnosis of a vulval condition (Y/N and what diagnosis)
  - Treatments received (Y/N and what treatment)
  - Treatment duration
  - Whether on active treatment at time of recruitment (Y/N)
  - Whether the patient has 'early or late' stage LS (assessed and recorded by managing clinician)
  - Presence or absence of each of the individual diagnostic features (Index test, see section 3.3.1)
  - Clinical photographs (optional for this study, see below)
  - Managing consultant's diagnosis (reference standard)
  - Biopsy taken or not – if so, result of biopsy. N.B. Biopsies will not be taken specifically for study purposes, only in line with national guidance[17].

- Participants will be approached by their usual care team for clinical photographs as per standard care. Depending on local site arrangements, photographs will be taken either by Medical Photography or by a departmental camera. During the consent process they will be given the option to allow use of their anonymised clinical images for research purposes. It will be explained that this is to aid the future development of a training manual. The decision to allow anonymised clinical photographs to be used for training/research will be entirely voluntary and at the discretion of the patient. It will be made clear that their decision will not affect their care. The clinical photographs of those who consent for research purposes will be uploaded onto the REDCap study database. If a situation arises where sites are unable to upload onto REDCap, the coordinating centre will first support the site remotely to resolve the issue. Should it not be possible to resolve, instruction to send the images securely by email will be given. Any identifiers will be removed from the images and they will be labelled as follows: Patient study number, Date of Image (DDMMMYYYY),_Image number. The images on the email trail will be deleted as soon as upload to REDCap is confirmed

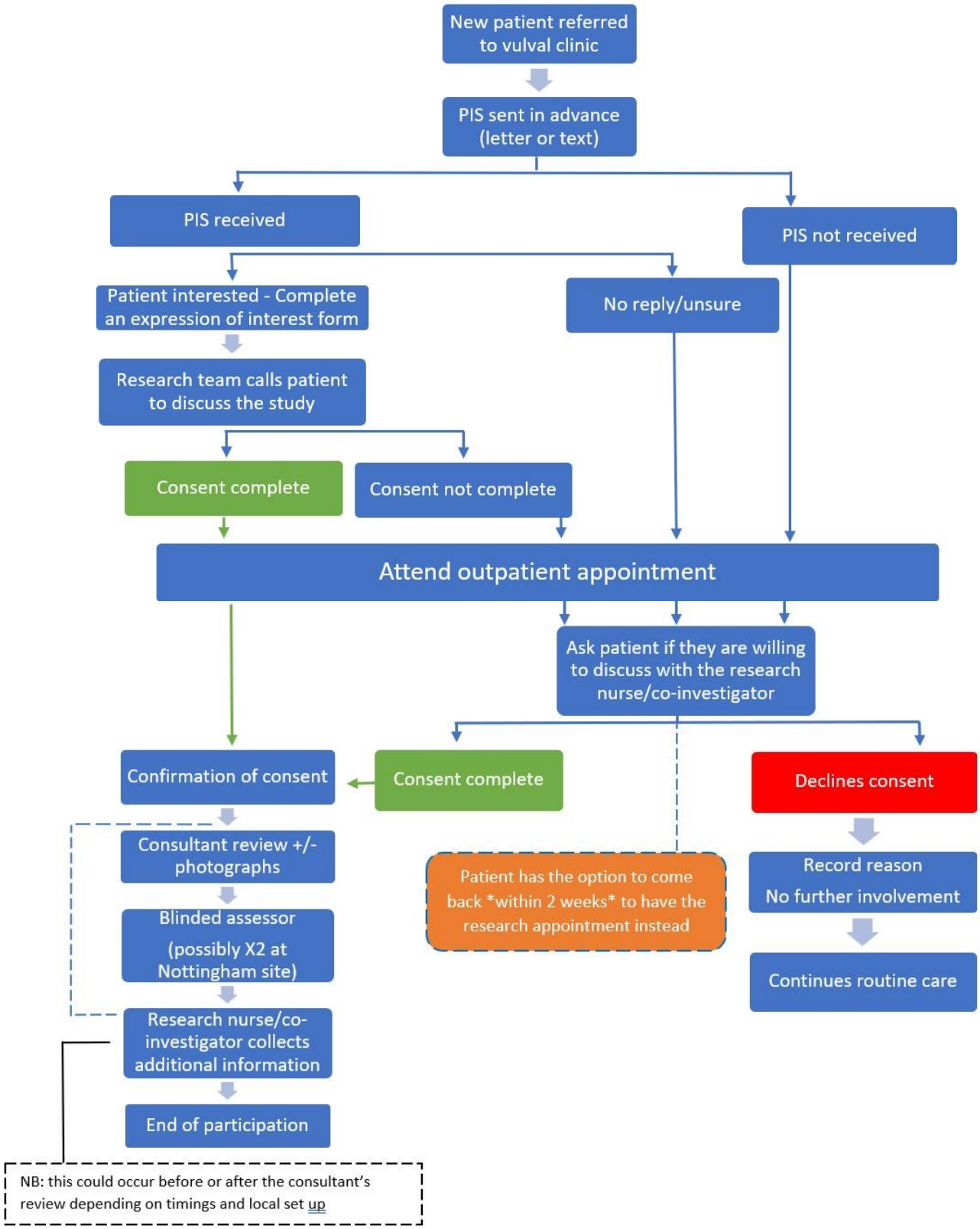


*Figure 1 – Study flow*

### 6.2 Assessors

Each site will have at least one blinded assessor who does not know the managing clinician's diagnosis. The independent assessor will examine the patient to record clinical diagnostic features as soon as possible after the clinician has made their assessment. The blinded assessor can be any individual included in the delegation log who is trained in vulval skin examination, and considered competent to do so by the Principal Investigator at the site. The individual is most likely to be, but not limited to the following groups: trainees, clinical fellows, or specialist nurses working alongside the managing clinician.

The research nurse/research support entering data into REDCap will be blinded to the consultant diagnosis.

### 6.3 Data entry

Data will be collected electronically by a research nurse/researcher blinded to the consultant's diagnosis using REDCap software. People with specific roles within the study will only have access to database forms relevant to their role meaning that blinding can be maintained within the database. In the event that the site do not have the ability to enter data directly into the REDCap database electronically, paper CRFs/worksheets have been created to ensure that relevant information is collected during the consultation. This includes the main CRF, the blinded assessment, and the managing clinician diagnosis. Data collected on paper will subsequently be transferred to REDCap by the local research team. These will be source documents that will be filed in the REDCap database and the investigator site file, and may also be stored as a copy in the medical notes.

### 6.4 Compliance

This is not an interventional study, so assessment of compliance is not applicable. If a participant does not have both the reference standard and the index test, they will be withdrawn from the study as it would not be possible to perform accuracy analysis.

### 6.5 Criteria for terminating the study

This is an observational study with no follow-up, so we do not anticipate the termination of the study for any reasons other than failure to recruit.

## 7 ANALYSES

### 7.1 Methods

Dr. Rosalind Simpson will undertake the analysis of the data under the supervision of Dr. Sonia Gran (Study Statistician).

Demographic data and participant characteristics will be analysed descriptively.

**Stage 1**

***Developing a diagnostic prediction model:***

i. Determining a predictive model of diagnostic criteria for vulval LS: All criteria identified will be included in a backward multivariable logistic regression model[22] with exit criteria p=0.157.[23]

ii. Quantifying the performance of the diagnostic prediction model: Explained variation will be measured by Cox-Snell R-squared. A calibration plot will assess how well predictions agree

with the observed data. Smoothed calibration curves will be plotted using a loess smoother.[24,25] All data for model development will be included for use in internal-external cross validation across centres (alongside bootstrapping). Discrimination will be measured using the C statistic.[26] The model will be fitted to this dataset.

iii. Clinical utility: Thresholds on the calibration plot will be based on clinical utility i.e. what defines high risk and trade-offs between benefits and harm, defined by patients and doctors.

**Stage 2**

***Model validation***
Internal validation is essential to (i) obtain an unbiased estimate of the developed model's predictive performance, and (ii) adjust (shrink) the developed model for optimisation (if necessary). Bootstrapping and uniform shrinkage techniques will be used for analysis.

Missing data: Missing data is not anticipated as the diagnostic features will be assessed by clinical examination. There will be a 'yes' or 'no' answer recorded in the CRF for each criterion in each patient. Only if a participant declines to continue the examination or declines to be examined by the blinded assessor do we anticipate missing index-reference test data pairs. However, the sample size is increased by 10% to account for a maximum of 10% missing data. This will be monitored and if less than 10% data are missing, recruitment target will be reduced accordingly.

c. ***Inter-observer variability***
The inter-observer reliability for assessing the individual diagnostic criteria on 20 cases and 20 non-cases from one of the sites will be calculated using the Kappa statistic. A value of Kappa >60% will be considered acceptable as 'good' agreement between observers.[27] At the site where these data are collected (Nottingham, lead site), there will be two independent assessors.

### 7.2 Sample size and justification

407 participants will be recruited for the study.

This calculation is based upon recommendations by Riley et al[28] using the recommended margin of error of </= 0.05, for a binary outcome that occurs in half of individuals attending the vulval clinic with up to nine predictors in the final dataset. A sample size of 370 people (185 people with the outcome LS and 185 non-LS) is needed to target a confidence interval of 0.45-0.55 for the overall outcome proportion of 0.5 and to target a mean absolute error of 0.062 between observed and true outcome probabilities. The final recruitment figure of 407 participants includes a 10% increase for missing data.

## 8 ADVERSE EVENTS

The occurrence of an adverse event as a result of participation within this study is not expected and no adverse event data will be collected. Patients will have their vulval condition diagnosed in line with usual clinical practice. They will be treated by their managing clinician based on the clinician diagnosis (reference standard), not based upon the Delphi-agreed diagnostic criteria (index test). If the clinician diagnosis is amended at a later stage, this will be recorded in the SHELLS database and their management will be amended according to usual practice.

# 8 ETHICAL AND REGULATORY ASPECTS

## 8. 1 Ethics committee and regulatory approvals

The study will not be initiated before the protocol, consent forms and PIS have received approval / favourable opinion from the 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 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 study 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 and the UK Department of Health Policy Framework for Health and Social Care, 2017.

## 8. 2 Informed consent and participant information

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

The participant will receive a copy of their consent as well as a saved version in the study database. They will receive an e-mailed version, plus on request, a paper copy can be printed from the REDCap database. It will be documented in the medical notes that the patient provided informed consent to participate in the study.

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

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

If the Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Consent Form by the REC and use of the amended form.

## 8.3 Ethical Issues

This study is observational and as such it is considered low risk. In addition, the study regimen is designed to align with the participant's usual care as the observations will be completed alongside the participant's clinic appointment. Therefore, there are no invasive (e.g. skin biopsy) or non-invasive investigations over what they would otherwise receive. Photographs taken of the participant's vulval condition is also part of usual clinical care. Consent for use of photographs for training/research purposes is optional in the context of this study. Participants will have the option to decline the study if they are uncomfortable with any aspect, particularly being examined by another clinician. They will be informed that this will not impact the quality of care that they receive.

Whilst vulval disease is a sensitive area, usual clinical care protocols will be followed. It is not likely that a participant will become more distressed as a result of taking part in the study than they would during their usual clinical care. Should the participant experience distress, they will have the opportunity to withdraw, and be signposted to relevant allied services (psychosexual counselling, psychological services).

### 8.4 Records

#### 8.4.1 Case report forms

Each participant will be assigned a study identity code number, for use on CRFs, other study documents and the electronic database. No personally identifiable information will be used on the central documents or database. Electronic records will be password protected, with frequent electronic and periodic physical back-up (stored off-site).

CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator (at site) will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Participant Study Number, to permit identification of all participants enrolled in the study, in case additional follow-up is required. This confidential list will not be transmitted to the co-ordinating centre. CRFs shall be restricted to those personnel approved by the Chief or local Investigator and recorded as such in the study records.

CRFs in this study will be primarily completed electronically on the REDCap database. These are the only documents that will be transmitted to the co-ordinating centre. Any member of the research team named on the delegation log for data entry shall be authorised to make entries. Should any paper CRFs be present, they will be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated. In the event that sites are unable to enter CRF data directly into the REDCap database, or the local IT systems fail, they will be provided with paper CRFs. In this situation, data will be entered onto the REDCap database by the local site research team and paper based documents retained at site as source documents. Paper CRFs held at sites may be accessed by study personnel on the study delegation log.

Personnel at the co-ordinating centre will have access to the REDCap database for monitoring and analysis purposes (Chief Investigator, research assistant, study statistician).

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

#### 8.4.2 Source documents

Source documents shall be filed at the investigator's site and uploaded to the REDCap database. A copy may also be uploaded to the patient notes. This may include but are not limited to, consent forms and study records (paper CRF, managing clinician diagnosis, blinded assessment). A CRF may also completely serve as its own source data. Only study staff shall have access to study documentation other than the regulatory requirements listed below.

### 8.4.3 Direct access to source data / documents

The CRF and all source documents shall be made available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities.

### 8.5 Data protection

All study staff and investigators will endeavour to protect the rights of the study's participants to privacy and informed consent, and will adhere to the Data Protection Act, 2018. The CRF will only collect the minimum required information for the purposes of the study. Paper CRFs will be held securely, in a locked cabinet. Access to the information will be limited to the study staff and investigators and any relevant regulatory authorities (see above). 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 study in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

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

## 9 QUALITY ASSURANCE & AUDIT

### 9.1 Insurance and indemnity

Insurance and indemnity for clinical study participants and study 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 study 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.

### 9.2 Study conduct

Study conduct may be subject to systems audit for inclusion of essential documents; permissions to conduct the study; CVs of study 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); accountability of study materials.

### 9.3 Study data

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

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

Study data and evidence of monitoring and systems audits will be made available for inspection by the REC as required.

### 9.4 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 at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The study 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, study databases and associated meta-data encryption codes.

### 9.5 Discontinuation of the study by the sponsor

The Sponsor reserves the right to discontinue this study at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice as appropriate in making this decision.

### 9.6 Statement of confidentiality

Individual participant medical or personal 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 patient record 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 study 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.

# 10 PUBLICATION AND DISSEMINATION POLICY

The study will be published in high impact peer-reviewed journals of relevant medical specialities (e.g. in dermatology, gynaecology and general medicine) and conference presentations at national and international meetings. Participants will not be identified in any publications. A presentation will be prepared for recruiting sites whereby it can be delivered at their journal club/departmental meetings. This will recognise the contribution that individual sites have made towards the research and will be a personalised method of feedback.

Primary care dissemination will be through key publications such as 'Pulse', local clinical care commissioning groups and the Primary Care Dermatology Society. Dr Simpson will work with local clinicians to incorporate results of this research with GP teaching material to increase knowledge and awareness of vulval skin disease. Presentation material will be shared with clinicians nationally to deliver to their local GP groups. All participants involved in the research (including the e-Delphi study) will be informed of the study outcomes in a final newsletter and through study updates on the Centre of Evidence Based Dermatology website. Patient representatives will highlight the project via posts on online social media support groups. Finally, infographics and an illustrated 'patient story' video will be developed that will be freely accessible. The patient story video will include a patient describing their experience of being diagnosed with LS and it will be available from the Centre of Evidence Based Dermatology's webpages. In addition to patient groups, specific sectors of the beauty industry will be targeted as beauty therapists may be able to pick up LS due to the nature of their work.

# 11 USER AND PUBLIC INVOLVEMENT

The research question *'What is the best way to diagnose LS'* was generated as a priority through the Lichen Sclerosus Priority Setting Partnership, a process involving 600 patients internationally.[29]

In developing the funding proposal, national patient support groups were engaged with: The Manchester Vulval Support Network (St Mary's Hospital, Manchester), The Lady Garden Club (Chelsea and Westminster Hospital, London) and patient representatives from the British Society for the Study of Vulval Disease.

A study advisory group including an independent clinician experienced in vulval disease, an independent clinician with expertise in diagnostic test accuracy studies and independent patients will oversee this research. The study advisory group will fulfil the following roles:

- Developing the study protocol to ensure it is acceptable to patients.
- Writing the PIS to make certain they are easy to read and understand.
- Reviewing and commenting upon patient facing documentation (e.g. advertising materials and invitation letters).
- Rewording final diagnostic criteria so that they can be understood by patients and the public.
- Contributing to reports and newsletters that will be used to share the results of this work to patients and the public.
- Acting as Research Champions to spread the word about this work during the dissemination process.

### 11.1 Dissemination

This study will work with these patient groups and the British Society for the Study of Vulval Disease to establish how to deliver the dissemination plan most effectively. This is anticipated to be a combination of presentations and social media campaigns using network connections.

# 12 STUDY FINANCES

### 12.1 Funding source

This study is funded by an NIHR Advanced Fellowship (NIHR301434)

### 12.2 Participant stipends and payments

Participants will be given a £10 shopping voucher for their participation.

# 13 SIGNATURE PAGES

### 13.1 Signatories to protocol:

**Chief Investigator:** Rosalind Simpson

Signature: 

Date: 10/10/2024

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