EROSIVE LICHEN PLANUS AFFECTING THE VULVA:

Defining the disease, developing outcome measures and designing a randomised controlled trial

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Abstract

Erosive lichen planus (ELP) is a chronic, inflammatory, scarring skin condition that occurs predominantly on the mucosal surfaces of the mouth and genital region. It is believed to be an autoimmune condition although the exact pathogenesis remains unclear.

This thesis focuses on ELP affecting the vulvovaginal region (ELPV). This is a rare condition with unknown incidence and prevalence. It causes painful raw areas at the vaginal entrance and subsequent scarring leads to anatomical changes with narrowing of the vaginal canal. Symptoms lead to difficulty in normal daily activities such as walking/sitting, washing, going to the toilet and can prevent normal sexual function. There is risk of cancerous change in affected skin of 1-3%.

A Cochrane Systematic Review of interventions for mucosal erosive lichen planus, published in 2012, found no randomised controlled trials (RCT) on which to base treatment for ELPV. Evidence for treatments has historically been based upon retrospective case-series and case reports. Retrospective case series suggest that super-potent topical corticosteroids an effective first-line therapy, although one third of patients fail to respond adequately and require

escalation of therapy. There is no agreement for which second-line agents should be used and this is where the greatest clinical need for therapeutic guidance exists.

The objective of this PhD was to begin to standardise practice for the management of people with ELPV and then develop a pragmatic protocol for those individuals who had failed to adequately respond to first line therapy with super-potent topical corticosteroids.

Initial work focused on current practice in the management of lichen planus, how response to therapy was documented and which outcome measures were routinely used. The following steps were taken to finally inform the design of an RCT to determine optimal second-line therapy for EVLP resistant to topical steroids

- A multi-centre retrospective review and audit of case notes to assess current clinical management in the UK. Variation in practice was found and uncertainties were identified. These uncertainties comprised methods of diagnosing the condition, outcome measures used to assess severity and impact of the disease and therapeutic choices.
- A qualitative investigation into UK clinicians' views and principles of management of vulval erosive lichen planus. This involved interviews with 25 UK clinicians and aimed to begin to address the uncertainties identified by the retrospective case note study.

- An international multi-disciplinary consensus exercise. This was performed to agree a set of diagnostic criteria for ELPV that are acceptable to the clinical community.
- A systematic review of the literature to assess existing outcome measure tools that have been used in randomised controlled trials of vulval skin disorders.
- A survey of a national patient group, the UK Lichen Planus Society which identified preliminary information about living with ELPV from the patient's perspective.
- Focus groups with patients. The themes identified from the UK Lichen planus Society survey, plus findings from the systematic review of outcome measures, were subsequently explored in greater detail through focus group work with patients. Focus groups were also used to obtain patient input into the proposed future RCT protocol

Evidence from this work has informed a randomised controlled trial (RCT) developed with input from patients and clinicians to pragmatically answer an important question of clinical significance

The resulting trial is a multi-centre, four-armed, open-label, pragmatic randomised controlled trial which will run in the secondary care setting. The trial will compare the medications hydroxychloroquine, methotrexate and mycophenolate mofetil against a standard care group of clobetasol propionate 0.05% plus a short course of oral prednisolone. These therapies were identified by

clinicians as likely to be most effective in clinical practice. However, amongst expert clinicians, there was no clearly preferred agent and insufficient data existed within the literature to demonstrate efficacy of any of these medications. It was therefore impossible to pick one comparator alone to test in a two-armed, placebo controlled RCT. As the disease is rare but chronic and resources limited in it was decided that a four-armed study would be the most appropriate as it would conserve patient numbers compared to running separate trials, and would give information on the three of the most commonly used systemic agents likely to be most effective. The primary outcome measure will be the proportion of participants responding to therapy at 6 months. This will be measured by a Patient Global Assessment score of 0 or 1 on a 4-point scale, and an Investigator Global Assessment of improvement from baseline judged by clinical images.

The randomised controlled trial protocol has received ethical approval by the National Research Ethics Committee and the necessary regulatory documentation has been completed for the trial to commence in summer 2014.

Impact of this research:

This will be the first randomised controlled trial to test systemic agents for patients with vulval erosive lichen planus and will add to the existing evidence base. The impact of this work will potentially

extend beyond improving care for patients with ELPV as the methodologies employed to develop the RCT protocol, and the trial design itself, may act as a template for clinical research into the therapeutic management of other rare inflammatory conditions.

Publications and presentations arising from this work

Peer reviewed publications

Simpson RC, Thomas KS, Murphy R. Comment on "management of vulvovaginal lichen planus: a new approach". *J Low Genit Tract Dis*. 2014 Jan;18(1):E23-4.

Simpson RC, Thomas KS, Murphy R. Outcome measures for vulval skin conditions: A systematic review of randomised controlled trials. *Br J Dermatol*. 2013 Sep;169(3):494-5

Simpson RC, Thomas KS, Murphy R. Vulval Erosive Lichen Planus: A qualitative investigation of UK clinician views and principles of management. *Br J Dermatol*. 2013 Jul;169(1):226-7.

Simpson RC, Thomas KS, Leighton P, Murphy R. Diagnostic Criteria for Erosive Lichen Planus Affecting the Vulva: An international electronic-Delphi Consensus Exercise. *Br J Dermatol.* 2013 Aug;169(2):337-43

Simpson RC, Murphy R. Critically Appraised Topic - Is vulval erosive lichen planus a premalignant condition? *Arch Dermatol*. 2012 Nov 1;148(11):1314-6.

Simpson RC, Murphy R *et al.* Real life experience from a UK multi-centre case note audit; management of vulval erosive lichen planus*. Br J Dermatol.* 2012 Jul;167(1):85-91.

Simpson RC, Murphy R. Considerations for Disease Impact and Outcome Measures in Vulvar Disease. *J Low Genit Tract Dis*. 2012 Oct;16(4):460-3.

Book chapter

Simpson RC, Murphy R, Nunns D: Vulval lichen sclerosus, erosive lichen planus and vulvodynia. In Williams HC , Bigby M, Diepgen T, Herxheimer A, Naldi L, Rzany B (eds) Evidence Based Dermatology 3rd Edition Chapter 72, Wiley Blackwell Publishers 2014.

Conference abstracts

Simpson RC, Thomas KS, Leighton P, Murphy R. Diagnostic criteria for erosive lichen planus affecting the vulva: An electronic-Delphi consensus exercise*. Br J Dermatol* 2013;169 (Suppl 1):4

Simpson RC, Thomas KS, Leighton P, Murphy R. Diagnostic criteria for erosive lichen planus affecting the vulva: An electronic-Delphi consensus exercise*. Journal of Investigative Dermatology* 2013; 133 (Suppl.):S38

Cheng S**, Simpson R,** Kirtschig G, Cooper S, Silcocks P, Thornhill P, Murphy R. A Systematic Review of Interventions for Erosive Lichen Planus *Affecting Mucosal Sites. J Low Gen Tract Dis* Oct 2011; (Suppl): S5.

Oral presentations

British Society for the Study of Vulval Disease (BSSVD) Biannual Meeting, Glasgow, March 2014

- Update on vulval erosive lichen planus randomised controlled trial

School of Clinical Sciences Research Committee Workshop, Nottingham, July 2013

- Patient and Public Involvement in the Clinical Research Cycle

British Association of Dermatologists Annual Meeting, Liverpool, July 2013

- Diagnostic criteria for erosive lichen planus affecting the vulva: An electronic-Delphi consensus exercise.

Sue Watson Postgraduate Oral Presentation Event, University of Nottingham, July 2013

- Diagnostic criteria for erosive lichen planus affecting the vulva: An electronic-Delphi consensus exercise.

THESIS' (The Skin Investigation Society) Annual Meeting, London, June 2012 (Invited speaker)

- 'Dreams, creams and aspirations'

British Society for the Study of Vulval Disease (BSSVD) Biannual Meeting, Newcastle, March 2012

- Audit of current UK practice in the Diagnosis and Management of Vulval Erosive Lichen Planus; Results, Lessons and Future Work

International Society for the Study of Vulval Disease (ISSVD) Biannual Meeting, Paris, September 2011

- Vulval Erosive Lichen Planus. Results of a Cochrane Systematic review and subsequent Multi-centre case note audit

Grant awards and prizes arising from this work

Year	Award	Role
2013	**British Association of Dermatologists 93rd Annual Meeting, Liverpool,** won Best Submitted Scientific Paper	Presenter (oral presentation)
	Postgraduate Research Forum, University of Nottingham, School of Medicine and Health Sciences, Sue Watson Presentation Competition. First Prize	Presenter (oral presentation)
	BAD /ESDR travel bursary for the International Investigative Dermatology meeting held every 5 years	Presenter at meeting (poster presentation)
2012	**NIHR Research For Patient Benefit Award** (£232 000 over 3 years)	Co applicant, Principal Applicant was Dr Ruth Murphy. When this award was made the NIHR Doctoral Research Fellowship had already commenced and it was not possible to accept both awards from the same funding body.
	NIHR Doctoral Research Fellowship Award (£330 000 over 3 years)	Principal applicant, supported by Dr R Murphy and Prof K S Thomas
	Postgraduate Research Forum, University of Nottingham, School of Medicine and Health Sciences. Poster competition – second prize	Presenter (poster presentation)
	BAD Educational Bursary to attend 'THESIS' course	Presenter at meeting (oral presentation)

2011	**BAD/Dowling Club Travel Bursary** towards International Society for the Study of Vulval Disease World Congress, Paris, 2011	Presenter at meeting (oral presentation)
	Nottingham University Hospitals Pump Priming Competition – Bursary towards retrospective case note review for Erosive Lichen Planus project (£9600)	Co-applicant. Chief investigator and principal applicant was Dr R Murphy

Table of Abbreviations

Please note that all abbreviations or acronyms are detailed here as well as in first use within the thesis.

ADR	Adverse Drug Reaction
AE	Adverse Event
BAD	British Association of Dermatologists
BCG	Bacille Calmette Guerin
BD	Bis die (twice a day)
BHPR	British Health Professionals in Rheumatology
BMZ	Basement Membrane Zone
BNF	British National Formulary
BSR	British Society of Rheumatology
BSSVD	British Society for the Study of Vulval Disease
CF	Informed Consent Form
CI	Chief Investigator overall
CRF	Case Report Form
DAP	Data Analysis Plan
DEJ	Dermo-epidermo Junction
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
e-Delphi	Electronic Delphi
ELP	Erosive lichen planus
ELPV	Erosive lichen planus affecting the vulva
EOT	End of Trial
FSFI	Female Sexual Function Index
FSDS	Female Sexual Dysfunction Scale
GCP	Good Clinical Practice
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale

HCQ	Hydroxychloroquine
HELP	'Therapy for vulval Erosive Lichen Planus' trial
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HRQoL	Health Related Quality of Life
IGA	Investigator Global Assessment
IMF	Immunofluorescence
ISSVD	International Society for the Study of Vulvovaginal Disease
LP	Lichen Planus
LS	Lichen Sclerosus
MDT	Multi-disciplinary Team
MHRA	Medicines and Healthcare products Regulatory Agency
MMF	Mycophenolate mofetil
MTX	Methotrexate
NHS	National Health Service
OD	Once daily
OLP	Oral Lichen Planus
PGA	Patient Global Assessment
PI	Principal Investigator at a local centre
PIS	Participant Information Sheet
PO	Per os – by mouth
P value	Probability value
QOL	Quality of Life
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research and Development department
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SCC	Squamous Cell Carcinoma
SF36	Short Form 36

SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
UKLP	United Kingdom Lichen Planus Society
USA	United States of America
VAS	Visual Analogue Scale
VIN	Vulval Intraepithelial Neoplasia
VVG	Vulvovaginal Gingival syndrome

Acknowledgments

This thesis would not have been possible without the support and inspiration of several key individuals. These individuals understood that the field of vulval dermatology had long been neglected and that time and attention was needed to advance knowledge in this area. In a world where rare diseases are only just being recognized as important, these individuals saw this from an early stage. They believed in my ability to carry out the work and make this project a success.

Ruth Murphy was my inspiration for taking on this work. She has been a mentor from the outset of my career as a dermatologist and possesses a high level of clinical skill and professionalism to which I aspire. Ruth enthuses trainees, consultant colleagues and nursing staff to constantly strive towards better care. She is a progressive individual whose tireless dedication to her patients and mentees has helped to push practice forward. She was the one who highlighted to me the lack of evidence based practice within the field of vulval dermatology and subsequent unnecessary suffering of patients. It is she who inspired my interest in this field. Ruth has provided constant support in her role as my clinical supervisor.

Kim Thomas has been key in developing my academic skills over the past three years. Her knowledge of the research cycle combined with her experience in trial design and protocol development has meant that this thesis has progressed through a number of stages to create fully worked up randomised controlled trial protocol. She has shared her wealth of knowledge of different research methodologies and her sound supervision has been instrumental in ensuring the project was a success.

Professor Hywel Williams and the Centre of Evidence Based Dermatology have shown great faith in me as a researcher and provided initial funding for this work. They continued to support me both financially and academically whilst seeking external funding to complete the project. The principles by which the Centre identify knowledge gaps, prioritise academic work and execute their clinical research will be paramount to how I practice in the future.

This project would not have been possible without the financial support of the Centre of Evidence Based Dermatology initially and then the Doctoral Research Fellowship that was awarded through the National Institute of Health Research. Achieving the Fellowship has been a real triumph for me personally, but more importantly reflects upon the fact that skin diseases, particularly rare conditions, are being given more recognition amongst the scientific community.

Within the Centre of Evidence Based Dermatology, the UK Dermatology Clinical Trials Network (UK DCTN) team have played an important role in this research. My introduction to clinical research was through the Specialist Registrar Fellowship which I was awarded by the UK DCTN in 2009. I would not have been introduced to this research project without this Fellowship. The UK DCTN have provided guidance throughout this research and Carron Layfield, Jo Chalmers, Tessa Clark and Maggie McPhee have helped me greatly with the work. Carron was involved in running Focus Groups; Maggie assisted in using Survey Monkey for the electronic-Delphi Consensus Exercise; Jo has guided me through the trial protocol development process and has been an invaluable member of the trial development group; and Tessa has worked tirelessly in helping to prepare the regulatory documentation required for the subsequent randomised controlled trial.

Matthew Sydes' and Daniel Bratton's expertise in trial design and statistical support has been fundamental to the development of the final RCT protocol. I am grateful to them and the Medical Research Council's Clinical Trials Unit for their support of this work.

Paul Leighton at the East Midlands Research Design Service has been key in advising in the qualitative methods used in this project and without him the focus groups and electronic-Delphi consensus exercise would not have gone so smoothly.

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The focus groups would not have been possible without the seven patients who voluntarily gave up their time to participate.

And finally, to my family. My parents whose values have made me the person I am today and my husband, Alastair who has stood by me and encouraged me to carry out the work to the best of my ability. It is he who has constantly reminded me of the reasons I am doing this work – to improve the lives of both patients through moving practice forward, and to improve our lives through my personal and professional development that has occurred over the past three years. Since having our son Cameron in October 2013, I realise more than ever the importance of having completed this thesis and demonstrating the skills required to do so. I hope to be an inspiration to him for the future and having my family around me has made this all worthwhile.

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Preface

Structure of the Skin and mucous membranes

The skin is an organ that consists of three layers: the epidermis, dermis and subcutis. These three structures are represented in Figure 1, Page 5.

i. The epidermis

The epidermis is the uppermost layer of the skin and is an epithelial surface. Squamous epithelium (from Latin *squama*, "scale") is characterised by its most superficial layer consisting of flat, scale-like cells. In the skin, keratinocytes, which are squamous cells, form a stratified epithelium, which consists of four distinct layers. These are the stratum basale (basal layer), stratum spinulosum (spinous, spiny or prickle cell layer), stratum granulosum (granular layer) and stratum corneum (horny layer), which are demonstrated in Figure 1, Page 5.

Stratified squamous epithelium is present on the skin and mucous membranes. The keratinocytes undergo a process of maturation as they develop from the basal and move outwards towards the skin surface. Cells in the basal layer divide and the keratinocytes subsequently migrate upwards. They progressively become flattened and lose their nuclei as they move towards the stratum corneum.

Skin, hair and nails are keratinized, which indicates that the outermost layer of the epidermis (stratum corneum) is formed by

dead, dried out keratinocytes. Figure 2, page 6 shows a haematoxylin and eosin stain of a section of normal epidermis. The four distinct layers are visible and the stratum corneum has a 'basket weave' appearance, which confers a hard and impermeable surface to the skin.

In contrast, mucous membranes are non-keratinised. Figure 3, page 6, demonstrates a typical haematoxylin and eosin stain of non-keratinising mucosa. There is still differentiation and maturation of keratinocytes as they progress upwards from the basal layer, but the stratum corneum is absent. Mucous membranes contain more glandular structures than keratinized skin, and so remain moist. It is glandular secretions, rather than keratin that act to protect mucous membranes.

The differences between keratinized and non-keratinised epithelia are important for this thesis on lichen planus as the disease can affect either type of surface. However, when it affects mucosal surfaces, lichen planus tends to be more resistant to treatment and causes greater morbidity.

Immediately below the basal layer is the basement membrane, a specialised structure that links the epidermis and dermis and has a vital role in maintaining skin structure.

Hair, nails and sweat glands are appendageal structures formed by a direct extension of the epidermis. These structures extend down into the dermis, but are lined by epidermal cells.

ii. The dermis

The dermis is composed of fibrous connective tissue. It contains mostly collagen and elastin which provide a supportive structure for the skin. Nerves, blood vessels, adnexal structures and cells (mast cells, immune cells, fibroblasts and specialised muscle cells) are also present in the dermis. When the skin is involved in disease states, inflammatory cells transiently infiltrate the dermis, and sometimes the epidermis and subcutis.

iii. The subcutis

The subcutis is a layer of fat which lies directly below the dermis. It consists mainly of adipocytes, nerves and blood vessels.

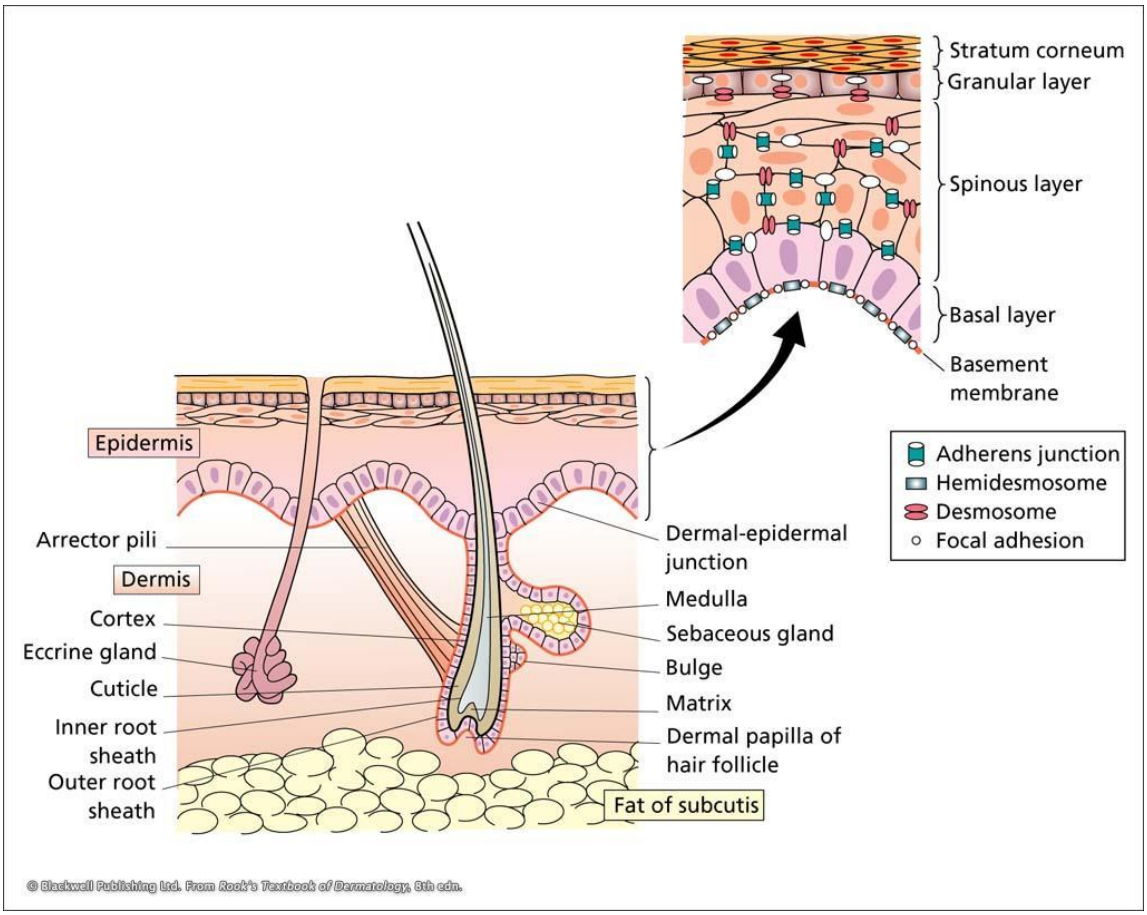

Figure 1: Schematic representation of the three layers of the skin (main diagram) and epidermis (insert).

Taken from Rook's textbook of Dermatology 8th Edition.

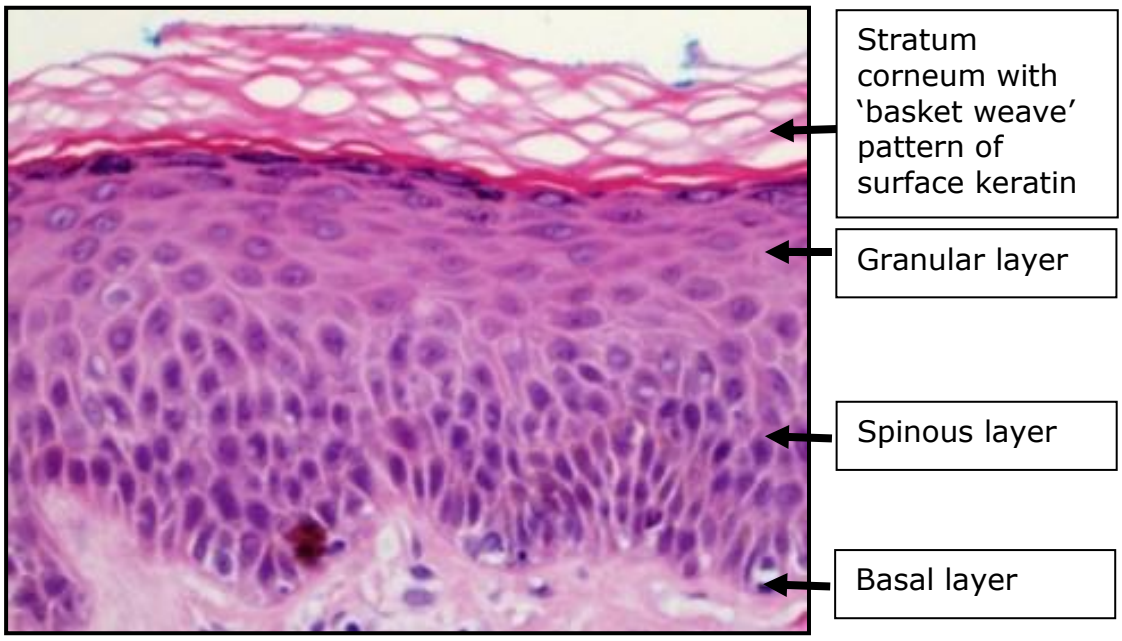

Figure 2: High power photomicrograph view of epidermis; keratinised stratified squamous epithelium. Haematoxylin and Eosin stain, x 100 magnification.

The four distinct layers of the epidermis are clearly seen with the hard, impermeable keratin layer providing a protective surface to the skin. Image taken from 'www.tissuepath.com.au'.

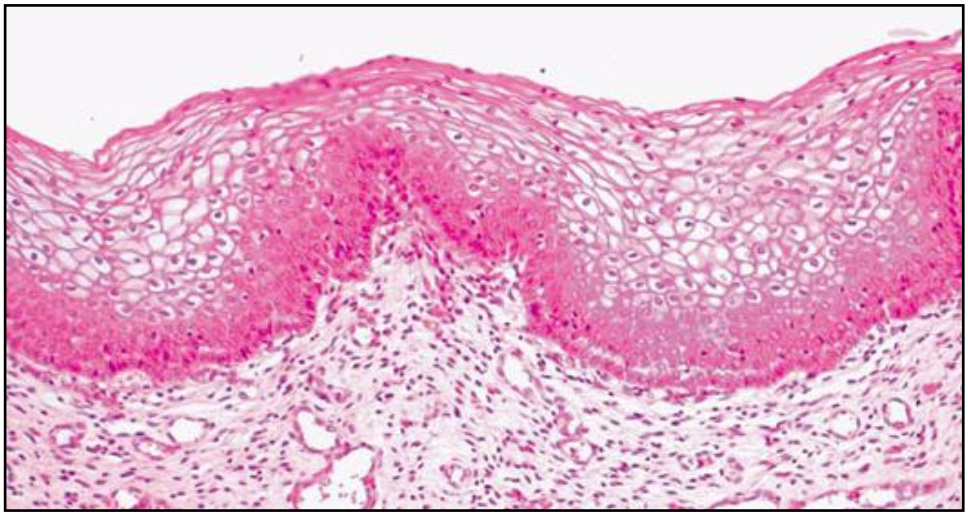

Figure 3: Low power photomicrograph of non-keratinising stratified squamous epithelium. Haematoxylin and Eosin stain, x 40 magnification.

In contrast to Figure 2 (above) there is no stratum corneum but there are increased glandular secretions that protect mucosal surfaces. Image courtesy of Dr S Deen.

Chapter 1 Introduction - Lichen Planus

1.1 What is lichen planus?

In this chapter, lichen planus, its epidemiology, understood pathology, clinical presentations and associations with other medical conditions will be discussed in detail. Since this thesis focuses predominantly on erosive lichen planus affecting the vulval region, whilst all clinical variants are described, greater emphasis is placed on vulval erosive lichen planus.

The term 'lichen' is used by dermatologists to describe the presence of flat-topped, papular lesions on the skin. Histopathologically, 'lichenoid' refers to a characteristic pattern of inflammation in which a band-like inflammatory cell infiltrate is seen in the upper dermis. This is described in greater detail later in this chapter.

Lichen planus (LP) was first described by Erasmus Wilson in 1869. It is an inflammatory mucocutaneous disorder that may involve any surface lined with squamous epithelium. The definition of 'squamous epithelium' is given in the introduction, section i (page 2). LP can affect both keratinized skin and mucosal surfaces. The structural differences in these different types of epithelia are also described in the introduction, section i (page 2).

The regions of the body which can be affected by LP and the typical lesions at these sites are illustrated on page 18, which shows a body map with some of the common and rarer sites of involvement. The

skin and oral mucosa are most frequently affected (Le Cleach 2012). Different forms of LP exist and are predominantly the plaque type (affecting keratinized skin) and the erosive type (affecting non-keratinised mucous membranes). Other types such as bullous or hypertrophic may also occur.

1.1.1 Histological changes in lichen planus

Classical histologic findings are the same in lichen planus, regardless of which site is affected. However, the site that a biopsy is taken from is important and it may be more difficult to demonstrate typical features in mucosal areas if an area of ulceration is sampled.

Characteristic histologic features of lichen planus are demonstrated in Figure 4, page 10 and Figure 5, page 11, and include:

- thickening of the stratum corneum;
- accentuation of the granular-cell layer;
- pointed 'rete ridges' and wedge shaped hypergranulosis (thickening of the stratum granulosum) that gives a 'saw toothed' pattern
- liquefactive degeneration of the basal-cell layer (basal cells degenerate and form 'colloid bodies');
- a band-like inflammatory-cell infiltrate (usually composed of lymphocytes).

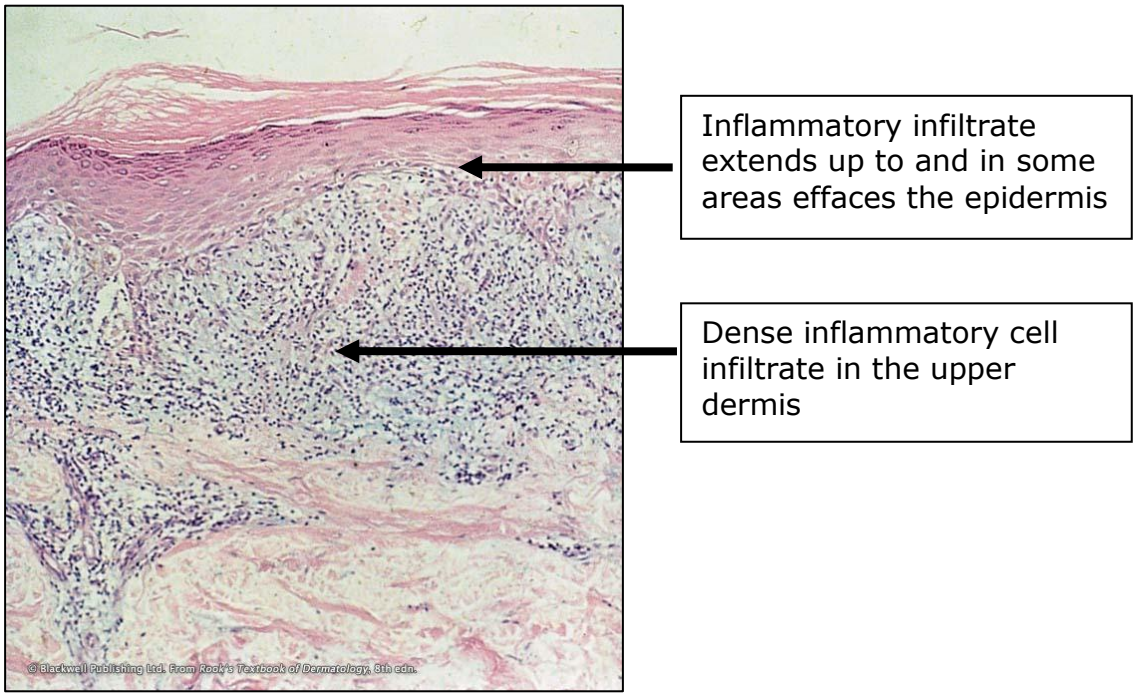

Figure 4: Low power photomicrograph of lichen planus affecting keratinising skin. Haematoxylin and Eosin stain, x 40 magnification.

An inflammatory infiltrate is present in the upper dermis which in some areas appears to infiltrate the epidermis. Image taken from Rook's Textbook of Dermatology 8th Edition.

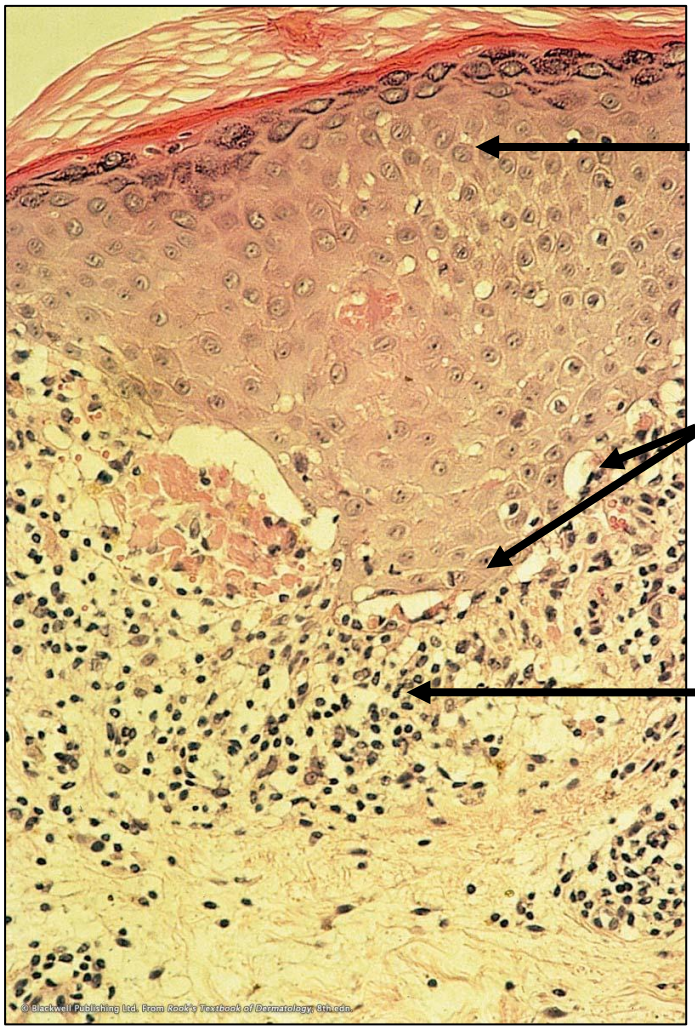

Figure 5: High power photomicrograph of lichen planus on keratinising skin. Haematoxylin and Eosin stain, x 100 magnification.

There is a band-like inflammatory infiltrate, effacement of the epidermis with degeneration of the basal cell layer and thickening of the granular cell layer of the epidermis. Image taken from Rook's Textbook of Dermatology 8th Edition.

1.2 Clinical variants of Lichen Planus

1.2.1 Classical Lichen Planus

The most common form or 'classical' form of lichen planus affects the skin and is termed *cutaneous* LP. It is estimated to affect 1% of the population (Boyd 1991). It presents with characteristic well-demarcated, polygonal plaques (flat-topped raised lesions) that are violaceous in colour. The surface of these plaques often display 'Wickham's striae', which is the clinical finding of white lacy lines (Rook 2010). The appearance of Wickham's striae is shown in Figure 6 (Page 18) where they are present overlying an erythematous plaque on the image of cutaneous LP. Plaques of cutaneous LP typically occur on the extensor surfaces of the wrists and ankles, however, the skin appendegeal structures, the hair and nails, may also be affected. The former presents with irregular pits, thinning/ridging of the nail plate and distal splitting that leaves a scar (pterygium). The latter causes a scarring alopecia (Rook 2010) and is shown in Figure 6, page 18, on the image of a scalp.

Lesions of classical cutaneous LP may also take on different morphologies, including papules which appear in groups, lines or rings (Rook 2010). In particular, linear lesions may occur following trauma, the so called 'Koebner phenomenon'. Circular (also termed 'annular') lesions may be formed by groups of papules arranged in rings, or by a single large papule, which clears centrally to leave an

active margin (Rook 2010). Annular lesions are most commonly seen on the penis (Rook 2010).

Classical LP can affect any cutaneous surface which includes the anogenital skin. When it affects the vulva and/or perianal region, presenting features are those of small, intensely itchy violaceous papules located on the external genital skin. Wickham's striae are often seen overlying these anogenital lesions (Goldstein 2005).

1.2.2 Hypertrophic lichen planus

If lesions of classical LP persist for a long time, they may enlarge, thicken and form a rough surface. This is known as hypertrophic LP, which causes severe symptoms of itching. Although hypertrophic lesions may eventually resolve they tend to leave considerable scarring (Rook 2010). Such lesions are most commonly found on the ankles, shins, palms and soles. Malignant transformation has been described in this variant (Yesudian 1985).

1.2.3 Bullous lichen planus

In bullous (blistering) LP, blisters appear near to, or in within the lesions of LP. This is a reflection of severe inflammation occurring in the basal cell layer of the skin. Due to destruction of this histologic layer, which is represented schematically in Figure 1, page 5, the epidermis and dermis separate, which causes bullae (blisters) to form. This eruption is usually of short duration but may lead to

diagnostic difficulty as other bullous disorders may present similarly. Histological and direct immunofluorescence examination of affected skin is important in these cases to reach the correct diagnosis.

1.2.4 Lichen Planus affecting mucous membranes

Mucous membrane lesions are common and may be present with or without concomitant skin lesions. Any mucous membrane may be affected by the condition, although the oral and genital mucosa are the most common mucosal sites to be involved. More than one mucosal site can be affected at any one time. This section is an introduction to how lichen planus can affect mucosal surfaces; vulval lichen planus, which is the focus of this work is described in much greater detail in sections 1.3 (page 19) to 1.12 (page 100).

1.2.4.1 Oral lichen planus

Involvement of the oral cavity, oral lichen planus (OLP) is believed to the most common presentation of LP worldwide and is sometimes the only manifestation of the disease in an individual (Rogers 2003). It has been suggested that the prevalence of OLP is 1-2% in people over the age of 15 years (Axell 1987).

The clinical presentation of OLP is often insidious with some patients being asymptomatic. Others report roughness of the mouth, sensitivity to foods (especially hot and spicy items), pain or

ulceration, or a combination of these. Symptoms largely depend upon the clinical subtype of disease.

Several distinct clinical subtypes of OLP are recognized *reticulate* LP (appearing as lacy white lines on the buccal mucosa) may or may not be symptomatic. *Hypertrophic* LP, forms fixed, white plaques on the buccal mucosa may be mistaken for candidiasis and is at potentially higher risk of malignant transformation than the other forms. *Erosive* lesions are usually highly symptomatic as they leave denuded, raw areas of mucosa that are slow to heal. Erosive LP may extend to the larynx or oesophagus (Abraham 2000) which leads to dyspahgia and formation of strictures. Patients with OLP may also have other mucosal sites affected, for example the genital and lacrimal mucosa.

Other clinical forms of OLP include papular, atrophic and bullous.

1.2.4.2 Genital lichen planus

Lesions affecting the male and female genitalia (vulva, vagina, penis) are well recognized albeit less common than OLP. On the penis, classical LP is most often seen. In females, erosions affecting the mucosal surface of the vulva are more frequent and it is termed erosive lichen planus (ELP). These erosions may extend to affect the vagina. Genital lesions are either seen alone or in conjunction with OLP. In a large case series of 339 patients with OLP, LP affecting the vulva and vagina was identified in 77 (19%) (Eisen 1999).

In a specific, severe variant, ELP may concomitantly affect the vulva, vagina and oral mucosa. This is known as the vulvovaginal gingival (VVG) syndrome and causes considerable morbidity as it is resistant to treatment. The equivalent in males is the penogingival syndrome.

1.2.4.3 Other mucous membrane sites

Other less commonly affected mucosal sites include the eyes (Neumann 1993), bladder, larynx, stomach, and anus (Eisen 1999). However, relatively little is known about these less common sites, especially when compared with the literature available for oral and cutaneous LP.

1.2.5 Who gets lichen planus?

Oral lichen planus presents at a mean age of 50-60 years (Carbone 2009, Bermejo-Fenoll 2010). The mean age at diagnosis for cutaneous LP is 40-45 years (Irvine 1991). Vulval erosive LP primarily affects peri or post menopausal females (Eisen 1999) and it is an uncommon condition.

Both oral and cutaneous LP have been reported in children, although this is usually considered rare, except for the Indian subcontinent (Kanwar 2010) where some studies have estimated the incidence of LP in childhood to be as high as 11% of all LP cases (Kumar 1993).

1.2.6 Prognosis of the different variants of lichen planus

Cutaneous LP tends to be self-limiting and is responsive to treatment with super-potent topical steroids. Post-inflammatory pigmentary changes usually occur, however these fade over time and permanent scarring is infrequent. Hair disease (lichen planopilaris) also tends to take a self-limiting course but is often resistant to treatment and leads to a scarring alopecia which is irreversible.

Nail LP is a scarring, destructive disease causing loss of normal nail architecture. It is more likely to require systemic immunosuppression, for example, with oral corticosteroids, to which response is variable. Hypertrophic LP is also treatment resistant and prolonged therapy with super potent topical corticosteroids or calcineurin inhibitors is often required.

In contrast to classical cutaneous LP, disease that affects *mucosal* surfaces such as the oral, genital and other mucosa takes a more chronic, relapsing/remitting course (Silverman 1985) and may be resistant to treatment. Super potent topical steroids are the widely recognised first-line therapy, however, up to one third of patients are refractory to these and are likely to have long-term inadequate control of their disease.

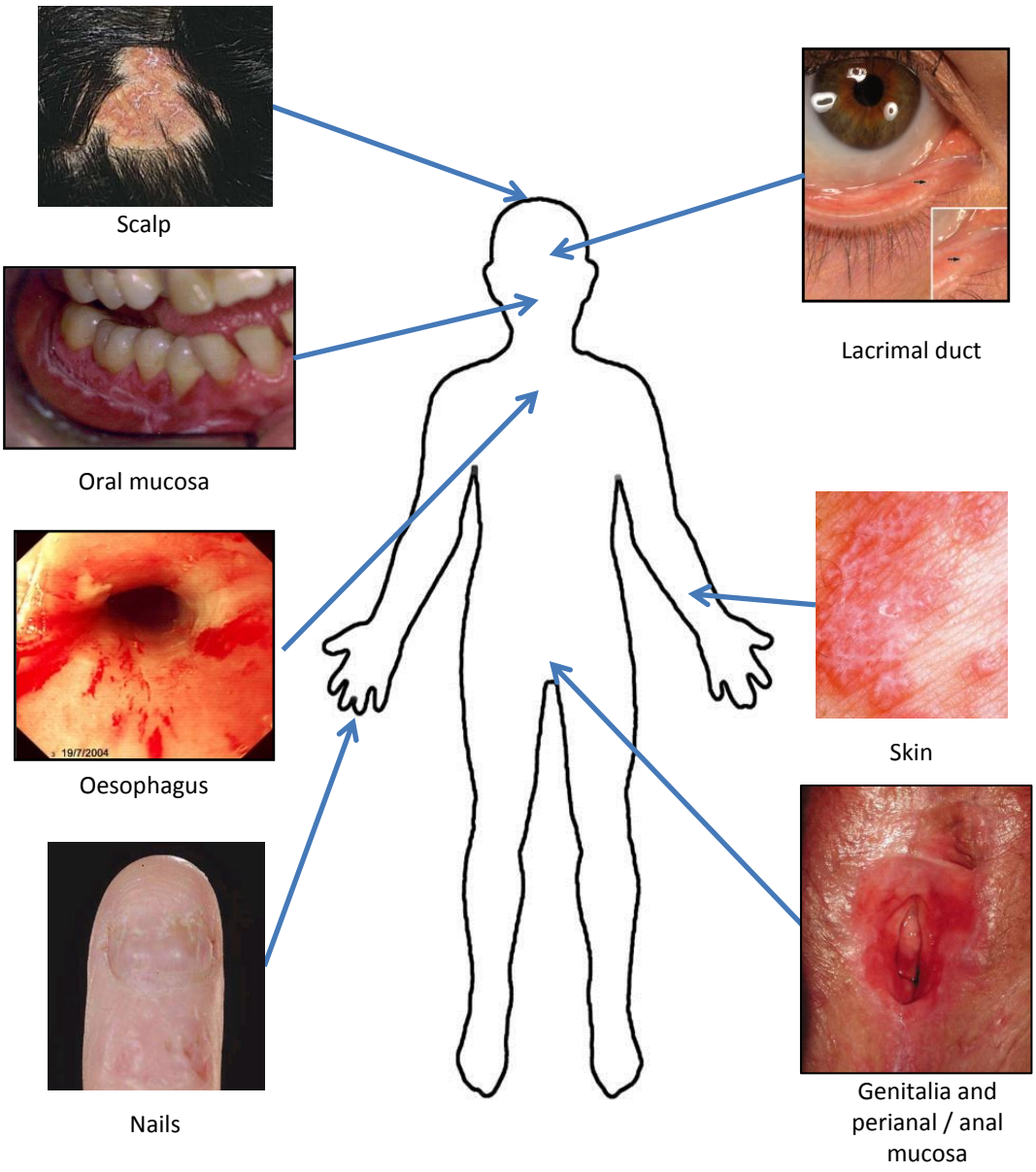

Figure 6: Schematic diagram demonstrating the distribution and type of lichen planus lesions on the skin and mucous membranes.

Wickham's striae are easily identified at the margin of the lesions at the labia minora and in the buccal sulcus.

1.3 Erosive Lichen Planus affecting the Vulva

This thesis focuses specifically on erosive LP affecting mucosal surfaces, specifically the adult female genitalia (erosive lichen planus of the vulva, ELPV). It is important though to consider ELPV as part of a disease spectrum involving other mucosal surfaces, especially the oral mucosa, as described in section 1.2.4. This section will therefore at times discuss vulval LP in conjunction with other mucosal variants, mainly oral LP. Furthermore as ELPV is much less common that oral LP, evidence is lacking in many aspects of this subset and at times inferences must be drawn from the oral literature.

1.3.1 Epidemiology of erosive lichen planus affecting the vulva

1.3.1.1 Incidence and prevalence

The true incidence and prevalence of ELPV is unknown. This is due to the variable clinical presentation, lack of clearly defined diagnostic criteria and reluctance of women to present to secondary care. A formal literature search was not able to identify any epidemiological studies that provide these data.

Studies of patients attending vulval specialty clinics have reported variable figures for the number of new patient referrals who were

subsequently diagnosed with with ELPV. These are currently the best available data and are detailed in Table 1, page 20.

Study	Duration of study	No. of new patients assessed	No. of patients diagnosed with ELPV	Proportion of new referrals diagnosed with ELPV
Hansen 2002	4 years	322	25	8%
Helgesen 2010	6 years	989	59	6%
Kennedy 2007	7 years	3983	113	3%

Table 1: Proportion of new referrals to vulvar specialty clinics who were found to have vulval erosive lichen planus.

The largest cohort of patients with vulval disease was described by Kennedy (Kennedy 2007) who found that of nearly 4000 patients presenting to a specialist clinic in a United States tertiary referral centre, 3% were diagnosed with ELPV. Helgesen (Helgesen 2010) and Hansen (Hansen 2002) found that in smaller cohorts of new referrals to vulval services, 6% and 8% had ELPV respectively.

A further study by Micheletti et al (Micheletti 2000) found a prevalence of 3.7% of ELPV from a case series of 3350 vulval biopsies taken between 1986-99 in a specialist vulval clinic.

Unfortunately as the size of the population that these cohorts of patients were from, it is not possible to calculate incidence and prevalence of ELPV.

However, the figures from these case series suggest that ELPV is not as rare as originally thought. Furthermore, the overall problem is likely to be underestimated for the following reasons: Genital lesions may be subtle (Moyal-Barracco 2004), patients may not associate their symptoms with LP elsewhere (Lewis 1996), and there remains a culture of patients delaying presentation to medical services to seek help for their genital problem (Lawton 2006). Therefore, although ELPV has previously been perceived as a rare disease, as more clinicians become aware of its existence it is being diagnosed more frequently, especially in women (Moyal-Barracco 2004).

Erosive lichen planus affecting the vulva often occurs in conjunction with other forms of lichen planus. In a study of 37 women with *cutaneous* LP, half had vulval lesions (Lewis 1996). Other studies evaluating patients with *oral* LP have found a prevalence of affected vulval skin in 57% (Belfiore 2006) and 19% (Eisen 1999).

1.3.1.2 Affected age group

Erosive lichen planus affecting the vulva (ELPV) typically affects females of peri- and post-menopausal age (Eisen 1999, Cooper

2006) although has been described in patients with ages ranging from teens to octogenarians (Micheletti 2000, Helgesen 2010).

1.3.2 Pathogenesis of erosive lichen planus affecting the vulva

The pathogenesis of the disorder is still not entirely clear. It is thought though that all types of lichen planus including that affecting genital and oral mucosa, have a similar autoimmune pathology (Cooper 2008).

The histology of erosive LP shows features the same as in classical LP, with basement membrane zone disruption due to lymphocytic infiltration (as demonstrated in the histopathological images in Figure 4, page 10, and Figure 5, page 11). The immunohistochemistry of cutaneous LP shows widespread changes in antigen expression and it is believed that the pathogenesis of cutaneous LP is broadly similar to that of ELPV.

Cooper et al (Cooper 2005) found disruption of major hemidesmosomal proteins found at the basement membrane zone in a study of 6 patients with ELPV. In another study (Sander) they also found reduced antioxidant defense mechanisms in conjunction with increased oxidative damage at the dermo-epidermal junction in ELPV patients, suggesting that the accumulation of severely oxidised

proteins at this site is relevant to the development of scarring and skin fragility seen in ELPV. The process of oxidative damage leading to T-cell activation and subsequent damage to the basement membrane is demonstrated in Figure 7, page 24.

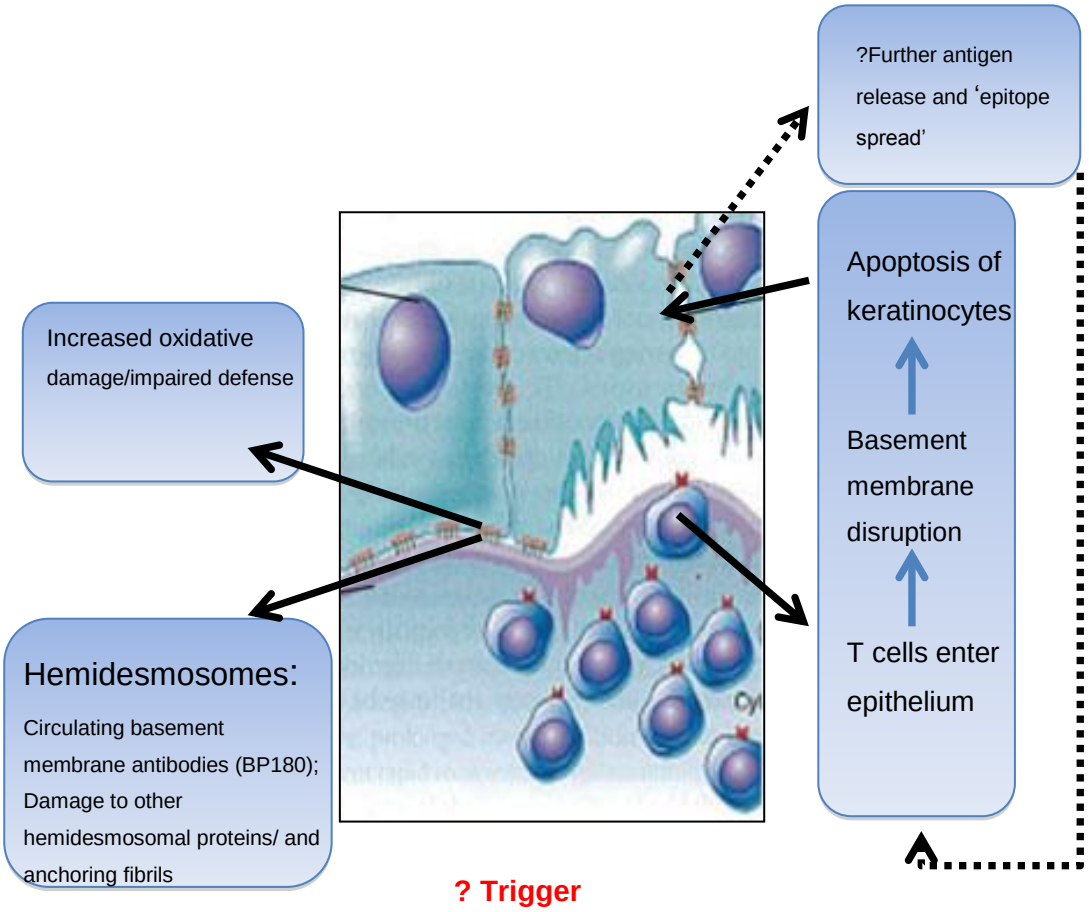

Figure 7: Schematic representation of the proposed pathogenesis of erosive lichen planus.

The image shows how in response to oxidative damage, subsequent T-cell mediated damage results in disruption of the basement membrane.

1.3.3 Aetiological factors in the pathogenesis of erosive lichen planus affecting the vulva

1.3.3.1 Autoimmunity and its association with erosive lichen planus affecting the vulva

Current thinking is that autoimmune mechanisms cause the pathological changes in patients with lichen planus affecting mucosal surfaces and that the disease is itself an autoimmune condition (Cooper 2008, Rook 2010). This is evidenced by studies that demonstrate an increased prevalence of other autoimmune disorders in patients with vulval erosive lichen planus. In these individuals, circulating autoantibodies targeted towards specific BMZ proteins were identified. Furthermore, *oral ELP* has been described in patients with autoimmune blistering conditions, suggesting occurrence of blisters and lichen planus may reflect an extension of the immune response to shared antigens (Shipman 2009).

Cooper et al (Cooper 2005), in a study of 56 cases of ELPV found 61% to have weakly circulating IgG BMZ antibodies. Of the 11 samples in this study sent for immunoblotting, the BMZ antibodies were found to be predominantly of the BP 180 subtype (8/11). This particular antibody is found in the autoimmune blistering skin condition, bullous pemphigiod. There were no major differences in clinical characteristics between those with positive and those with negative BMZ antibodies. It was concluded that the study probably

provides evidence for an autoimmune process in ELPV, although the detection of these BMZ autoantibodies are more likely a marker for disease rather than being directly pathogenic. The same group (Cooper 2002), in a study of 37 patients with ELP found that the presence of BMZ does not confer adverse prognosis, particularly in terms of disease severity and the presence of scarring.

T cells reactive to the NC16A domain of BP180 were found 2/5 patients with vulval LP compared with 0/10 controls in a study by Baldo in 2010 (Baldo 2010). This was a small study that predominantly investigated patients with *lichen sclerosus* rather than LP. It was not specified whether the patients had erosive LP, or other subtypes, and diagnostic criteria for inclusion were not specifically stated. Terlou et al (Terlou 2012) subsequently demonstrated that a high level of pro-inflammatory cytokines in LP result in a dense T cell infiltrate in a study involving nine vulval LP patients. Although patient numbers were small in both Baldo and Terlou's studies, both implicated antigen specific T cells in vulval LP and therefore suggest that treatment of ELPV should be aimed at immunosuppression.

A subsequent cohort study of 126 patients with ELPV (Cooper 2008) found 29% to have one or more alternative autoimmune disease, compared with 9% in the control group ($p<0.001$). Thyroid disease was most prevalent (15% vs 8%; $P<0.001$), followed by alopecia areata (4% vs 0.1%; $P<0.001$), and coeliac disease (2% vs 0.2%;

P=0.01). 31% ELPV cases had positive family history of one or more autoimmune diseases in a first-degree relative. 41% of ELPV cases had positive autoantibodies compared with 20% of controls (p=0.002). The authors concluded that the results were highly suggestive that ELP is associated with autoimmune disease and therefore has an autoimmune basis. However, one aspect that was not clear from this study is how well matched the control and case groups were with regards to ethnicity and this may be relevant as certain ethnic groups experience a higher prevalence of autoimmune conditions. Setterfield et al (Setterfield 2006) demonstrated similar findings in a case series of 40 patients. In this study, 32.5% of patients suffering from ELPV, as part of the vulvovaginal syndrome, were found to have a first degree relative affected with autoimmune disease and 30% had a personal history of autoimmune disease. Ebrahimi et al (Ebrahimi 2012) noted 10% of 120 patients with mucosal LP had thyroid autoantibodies compared with 6% of 83 controls. P values for this were not given.

1.3.3.2 Genetic contribution to the pathogenesis of erosive lichen planus affecting the vulva

Setterfield (Setterfield 2006) found patients with the vulvovaginal syndrome to be more likely to possess the HLA DQB1*0201 gene than controls (80% versus 41.8%). This particular gene allele has been linked to autoimmune disorders, such as thyroid and coeliac disease. From this paper it is not clear though whether there is a

pathogenic link between this particular HLA or whether its presence is a confounding factor due to the increased presence of autoimmune conditions in the patient cohort.

Several familial cases have been reported in *oral* LP (Bermejo-Fenoll 2006), which further adds weight to the role of genetic background in all subsets of mucosal LP.

1.3.3.3 Association of triggers with erosive lichen planus affecting the vulva

Most cases of LP are idiopathic, although some are thought to be drug-induced and infections have been implicated in others (Sawardekar 2011). Triggers for *reticulate* LP may be different to those of *erosive* LP.

1.3.3.4 Infective triggers

A link between liver disease, in particular infection with the hepatitis C virus has been suggested with lichen planus in general, however, studies that have demonstrated this were performed by groups from countries where there is a higher prevalence of such infections (Sanchez-Perez 1996, Mignogna 1998, Nagao 2008). Reports from UK-based populations have found no link to oral (Ingafou 1998), cutaneous (Tucker 1999) or vulval (Cooper 2004) LP. It has been suggested that although routine serological screening for hepatitis C in all patients with LP would not be cost effective, patients should at

least be asked about any major or minor risk factors (Bigby 2009). If any do exist, then serological testing can then be performed.

Some authors have putatively suggested a link with herpes simplex virus infection (Ebrahimi 2012). There was a statistically significant difference in antibodies against herpes simplex virus in mucosal LP cases compared with control (60% v 44%, $p<0.03$). Furthermore, patients with significantly higher titres had more oral symptoms than the other patients. These figures were from a retrospective case series of patients and further work is required to confirm or refute this potential association.

1.3.3.5 Association of lichen planus with specific medications

Systemic medications have been associated with lichenoid skin and mucosal changes (Rook 2010). One study found increased use of beta-blockers and non-steroidal anti-inflammatory agents amongst patients with mucosal LP (Clayton 2010) and suggested withdrawal of these drugs in such patients. However, this was a retrospective, questionnaire based study with high risk of recall bias and little theoretical explanation for how these drugs could cause mucosal ulceration. However, most of these medications have been found to induce *reticulate* rather than *erosive* LP.

Antimalarial drugs, other antihypertensive agents, oral hypoglycaemic agents and antiretroviral agents have also been reported to cause oral lichenoid eruptions (Ismail 2007).

1.3.3.6 Other factors influencing disease presentation

Exacerbations of LP affecting mucosal sites have been linked with periods of psychological stress by some studies. Tobacco chewing and dental materials such amalgam, metals and composite restorations have been associated with oral, but not vulval LP (Ismail 2007).

1.4 Exacerbating factors in erosive lichen planus of the vulva

1.4.1 Oestrogen deficiency

Vulvovaginal atrophy resulting from oestrogen deficiency in postmenopausal females is a common condition. Symptoms include dryness, irritation, dyspareunia along with urinary frequency, urgency and urge incontinence (Mac Bride 2010). The prevalence of vulvovaginal atrophy symptoms is most common in postmenopausal females with estimates of prevalence ranging from 4-47% (Mac Bride 2010). Given that the peak incidence of ELPV is in this age group (Mann 1991, Eisen 1994, Cooper 2006), it may be difficult to untangle the symptoms of vulvovaginal atrophy from those of ELPV. Physicians treating ELPV should be mindful of this fact, especially if ELPV is resistant to first-line therapy as vulvovaginal atrophy may be an exacerbating factor.

1.4.2 Irritation from urine and faeces

Irritation (contact irritant dermatitis) secondary to urine and faeces is a common cause of vulval symptoms and may worsen the effects of a pre-existing vulval skin condition. As the barrier function of the skin is impaired in inflammatory conditions, there is greater susceptibility to irritant contact dermatitis. History taking for a genital skin complaint should specifically include enquiring about incontinence of urine or faeces as patients will not usually volunteer this information (Lawton 2006). Conversely, patients with ELPV may actually present with symptoms of dysuria due to the effects of urine burning eroded vulval skin. This in itself may lead to secondary incontinence.

Any patient with a vulval skin disease should have symptoms of urinary or faecal incontinence addressed as improving these is likely to improve their overall condition.

1.4.3 Contact irritants

Contact with irritants in topical agents, particularly cleansing products such as bubble bath, soaps, wet-wipes and medicaments may all cause an irritant dermatitis (Bunker 2010). Patients with vulval skin conditions are more likely to use such products frequently in an attempt to cleanse the area as they perceive this to be helpful. Unfortunately, the consequence of this is often the opposite and worsening of the skin condition may occur.

1.4.4 Allergic contact dermatitis

Allergic contact dermatitis of the vulval area is much less common than irritant dermatitis, however, allergy to topical medicaments may occur (Lewis 1997) and patch testing is important if signs of this are present in surrounding skin.

1.4.5 Stress

Stress is anecdotally felt to worsen inflammatory skin conditions and studies have shown a positive correlation with stressful events in cutaneous LP (Manolache 2008) compared with controls. Furthermore, it is felt that stress may contribute to the initiation and propagation of oral LP (Ivanovski 2005). Given these findings and through anecdotal evidence (personal communication) it is possible that ELPV is linked with stress in some way.

1.5 Clinical subtypes of vulval lichen planus

There are three distinct clinical patterns of lichen planus affecting the vulval area and more than one variant may be present in any given patient (Moyal-Barracco 2004).

The most common form of LP affecting the vulva is the *erosive* type, vulval erosive lichen planus (ELPV). In ELPV, well demarcated erythematous lesions are present (Figure 8, page 34). These inflammatory areas often ulcerate, although erosions are not always present (Kirtschig 2005). The reticulate pattern (white reticulate

lines with a lacy appearance), may be present in conjunction with erosions. The vulvo-vaginal gingival syndrome (VVG) is a severe variant of ELP encompassing erosions of the vulva, vagina and gingiva. This variant was first described in 1982 (Pelisse 1989).

Classical LP, which is the variant usually seen affecting the skin (as described in section 1.1) may be seen solely affecting the vulva. In this situation, presenting features are those of small, intensely itchy violaceous papules located on the external genital skin, which can be seen in Figure 9, page 34. Wickham's striae are often seen overlying these lesions (Goldstein 2005).

The final variant of LP affecting the vulva is *hypertrophic* LP which consists of hyperkeratotic areas with a thickened, irregular surface. This is similar to hypertrophic LP affecting the skin (see section 1.2.2, page 13).

Of these three subtypes, it is ELPV, particularly the VVG syndrome which are typically difficult to treat (Moyal-Barracco 2004) and although improvement in the condition is sometimes seen, cure is not possible and complete control rarely occurs. Vulval erosive lichen planus appears to cause the most suffering in the clinical setting.

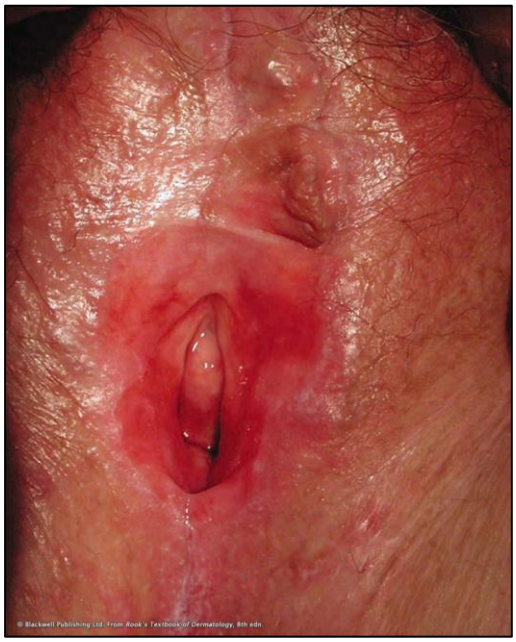

Figure 8: Erosive lichen planus affecting the vulva.

There is an erythematous area with a slightly hyperkeratotic border at the entrance to the vagina. The lesion is surrounded by lacy white lines, particularly in the perineal area. Image taken from Rook's Textbook of Dermatology, 8th Edition.

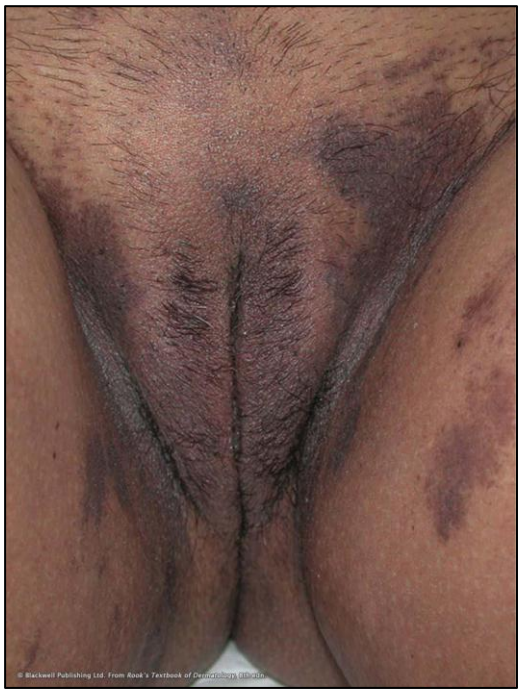

Figure 9: Classical lichen planus affecting the external genitalia.

There are well demarcated areas of inflammation and post inflammatory hyperpigmentation affecting external genital skin. Taken from Rook's Textbook of Dermatology, 8th Edition.

1.5.1 Erosive lichen planus affecting other mucosal sites

Erosive lichen planus is a *multisystem* disease (Figure 6, page 18). Until 1999, there had been few reports documenting the concomitant involvement of other sites in addition to the oral or genital mucosa (Eisen 1999). Eisen et al evaluated a case series of 584 patients with *oral* LP for extra-oral involvement. They found involvement of the skin (16%), genitals (19% of 399 women who underwent genital examination), nails (2%), scalp (lichen planopilaris, 1%), oesophagus (1%) and conjunctiva (0.02%).

Subsequent cohort studies involving women with ELPV have reported a varying prevalence of LP affecting other skin/mucosal sites. The oral mucosa and skin are most commonly associated with LP. The scalp may demonstrate a scarring alopecia. The oesophagus, outer ear and lacrimal duct are rarer sites of involvement. However, it is believed that the prevalence of oesophageal disease has been underestimated as patients are infrequently asked about symptoms such as dysphagia, or it may be asymptomatic (Fox 2011). Dickens et al (Dickens 1990) demonstrated that oesophageal LP was present in 5 of 19 patients presenting to a dermatology department with cutaneous LP. Four of the five patients had concomitant oral disease.

Furthermore, it is not just the vulvovaginal mucosa that undergoes a scarring process. The result of chronic inflammation elsewhere can

lead to detrimental effects such as oesophageal strictures and lacrimal duct scarring (Webber 2012), which may be bilateral (Durrani 2008).

1.5.2 Differential diagnosis of erosive lichen planus affecting the vulva

Erosive lichen planus affecting the vulva may be difficult to diagnose. Conditions which may present in a similar manner include vulval squamous cell cancer as seen in Figure 10 (page 37), vulval intraepithelial neoplasia, as seen in Figure 11 (page 38) and autoimmune bullous disease (e.g. bullous pemphigoid, pemphigus vulgaris) as seen in Figure 12 (page 39). These conditions require a different management approach to ELPV. In the case of squamous cell carcinoma and vulval intraepithelial neoplasia, there is a high chance that standard ELPV treatment will progress the neoplasia. It is therefore important to use accurate clinical and histopathological information to ensure the correct diagnosis is made.

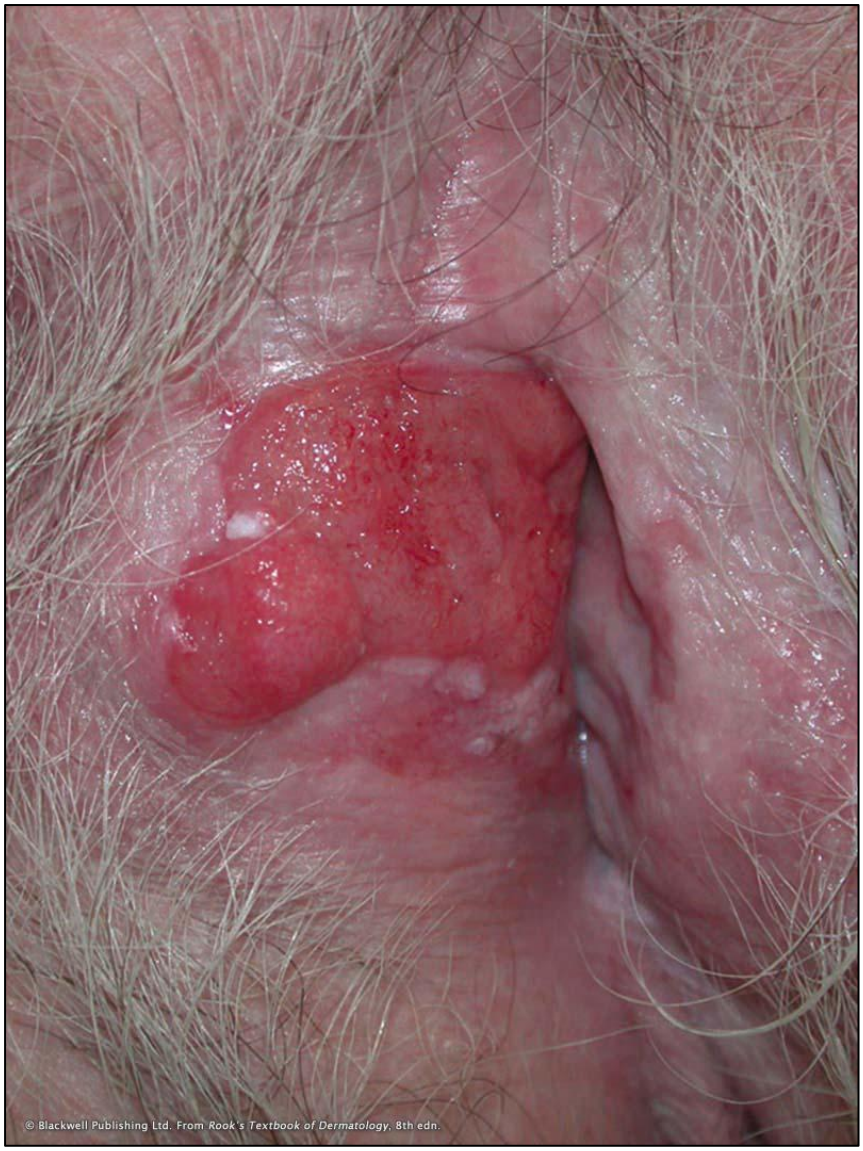

Figure 10: Squamous cell carcinoma on the right labia minora

The malignancy has developed secondary to pre-existing lichen sclerosus. The image demonstrates erythematous ulceration with granular morphology which is suggestive of malignant or pre-malignant change. Image taken from Rooks textbook of Dermatology 8th Edition.

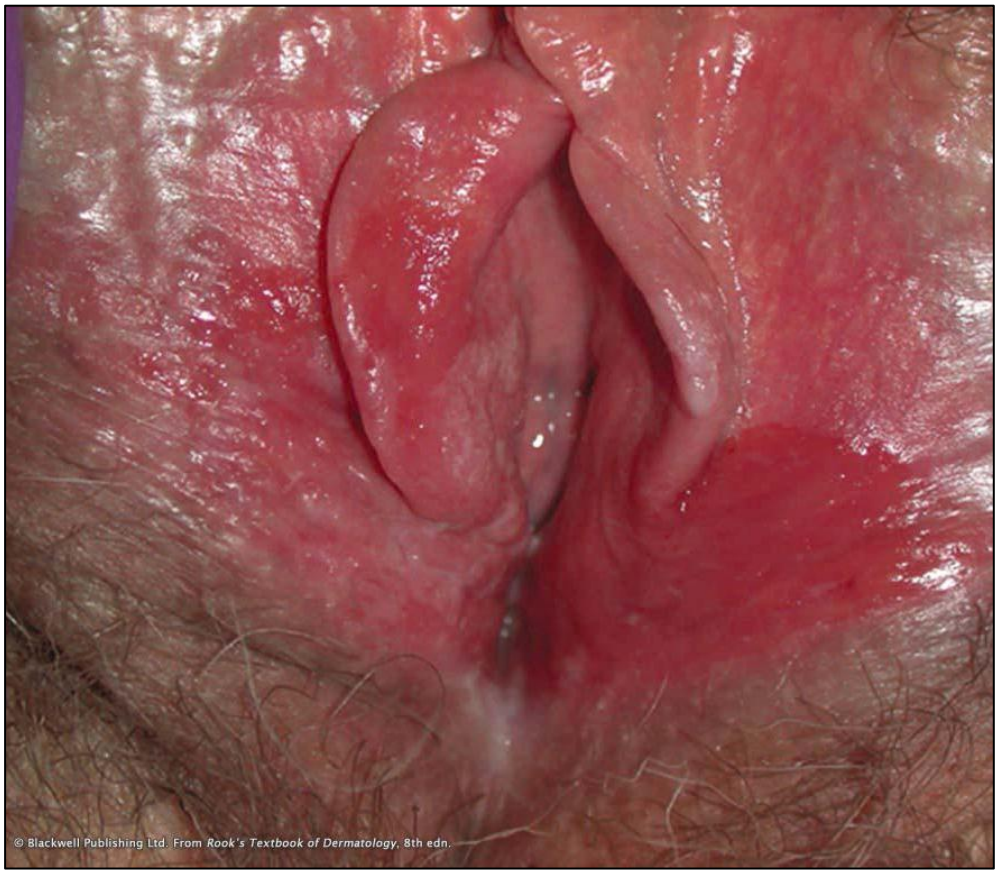

Figure 11: Vulval Intraepithelial Neoplasia.

In this image the disease is presenting as a unilateral eroded plaque on the left labia majora. Erosive lichen planus would most likely be bilateral in its appearance. Image taken from Rooks textbook of Dermatology 8th Edition

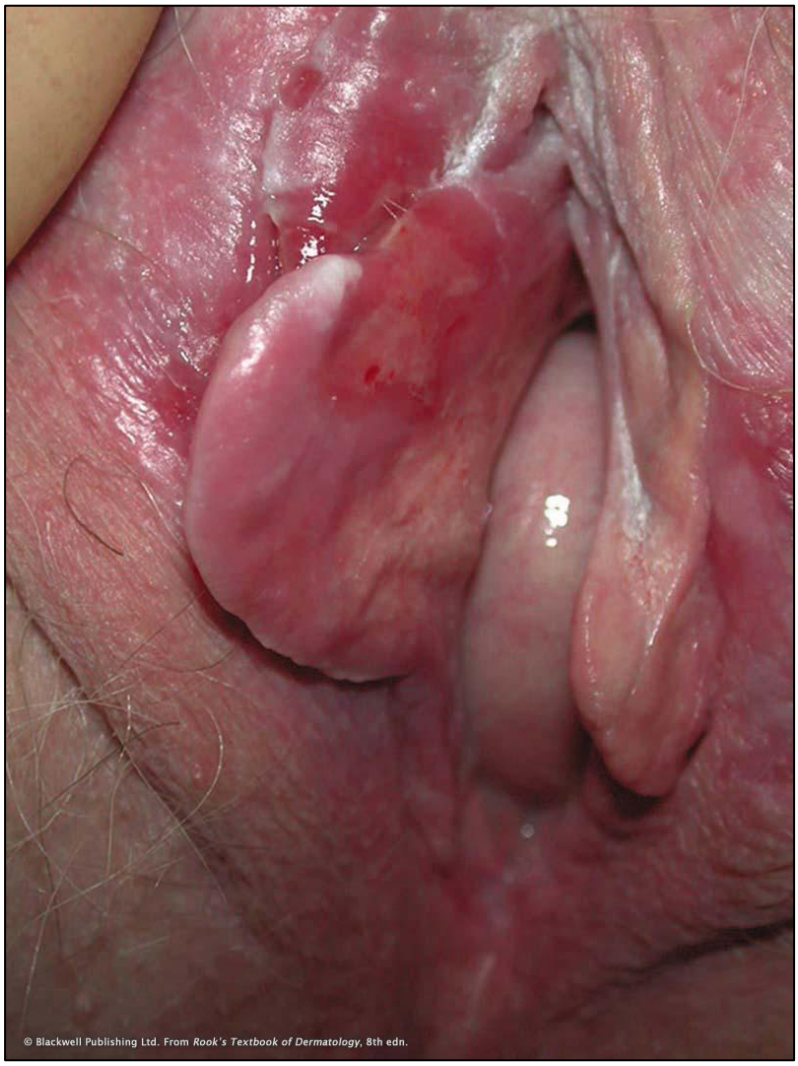

Figure 12: Mucous membrane pemphigoid affecting the vulva.

There is a well demarcated, annular erosion on the right labia minora with a slightly hyperkeratotic border. Erosive lichen planus would most likely be bilateral and symmetrical in its appearance, although more extensive mucous membrane pemphigoid may be difficult to distinguish clinically. Image taken from Rooks textbook of Dermatology 8th Edition

1.5.2.1 Conditions which co-exist with vulval lichen planus

Erosive lichen planus may also overlap with other vulval skin disorders. Clinicians need to be aware of these as choice of therapy, follow up and prognosis may vary depending upon the overlap diagnosis.

1.5.2.1.1 Lichen sclerosus

Lichen sclerosus (LS) was previously considered the same entity as vulval LP, however, clinicians now recognise these as separate diseases. Both LS and LP may co-exist in a single patient (Marren 1994), however, personal communication with experts suggests this is a rare occurrence. LS is believed to be an autoimmune condition driven by T lymphocyte activity. Histological features differ from LP as there is atrophy (rather than thickening) of the epidermis and sclerotic changes occur in the papillary dermis. Patients with an overlap LS/LP diagnosis are more likely to respond poorly to treatment than if they have pure LS (Marren 1994).

1.5.2.1.2 Plasma cell vulvitis

Plasma cell vulvitis is a condition which causes erythematous/orange glazed lesions in the vulval introital area. It is usually asymptomatic. Histological features consist of a thinned epidermis and a plasma cell rich infiltrate in the dermis in association with dilated blood vessels. There is controversy as to whether plasma cell vulvitis is a

distinct clinical entity (Scurry 1993). There has been separation into primary plasma cell vulvitis (probably related to vulvovaginal atrophy due to lack of oestrogen) or plasma cell vulvitis that is secondary in nature (Wendling 2011). Cases that are secondary usually have an unrecognised inflammatory skin condition such as LP or LS present.

1.5.2.1.3 Desquamitive inflammatory vaginitis

Desquamitive inflammatory vaginitis is another presentation of vulvovaginal disease that is a result of an underlying inflammatory process, most commonly ELP. Desquamitive inflammatory vaginitis is not in itself a condition, but a symptom/clinical presentation that consists of discomfort, irritation, painful intercourse and copious vaginal discharge (Murphy 2004). Vulval examination is often normal, except for the presence of vaginal discharge, and vaginal examination with a speculum is necessary to elicit clinical signs. ELP, pemphigus vulgaris and mucous membrane pemphigoid may all cause this presentation. There is controversy whether an idiopathic subset exits, with some authors believing that cases without an obvious diagnosis are all due to underlying vaginal ELP (Edwards 1992).

1.5.2.1.4 Vulval pain

Vulval pain, particularly provoked pain (e.g. during sexual intercourse) may occur as a result of the inflammation in ELP and is

discussed in section 1.8.2. This is another way in which ELP may present rather than with more typical presenting features that are described in section 1.5.

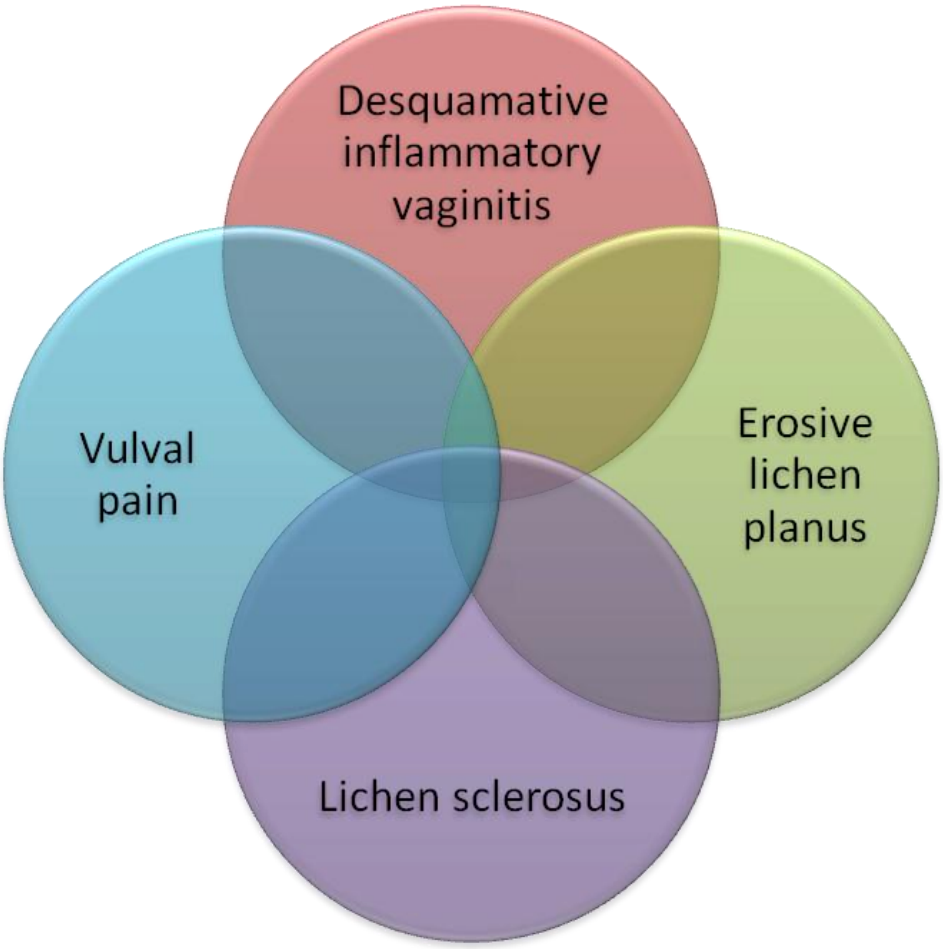

Figure 13: Relationship of vulval erosive lichen planus with other vulval conditions

1.6 The management of vulval skin disease in the UK

In this section the current UK pathways for managing patients with vulval skin diseases are explained.

1.6.1 Infrastructure of services for patients with vulval skin disease

Symptoms and signs of vulval skin disorders are common. Data regarding the incidence and prevalence of these conditions are not available in the literature, however U.S based community surveys suggest that one-fifth of women have significant vulval symptoms that last for longer than 3 months (Harlow 2001). In the UK, women will usually present first to their general practitioners but may subsequently be referred to a range of health care services including, dermatology, gynaecology or genitourinary medicine. There is no common pathway for GPs to follow in terms of referral and so the specialist to whom they refer will depend upon the GPs assessment of the problem. Common causes for referral to secondary care are dermatitis, lichen simplex, candidiasis, lichen sclerosus and lichen planus (RCOG 2011).

An estimated 80 specialist vulval clinics are present in the UK. The configuration of these is mixed, with approximately one third being single discipline and two thirds multi discipline. However, little more

is known about the structure and running of these clinics, including the quality of care offered (Nunns 2012).

Given the sensitive nature of the subject matter, it is preferable for women to be managed by a dedicated vulval service or a vulval clinic rather than a general outpatient clinic. Vulval clinics, although not always multidisciplinary, are usually set up to allow more time per appointment than a general outpatient appointment. This enables a detailed history and examination to be taken in a non-rushed environment and helps the patient to feel more comfortable discussing her sensitive condition with the clinician.

A 'vulval service' is defined as an multidisciplinary team of health professionals interested in vulval disorders across different specialties (Nunns 2012) . In addition to the previously mentioned medical specialties, the MDT may include specialist nurses, physiotherapists and sexual therapists. Many consider such services to be the gold standard way of managing patients with vulval skin disease. The model provides the patient rapid access to relevant specialists and the joint expertise provided is important for effective management of those with complex conditions.

Both the Royal College of Obstetrics and Gynaecology (RCOG 2011) and the British Association for Sexual Health and HIV (HIV. 2007) have published individual guidelines for the for the management of vulval skin conditions, however, guidelines and standards of care for

vulval services have not been addressed until recently (Nunns 2012).

1.6.2 Teaching of vulval skin disorders

Teaching and training opportunities for practitioners with an interest in vulval disorders have historically been suboptimal, as evidenced by a survey of the British and International Societies for the Study of Vulval Disease (see section 1.7.1, page 47) (Murphy 2007). In this survey 37/107 (29%) respondents had been self-taught in the specialty. The curriculum for dermatology trainees now includes compulsory modules for training in vulval disease. Gynaecology and Genitourinary medicine trainees have the opportunity to take up a specialist interest in vulval skin disorders and may complete a specialist rotation in this field. It is therefore hoped that knowledge and competence in managing vulval skin disorders will improve considerably amongst these specialties.

1.7 Professional societies dedicated to the care of women with vulval skin conditions

There are national and international professional societies dedicated to the care of women with vulval skin conditions. Vulval medicine is a relatively new branch of medicine and has traditionally been practiced by multiple specialties. It is important that there is

collaboration between these groups to enable physicians to share expertise, which will ultimately improve knowledge and patient care.

1.7.1 The International Society for the Study of Vulvovaginal Disease

The International Society for the Study of Vulvovaginal Disease (ISSVD) was founded in 1970 with the goal:

> "To promote international communication among gynecologists, pathologists, dermatologists, and related disciplines and to establish international agreement on terminology and definitions of vulvovaginal diseases."

The ISSVD has 280 members from different specialist areas including Dermatology, Gynaecology, Genitourinary Medicine, Histopathology and Sexual Health. Of note, terminology is slightly different in the United States where 'vulvar disease' is used compared with 'vulval disease' Europe.

1.7.2 The British Society for the Study of Vulval Disease

The British Society for the Study of Vulval Disease (BSSVD) was founded in the 1990s and currently has over 160 members. It comprises a similar mix of specialist groups to the ISSVD.

In addition, to aiding communication between specialties, the BSSVD and ISSVD promote research (basic and clinical) and

dissemination of knowledge in the field of vulval skin disorders. The Societies attain these goals through regular meetings, publications and communication with their members. Furthermore, patient information leaflets are freely available in the public domain from the Societies' websites and they provide links with patient support groups.

1.7.3 Support groups for patients with vulval skin disorders

There are many support groups that have been set up to support patients with skin diseases. They are often run by volunteers who suffer from the disease themselves, and many patients find it valuable to have such contact with others both for support and for practical help ("British Association of Dermatologists website section on patient information" 2012). Such groups often support research efforts and are an effective way for researchers to engage with the patient community, promote ongoing research projects and disseminate findings.

1.7.3.1 The UK Lichen Planus Society

UK Lichen Planus (UKLP) ("UK Lichen Planus (UKLP) Society website" 2012) is a support group that was set up in 2007 to help people who live with LP. UKLP is run by those living with LP for those living with LP, and helps patients to cope with the diagnosis, as well as offering practical tips and ideas on how to manage their condition. The support group is available for people with all subtypes

of LP. It has a number of patrons, who are practicing clinicians and experts in this field, who approve information which is posted on the UKLP website. In addition to electronic patient information, the group holds a regular workshop with guest speakers to encourage networking and communication between members.

1.7.4 Information available to patients diagnosed with vulval erosive lichen planus

Information is an important part of the patient journey and is paramount to improving most patients' experience of their management. Good information enables people to be involved in their conditions and its treatment, especially as it reinforces information given in the clinical setting and provides them with the power to make informed decisions about their healthcare, should they wish. A high quality patient information leaflet written in clear and simple language will help to ensure that standard of care is as high as possible in a health care setting.

Unfortunately, for ELPV, relevant patient information is not easy to locate. Most information identified was web-based only which is only relevant if the patient population in question has a confident grasp of internet use. This includes information by the UK Lichen Planus Society, the BSSVD and the British Association of Dermatologists (BAD). Many patients with ELPV are from an older generation, many of whom do not have computers or the internet at home. According

to 'Ofcom', compared to the general adult population, adults aged 60 and over are less likely to live in households with the internet and are less likely to regularly use newer media devices such as mobile phones (Ofcom 2009).

The ISSVD have produced a comprehensive patient information leaflet about vulval lichen planus ("Vulval Lichen Planus" 2010) (Appendix 1), however, other relevant societies have scarce information available in the public domain. Indeed, many sources only describe ELPV in brief within information about lichen planus in general. This is insufficient for patient needs given the severity and nature of the condition.

Relevant, up to date patient information sources appear to be an area that needs improving as a matter of urgency in this field.

1.8 Managing erosive lichen planus: How the diagnosis of erosive lichen planus affecting the vulva is made

1.8.1 History

The diagnosis of ELPV is primarily clinical with the appropriate histological confirmation (Ball 1998). The symptoms described by the patient vary according to clinical subtype of disease. The predominant symptoms described by females with ELPV are soreness and burning (Eisen 1999, Micheletti 2000, Anderson 2002,

Cooper 2006, Kennedy 2007, Santegoets 2010) with associated dyspareunia (Micheletti 2000, Anderson 2002, Cooper 2008, Helgesen 2010). Itch and irritation occur less frequently. Post coital bleeding, difficulty in urination and vaginal discharge are variably present (McPherson 2010). It is possible that ELPV may present with isolated vulval splitting. In a case series of nine patients presenting to a specialist vulval clinic with vulval splitting, eight were found to have features of LP on biopsy (Wong 2004). Although this is not the usual presentation of the disease, it should certainly be considered in new patients presenting to the outpatient clinic.

In contrast, reticulate vulval LP may be asymptomatic (Lewis 1996, Eisen 1999, Micheletti 2000, Belfiore 2006), or mildly pruritic, although this subset occurs less frequently than erosive vulval disease.

Patients may have symptoms for many years before presenting to medical services (Helgesen 2010) and may not link genital symptoms to a diagnosis of LP elsewhere (e.g. on the skin or mouth as depicted in Figure 6, page 18).

1.8.2 Diagnostic Data Set for erosive lichen planus affecting the vulva

Early recognition of vulvovaginal lichen planus is important to minimise unnecessary medical or surgical procedures and to instigate prompt treatment and alleviation of symptoms (Pelisse

1989, Eisen 1999). However, the clinical diagnosis of ELPV can be challenging as it may mimic other conditions such as lichen sclerosus (also overlapping histpoathologically (Marren 1994, Niamh 2009, McPherson 2010)), autoimmune bullous disorders and intraepithelial carcinoma (McPherson 2010). As LP is not a common disease for non-dermatologists, e.g. gynaecologists, to recognise and treat (Belfiore 2006), a set of criteria for physicians to follow in making the diagnosis is important.

Oral lichen planus has a set of diagnostic criteria which was published by the World Health Organisation in 1978 (Kramer 1978) and subsequently modified in 2003 (van der Meij 2002). However, the equivalent does not exist for ELPV.

In 2007 the ISSVD developed new nomenclature for vulval dermatoses (Lynch 2007) and placed vulval LP under the pathologic subset of dermatoses with a 'lichenoid pattern'. However, they did not expand its classification in any further detail than this.

Following a review of the literature for studies involving case series of patients with ELPV, the clinical and pathological features of ELPV used in these reports have been summarised in the following sections.

1.8.2.1 Clinical features of vulval erosive lichen planus

The clinical features of ELPV, as documented by previous studies of the condition are summarised in Table 2 on page 57.

As its name suggests, erosive lichen planus typically shows well demarcated erythematous areas or erosions as seen in Figure 14 (p55). These are usually located at the entrance to the vagina (the 'vaginal introitus'). Erosions, when seen are actually secondary to intense inflammation and it is therefore considered by some that the term 'erosive LP' is inaccurate (Kirtschig 2005). Hyperkeratosis is often present (Pelisse 1989, Santegoets 2010) and the erosions are usually edged by a hyperkeratotic white border as seen in Figure 14 (p55). Features of classical lichen planus, such as Wickham's striae may also be present (Eisen 1994, Santegoets 2010). Biopsy from the edge or areas containing Wickham's striae is most likely to yield classical pathological features of LP (as described in section 1.1.1, page 9).

Vaginal manifestations of ELP include appearances of a diffuse erosive vaginitis (Edwards 1989, Pelisse 1989, Eisen 1994) which may, or may not be superimposed on a white reticular network (Pelisse 1989). Patients may present with symptoms of desquamative inflammatory vaginitis (described in section 1.5.2, page 41). In one case series (Helgesen 2010) where vaginal examination was performed in 58 patients with vulval signs of LP,

involvement of the upper vagina was found in over two thirds. Vaginal examination, however, is often difficult to perform due to adhesions, pain and bleeding on insertion of the speculum (Pelisse 1989). Examination may need to be performed under general anaesthesia (Helgesen 2010).

A significant complication of the inflammation caused by ELP is scarring (Figure 15, p55), which manifests as loss of normal architecture through the formation of adhesions, also known as 'synechiae'. Narrowing of the vaginal introitus (Pelisse 1989, Santegoets 2010), vulval adhesions (Pelisse 1989) and loss of the labia minora (Pelisse 1989) are frequently described anatomical changes caused by the disease and are demonstrated in Figure 15, page 55.

Scarring is present to some extent in most patients with ELPV. Cooper et al reported 95% of 114 patients to have scarring, 73% were graded moderate or severe. Scarring is often present at the time of diagnosis. It is believed that prompt recognition of the condition with appropriate treatment can prevent this complication (Eisen 1999).

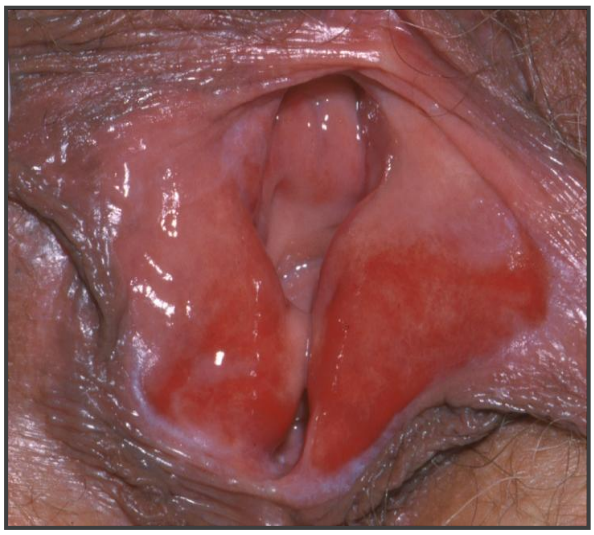

Figure 14: Well demarcated vaginal introital erosions in vulval erosive lichen planus

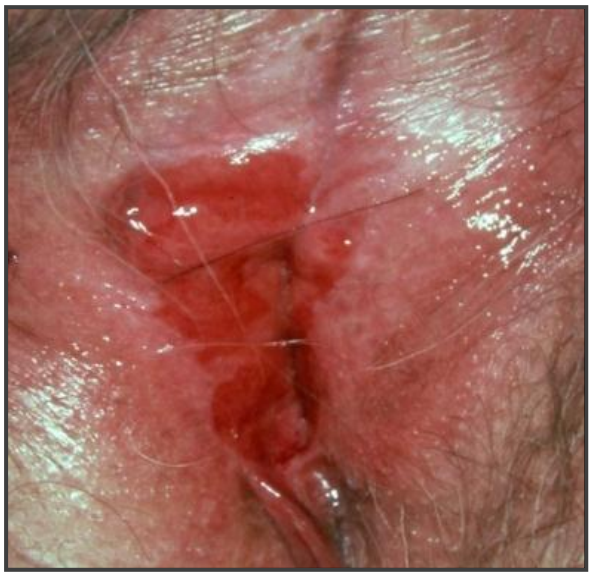

Figure 15: Advanced vulval erosive lichen planus with scarring

There is destruction of the normal vulval anatomy. Compared with Figure 14, there is loss of the labia minora, clitoral burying and vaginal introital narrowing. Images courtesy of Dr Ruth Murphy

Author	Clinical Features (% of participants with feature)					
	Erythematous erosions/areas	**Hyperkeratosis**	**Wickham's Striae**	**Lesions located at vaginal introitus**	**Erosive vaginitis**	**Scarring**
Pelisse 1989	94.7%	Present in 'most cases' (figures not given)	Not commented	Not commented	Present but numbers not given	'Vulval architectural change' in 31.5% 'Several' cases unable to pass speculum
Eisen 1994	62.5%	Not commented	37.5%	Not commented	31%	Present in 31%
Lewis 1996	Not commented	Not commented	Not commented	Not commented	Not commented	Not commented
Anderson 2000	Erythema 97.7% Erosions 65.1%	Not commented	Not commented	Not commented	81.4% vaginal lesions	37.2% vaginal stenosis
Mitcheletti 2000	Erosive 17.6%	'White' 66.4% 'White-erosive' 16%	Not commented	Not commented	Not commented	Not commented
Kirschig 2005	100%	Not commented	Not commented	100%	Not commented	Vaginal fusion in 45% patients but not clear how many had gynaecological examination.
Cooper 2006	97%	22%	82% reticulation	Not commented	Not commented	95%
Kennedy 2007	Inclusion criteria not stated					
Kennedy 2008	Not commented	Not commented	Presence on mucous membranes	Not commented	Not commented	Not commented

Cooper 2008	Erosion 74% Erythema 66%	Not commented	56%	Not commented	34% discharge	63%
Santegoets 2010	81.1%	14.7%	35.8%	69.5%	Not commented	Vaginal narrowing in 16.8%
Helgesen 2010	Erythema 100% Erosions 81%	Not commented	Not commented	74% lower vagina	67% lesions upper vagina	Vulval scarring 36% Vaginal scarring 50% Vaginal obliteration 15.5%
Fischer 2013	Not commented	Not commented	7.6%	90.1%	38.2%	Labial fusion in 42%

Table 2: Summary of clinical features adopted for the diagnosis of ELPV used by published case series in the literature.

N.B. These case series were identified through a systematic review of the literature. All studies that explained how they made the diagnosis were included in this table.

1.8.2.2 Pathological features of vulval erosive lichen planus

The histopathological features of ELPV, as documented by previous studies of the condition are summarised in (Table 3, page 63).

Many case series reporting patients with ELPV have *not* documented the specific histopathological features which they sought to make the diagnosis (Lewis 1996, Micheletti 2000, Anderson 2002, Cooper 2006, Cooper 2008). In contrast to classical cutaneous LP which has characteristic histological findings (Figure 4 and Figure 5, page 11), the findings in ELPV are often inconclusive (Pelisse 1989, Ball 1998, Kirtschig 2005, Cooper 2006). Biopsy specimens are found to be most characteristic when taken from the white hyperkeratotic margin of erosions (Figure 16, Figure 17, page 62) (Pelisse 1989).

Assessment of vulval biopsies should be by a dermato- or gynae-pathologist. Changes of LP seen in specimens taken from ELPV are often subtle and there is a possibility of an incorrect diagnosis being made by pathologists who are inexperienced in this field (Bowen 2008).

In a study to investigate histopathological findings of 31 vulval biopsies (from patients with a range of different diagnoses), Leonard et al (Niamh 2009) found that 10 of the reviewed specimens were from patients with vulval LP. They found the most powerful predictor of LP to be the presence of an inflammatory band at the dermo-

epidermal junction (present in 9/10 specimens). They also stated that 'basal squamatisation' was a predictor of vulval LP, but did not explain what this term meant, nor did they provide data for the frequency of this feature in assessed specimens. Characteristic features of LP that are often seen on biopsies from non-vulval skin were seen *infrequently*; pointed rete ridges (2/10), wedge-shaped hypergranulosis (3/10), and civatte bodies (4/10). These features of classical LP have already been described and are demonstrated in Figure 4 and Figure 5 on page 11 (section 1.1.1, page 9).

Belfiore (Belfiore 2006) and DiFede (Di Fede 2006) adapted the pre-existing World Health Organisation criteria proposed in 2002 (van der Meij 2002) for the diagnosis of OLP, to extend to vulval LP. They looked for the presence of basal cell layer degeneration, a well-defined cellular infiltrate confined to the superficial connective tissue layer and the strong predominance of lymphocytes in the infiltrate. When all of these features were present, the case was categorised as 'histologically diagnostic of vulval LP', if only two features were present, a histological diagnosis of 'compatible with vulval LP' was made. All other cases were classed as 'non-consistent' with vulval LP. Immunohistochemical staining was subsequently performed on all 'diagnostic' and 'compatible' cases to look for a predominance of T-lymphocytes, which would confirm the diagnosis.

Kirtschig et al (Kirtschig 2005) in a retrospective study of 44 females with ELPV diagnosed clinically found that of 38 who were

biopsied from the edge of an erythematous area, 18 showed diagnostic features for LP, including wedge-shaped hypergranulosis, civatte bodies and band-like inflammation at the DEJ. A further 7 patients showed features consistent with ELPV (band-like inflammation at the DEJ only). The remainder of biopsies showed non-specific inflammation only.

Eisen (Eisen 1994) found 'characteristic changes of lichen planus' in all 100% vulvar biopsies taken from a series of patients with the vulvovaginal-gingival syndrome (n=6). 22 patients in the full series had undergone oral biopsy showing ELP.

Helgesen et al (Helgesen 2010) in a retrospective analysis of 58 females with genital ELP found that 14/ 49 biopsies were diagnostic and 21/49 were 'consistent' with lichen planus. 14/49 showed non-specific features, of which 4 were concluded to be plasma cell vulvitis (>50% infiltrate was plasma cells). They looked for specific features of lichen planus in the mucosal sites as in Kirtschig's study. These authors also performed direct immunofluorescence (IMF) on 22 samples and concluded 7/22 were consistent with lichen planus. The remaining 15/22 were non-specific. However, the authors did not stipulate which IMF features they were specifically looking for.

It is clear that that diagnosing ELPV is difficult and varying clinicopathological features may be present in any one case. Clinical and pathologic features need to be standardised to prevent the

misdiagnosis of ELPV and to ensure prompt management of the condition where possible. A way of ensuring this would be to reach a consensus opinion with expert physicians from the BSSVD and ISSVD. Usually a biopsy in this condition serves as much to exclude other pathologies such as vulval or vaginal intra epithelial neoplasia or pemphigus as the standard treatments for EVLP would not be appropriate for these conditions.

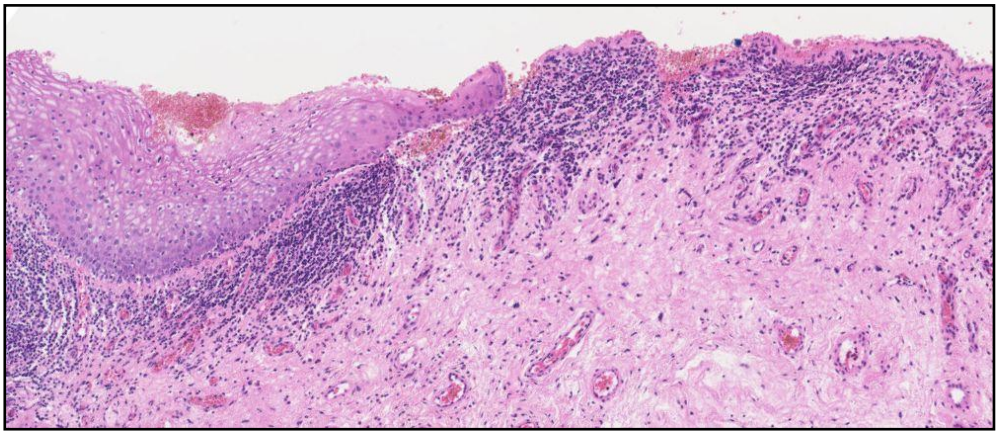

Figure 16: Low power histopathological image from erosive lichen planus affecting the vulva. Hematoxylin and Eosin stain x 5 magnification.

This biopsy specimen has been taken from from non-keratinined squamous epithelium. A lichenoid infiltrate is present in the superficial dermis and along the basement membrane. The epidermis is missing on the right hand side due to erosion. Courtesy of Dr S. Deen

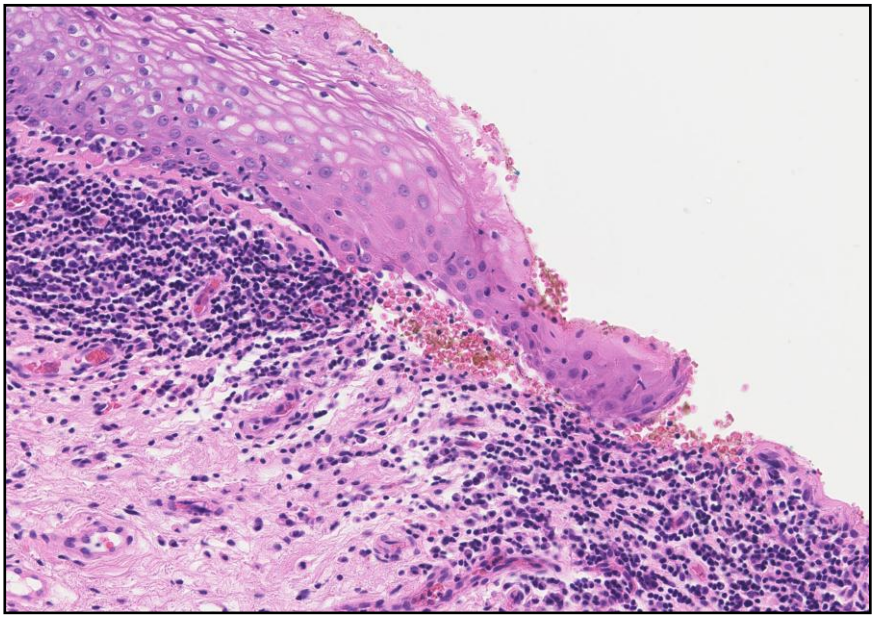

Figure 17: High power histopathological image from erosive lichen planus affecting the vulva. Hematoxylin and Eosin stain x 40 magnification.

This biopsy specimen has been taken from from non-keratinined squamous epithelium. The image demonstrates complete effacement of the basement membrane by lymphocytes, degeneration of the basal cell layer and the presence of civatte bodies. Courtesy of Dr S. Deen

Author	Number of patients in series (number of patients with biopsies taken)	Biopsies consistent with ELPV (%)	Other histopathological findings (n)
Eisen 1994	22 (6)	100%	-
Pelisse 1989	19 (16 patients had a total of 20 vulvar biopsies taken)	65%	Lichenoid features (2) Non-specific inflammation (5)
Kirschig 2005	44 (38)	65.7%	Non-specific chronic inflammation (13)
Belfiore 2006	32 (32)	75%	LS (5) Other dermatitis (3)
Cooper 2006	114 (97)	77% graded 'diagnostic' or 'probable' 14% 'possible' ELP	'Non-diagnostic' (7) although alternative diagnoses not given
Santegoets 2010	95 (93)	75.8%	Chronic non-specific inflammation (16) Lichen sclerosus (1) Uncertain (4)
Helgesen 2010	58 (49)	71.4%	8.1% plasma cell vulvitis (4) Non-specific (10)
Fischer 2013	131 (62)	21%	22.5% reported as 'lichenoid', although not specifically stated as being consistent with LP 3.2% full thickness vulval intraepithelial neoplasia

Table 3: Summary of histopathological features adopted for the diagnosis of ELPV used by published case series in the literature.
NB These case series were identified through a systematic review of the literature. All studies that explained how they made the diagnosis were included in this table.

1.9 Therapy for vulval erosive lichen planus

The management of erosive lichen planus affecting any surface is challenging and there is no clear agreement with respect to the best first-line management in oral or genital disease or indeed as to whether first-line therapy should be the same at both sites (Cheng 2012). The commonly *accepted* first-line therapy for ELP is super-potent topical corticosteroids, however, patients often respond poorly. There is no standardisation in second-line therapy and a variety of other topical agents (alternative topical corticosteroids, topical immunomodulators) or systemic immune suppressants (oral corticosteroids or steroid sparing agents) may be used. There is no clinical agreement on which therapy is optimum for patients who have failed super-potent topical corticosteroids.

Treatments for both oral and genital LP are similar and it is likely that effective treatment for ELP in the oral region would be beneficial in the genital region and vice versa, however, there is no evidence to demonstrate this (Cheng 2012).

A Cochrane Systematic Review of Interventions for ELP affecting mucosal sites (Cheng 2012) found *no RCT evidence* for the treatment of genital ELP. Fifteen RCTs met inclusion criteria and were included in the Cochrane review, but all of these studies involved patients with *oral* disease. These studies had a total of 473

patients with oral ELP, and found only *weak evidence* for the effects of topical treatments in this subset, including topical corticosteroids. The authors were not able to pool data due to heterogeneity in the interventions, design methods, and outcome variables used between studies. The two main recommendations were that more RCTs on a larger scale are required for the oral and genital ELP populations, and that standard outcome variables need to be used in such studies.

Subsequently, Davari et al (Davari 2012) in a conference abstract published in 2012, presented a systematic review and meta-analysis of treatments for LP (both cutaneous and mucosal subsets). Of 54 identified RCTs involving mucosal LP, only 1 was for vulval disease, the remainders were performed in patients with oral disease. Again, these authors commented upon the lack of clear and accurate measurements of disease outcome or severity. With their findings they were able to perform a meta-analysis which showed that the potent topical corticosteroids, betamethasone valerate and fluocinolone are more beneficial than placebo in *oral* ELP. However, as this is only a conference abstract, it is not been possible to assess the methods used for the search and meta-analysis.

In general, there is a dearth of evidence for the management of ELPV with the majority of studies being retrospective case series and case reports.

The results of a systematic review of the literature performed for this thesis that followed publication of the Cochrane systematic review identified two randomised controlled trials; these consisted of a poorly designed and poorly reported RCT comparing aloe vera gel against placebo (Rajar 2008), and a conference abstract describing the use of topical photodynamic treatment against high-potent steroid cream (Helgesen 2013). The literature search also identified two cohort studies (Lonsdale-Eccles 2005, Cooper 2006) that *prospectively* assessed treatments in ELPV.

A wide range of treatment strategies have been described for the management of ELPV and are summarised in tables 3-13 (pages 78-89). This summary has been formulated through a systematic literature review with databases last searched on 9th March 2014. In total, treatment of ELPV in 1126 patients (from a mixture of case reports, case series and two RCTs) have been described in the literature and are described below.

1.9.1 Topical treatments

1.9.1.1 Topical corticosteroids

The greatest evidence is available for the use of super-potent topical steroids (clobetasol propionate 0.05%) with the level of response being deemed as 'good' or 'partial' in a relatively high number of patients in published studies (Table 4, page 78). These were, however, case series, not RCTs. Cooper et al (Cooper 2006)

reported that of 89 women treated with superpotent topical steroids, 71% (63/89) became symptom free whilst on treatment. This response in general continued with longer-term maintenance therapy. Santegoets et al (Santegoets 2010) reported 64 women treated with clobetasol proprionate 0.05%, and suggest approximately 70% showed 'slight to moderate improvement'. The remainder showed no improvement at all. Outcome measures to assess the cases were not specified. In keeping with these studies, Maor et al (Maor 2013) report in a conference abstract documenting the results of a retrospective case note review found 72.5% of 80 women to have improvement following superpotent topical steroid use.

Potent topical corticosteroids (Table 4, page 78) in the form of suppositories or enemas may be used to treat vaginal disease. In a study of 60 women with vaginal ELP, hydrocortisone suppositories over a mean duration of treatment of 28.1 +/- 38.5 months, relieved symptoms but did not improve the complications of scarring or vaginal stenosis (Anderson 2002).

A variety of lower strengths of topical steroids have also been reported upon (Table 4, page 78), however, the number of patients assessed were small, reported response rates were mixed, and method of data collection was largely retrospective. Cooper et al (Cooper 2006) did find a good response to a combined moderate potency topical steroid/anti fungal/antibiotic preparation (Table 11,

page 86) with 13/14 patients treated with this showing good and 1/14 showing partial response. No other studies have commented upon this preparation.

1.9.1.2 Aloe vera gel

One RCT comparing aloe vera gel against placebo in 34 patients with ELPV has been published (Rajar 2008). This was poorly reported and as a result appeared methodologically flawed. As the authors included a variety of participants (i.e. erosive and non erosive LP) it was not included in the Cochrane review (Cheng 2012). Although the authors report a statistically significant result in favour of aloe vera with a good response seen in 85% versus 4% ($P<0.001$), it was not clear how patients were randomised, what their baseline characteristics were, how allocation was concealed or whether an intention to treat analysis was used. Furthermore, the outcome scale used in this study is non-validated and was devised for *oral* not vulval LP (the 'Thongprasom' score (Thongprasom 1992)).

1.9.1.3 Topical immunomodulators

Topical immunomodulators are steroid-sparing agents that are prescribed as second-line therapy for many skin conditions. Topical tacrolimus and pimecrolimus are licensed for use in atopic dermatitis that has not responded to first-line treatments. These agents inhibit T-cell activity and also cause downregulation of inflammatory

cytokines, hence regulating the local immune response in the skin. Topical ciclosporin is a calcineurin inhibitor which also leads to down regulation of inflammatory cytokines on keratinocytes and causes local immunosuppression.

In general, case series of patients using topical tacrolimus, pimecrolimus and ciclosporin, have reported a good or partial response (Table 6, page 80). The greatest numbers of patients reported are those who were treated with tacrolimus, but the ways in which response was assessed in the studies reviewed is not clear.

Theoretical concerns have been raised about the use of topical immunomodulators in conditions which may have pre-malignant potential as they suppress the local immune system. Furthermore, these agents, particularly topical tacrolimus are often poorly tolerated as they cause sensations of stinging, burning and irritation. Interestingly, a patient satisfaction questionnaire survey comparing patients treated with topical clobetasol against those treated with topical tacrolimus, found tacrolimus use to be more satisfactory than clobetasol (Jensen 2004). The authors also reported a similar level of side effects to be experienced between the two groups, this differs from what is usually observed in clinical practice (Simpson 2012). This particular study does have some severe limitations, as acknowledged by the authors, such as non-random subject allocation, potential recall bias, open-label treatment and small numbers of patients (n=17) (Jensen 2004).

Additionally, inclusion and exclusion criteria were not stated and the questionnaire used not validated. In the absence of any other similar studies, and in the light of personal clinical experience, it is probably best to reject these findings at present.

Concerns have also been raised about the potential development of infections of skin treated with topical immunomodulators. The development of vulval warts have been described in a female using 0.1% tacrolimus ointment to treat genital psoriasis (Amstey 2003). It is important to bear such potential complications in mind when using such treatments.

1.9.1.4 Topical oestrogens

Given that ELPV is a disease mainly of post menopausal women, some studies have utilized topical oestrogens in conjunction with topical steroids to treat ELPV (Table 7, page 81). Kennedy et al (Kennedy 2007) reported 39/114 women in a retrospective case series having been treated with topical oestrogens, however, they did not comment upon the outcome of therapy. Santegoets (Santegoets 2010)used hydrocortisone acetate 10% in oestrogen cream intravaginally but again did not specifically comment on the effectiveness of this regimen.

1.9.2 Systemic treatments

The overall number of patients treated with systemic agents, as described in the literature, are small.

1.9.2.1 Oral corticosteroids

Oral prednisolone has been described in the greatest number of patients, and in general a good response has been reported (Table 8, page 82). It works as an immunosuppressant, however, if used long-term carries the risk of considerable side effects such as hypertension, diabetes, osteoporosis and weight gain. Therefore oral corticosteroids are not an appropriate long-term management strategy for a chronic disease such as ELPV.

1.9.2.2 Other systemic immunosuppressants

Azathioprine, ciclosporin, methotrexate and mycophenolate mofetil are all immunosuppressant agents that are used frequently in dermatological practice. They have been described as treatments for ELPV but definitive evidence for their efficacy is lacking (Table 8, page 82).

1.9.2.3 Systemic antibiotics

Systemic antibiotics, particularly those in the tetracycline group, have additional functions to treating bacterial infections. In fact, tetracycline antibiotics are rarely the drug of choice for skin conditions with an *infective* component, except for acne vulgaris

(Rook 2010). However, tetracyclines have been studied as agents with *anti-inflammatory* properties and there is evidence that they inhibit the T-lymphocyte response (Sapadin 2006) and are therefore utilised in a range of inflammatory skin conditions, including LP, although an open-label study reported disappointing results in 14 cutaneous LP patients (Hantash 2007). When used in this capacity, antibiotics are used on a long-term basis, for example 6 months.

Small numbers of patients with ELPV have been reported in case-series following treatment with antibiotics (Table 9, page 83), but the overall response was poor.

1.9.2.4 Other systemic agents

A range of other systemic agents have been reported as treatments for ELPV (Table 10, page 83).

1.9.2.4.1 Hydroxychloroquine

Hydroxychloroquine, a non-steroidal systemic agent which traditionally has been used as an anti-malarial medication, is also used as an anti-inflammatory agent in dermatological and rheumatological conditions. Its mechanism of action in the latter role is not fully understood. The largest case series of ELPV patients treated with hydroxychloroquine included 15 patients (Hubbard 2003). This was a retrospective review of clinical notes and a good response to hydroxychloroquine was reported (Table 10, page 83).

A severity index to score the degree and extent of LP was devised, although the methodology of this was not specified. At a dose of 200mg twice daily, 13/15 patients showed improvement at six-months, with a mean improvement of 64.2% in severity score. The authors concluded that hydroxychloroquine is an effective treatment for vulval LP. However, due to the retrospective nature of the study, unclear assessment methods and brief nature of the conference abstract report, it is impossible to make a full critical assessment of their findings.

1.9.2.4.2 Retiniods

Systemic retinoids are principally used for psoriasis and disorders of keratinisation. One double-blind RCT involving 65 patients showed Acitretin to be efficacious in cutaneous LP (Laurberg 1991). Smaller case series have shown a good outcome with the retinoid Etretinate in oral LP patients, however, these studies were found difficult to assess in a systematic review due to 'lack of precise criteria' (Cribier 1998). Studies reporting systemic retinoids in ELPV, in general, did not find good effect (Table 10, page 83).

1.9.2.4.3 Griseofulvin

Griseofulvin is an oral anti-fungal agent that has received mixed reviews for its efficacy in oral LP as assessed by a review article (Eisen 1993). Three case series with a total of 6 ELPV patients

treated with griseofulvin have reported poor results overall with this systemic medication (Table 10, page 83).

1.9.2.4.4 Anti-neutrophilic agents

Colcichine, an agent traditionally used to treat gout, and Dapsone, an anti-leprosy medication are both used within dermatology for inflammatory skin conditions. It is thought that they possess anti-neutrophilic properties (Debol 1997) (Altinor 2003) and may be useful in treating recurrent mucosal apthous ulceration (Lynde 2009). Dapsone has been reported useful in isolated cases of oral LP (Cribier 1998) but this is not the case for ELPV (Table 10, page 83). In their case series, Cooper et al (Cooper 2006) treated 1 patient with ELPV with colchicine but poor result was noted.

1.9.2.4.5 Other agents

Rituximab, an interleukin-1 inhibitor was used to treat a patient with concurrent ELPV and pyoderma gangrenosum (McAleer 2010). Complete resolution of ELPV was reported, however, Rituximab was primarily administered to manage therapy-resistant pyoderma gangrenosum and improvement of the patient's ELP was a coincidental effect. Rituximab is an unlikely treatment of choice for pure ELP as it is a relatively new biologic therapy, has potential serious side effects and is subject to strict prescribing regulations.

Thalidomide has immunomodulatory and anti-inflammatory effects. It has demonstrated good response isolated cases of oral lichen planus, but has not seemed effective in ELPV (Table 10, page 83).

Sulpiride, which is usually an antipsychotic agent, was reported to have 'remarkable effects' on ELPV by Pelisse (Pelisse 1989), however, no information was given as why this treatment was chosen or how efficacy was measured.

1.9.3 Combined treatments

It is of note that patients who have inadequate response to topical therapy will usually be given additional systemic treatment (Table 13, page 89). Theoretically, systemic agents may take a period of time to reach maximum therapeutic response. Even though by definition, the topical treatment has had inadequate effect, it is likely that a baseline level of control will occur and stopping the topical agent whilst waiting for the systemic to take effect, may cause rebound of symptoms. Therefore physicians will use both in combination and the topical can be weaned down gently depending upon response.

Bradford et al (Bradford 2013) in a retrospective case note review described that 48 out of 131 patients who achieved induction of remission with superpotent topical corticosteroids (+/- an initial course of oral corticosteroids), required multimodal therapy to maintain disease control. Combination therapies included tacrolimus

plus topical corticosteroid (n=15), tacrolimus plus methotrexate (n=7), regular courses of oral prednisolone in conjunction with topical treatment (n=7) and low dose methotrexate in conjunction with usual topical treatment (n=11). See Table 12, page 87 and Table 13 page 89

1.9.4 Surgical treatments

Surgical intervention is sometimes required in patients who develop severe scarring secondary to ELPV. It is of note that all patients undergoing surgical intervention were given concurrent topical (+/- systemic therapy) to reduce postoperative inflammation and prevent early recurrence of synechiae formation (table 13, page 89). Bradford et al recommended doubling of the frequency of preoperative topical therapy (Bradford 2013).

Numbers of patients described having been treated by surgical division of adhesions were again small and follow up duration not specified by the reports. The largest number of patients were documented by Helgesen (Helgesen 2010) who reported 'good' response in 13/17 patients who underwent dilatation procedures in conjunction with topical steroids. However, relief was to a varying degree, often with some recurrence. Combining surgical dilatation with methotrexate seemed to reduce the rate of re-stenosis in a case series of 5 patients (Kortekangas-Savolainen 2007).

In conclusion, the evidence for the optimal first and second-line therapies used in the management of ELPV is lacking. However, since erosive lichen planus is a chronic disease, it is important to choose therapies which can be used long-term with minimal side effects.

Medical Therapy

Table 4: Topical corticosteroids for the treatment of ELPV

Treatment	Author	Type of study	Outcomes of treatment	No. of patients assessed
Clobetasol proprionate 0.05%	(Santegoets 2010)	Retrospective case series	Partial response	64
	(Cooper 2006)	Prospective cohort	Good	89
	(Kirtschig 2005)	Retrospective case series	Mixed	32
Hydrocortisone 10% foam	(Cooper 2006)	Part of prospective cohort	Partial	1
Hydrocortisone suppositories	(Anderson 2002)	Cohort (unclear if retrospective or prospective)	Symptoms improved, scarring/stenosis did not	60
Betamethasone Valerate 0.1%	(Borrego 1993)	Case report	No benefit	1
	(Cooper 2006)	Prospective cohort study	Partial response	3
Mometasone furoate 0.1%	(Cooper 2006)	Part of prospective cohort study	Good	1

Beclomethasone diproprionate 0.025%	(Kirtschig 2005)	Retrospective case series	Good	11
	(Cooper 2006)	Prospective cohort study	Partial response	5
Fluticasone proprionate 0.05%	(Santegoets 2010)	Retrospective case series	Partial response	27
Hydrocortisone 1%	(Cooper 2006)	Part of prospective cohort study	Good response	1
'Ultrapotent topical steroids' (formulation not specified)	(Helgesen 2010)	Retrospective case series	Partial response	56
	(Maor 2013)	Retrospective case series	Good response	80
	(Bradford 2013)	Retrospective case series	Response not specified	72
'Potent topical steroids' (formulation not specified)	(Lewis 1996)	Case series (unclear if prospective or retrospective)	Poor response	19
Corticosteroids (Potency not specified)	(Kennedy 2007)	Case series	Long term maintenance treatment required. Response not specified	108
	(Eisen 1994)	Retrospective case series	Partial response	22
	(Pelisse 1989)	Retrospective case series	Poor	19

Table 5: Intralesional corticosteroids for the treatment of ELPV

Treatment	Author	Type of study	Outcomes of treatment	No. of patients assessed
Intralesional corticosteroid	(Borrego 1993)	Case report	No benefit	1

Table 6: Topical Immunomodulators for the treatment of ELPV

Treatment	Author	Type of study	Outcomes of treatment	No. of patients assessed
Topical ciclosporin	(Borrego 1993)	Case report	Remission after 4 months (relapse 8 months after cessation)	1
Topical tacrolimus	(Bradford 2013)	Retrospective case series	Response not specified	1
	(Helgesen 2010)	Retrospective case series	Partial	22
	(Cooper 2006)	Prospective cohort	Partial	7
	(Byrd 2004)	Retrospective case series	Good	16
	(Lotery 2003)	Case report	Good	3
	(Kirtschig 2002)	Case report	Good	2
Topical pimecrolimus	(Cooper 2006)	Part of prospective cohort	Partial response	1
	(Lonsdale-Eccles 2005)	Prospective case series	Complete resolution 55%, Partial response 27%	11

			Intolerable 18%	
'Topical immune suppressants'	(Kennedy 2007)	Retrospective case series	Mixed response	47

Table 7: Other topical treatments for the treatment of ELPV

Treatment	Author	Type of study	Outcomes of treatment	No. of patients assessed
Topical photodynamic therapy	(Helgesen 2013)	Randomised controlled trial	No significant difference from clobetasol propionate comparator group	19 (38 included in whole trial)
Topical oestrogens (in combination with topical steroid)	(Santegoets 2010)	Prospective cohort	Not specified	4
	(Kennedy 2007)	Retrospective case series	Not specified	39
Aloe vera gel	(Rajar 2008)	Randomised controlled trial	Good response compared with placebo	17 (34 included in whole trial)

Systemic Therapy

Table 8: Systemic immunosuppressants for the treatment of ELPV

Treatment	Author	Type of study	Outcomes of treatment	No. of patients assessed
Azathioprine	(Cooper 2006)	Part of prospective case series	Poor	1
Ciclosporin	(Cooper 2006)	Prospective case series	Poor	2
	(Eisen 1994)	Retrospective case series	Complete Resolution	2
Methotrexate	(Genadry 2006)	Case report	Mixed response	2
Mycophenolate mofetil	(Frieling 2003)	Case report	Good	3
Oral prednisolone	(Bradford 2013)	Retrospective case series	Response not specified	22
	(Cooper 2006)	Prospective cohort	Resolution	3
	(Eisen 1994)	Retrospective case series	Good	6

	(Borrego 1993)	Case report	No benefit with 20mg/d over 4 months	1
	(Pelisse 1989)	Retrospective case series	Good	10

Table 9: Systemic antibiotics for the treatment of ELPV

Treatment	Author	Type of study	Outcomes of treatment	No. of patients assessed
Doxycycline	(Eisen 1994)	Retrospective case series	Poor	3
Erythromycin	(Cooper 2006)	Prospective cohort	Mixed response	6
Minocycline and nicotinamide	(Cooper 2006)	Prospective cohort	Poor	5

Table 10: Other systemic agents for the treatment of ELPV

Treatment	Author	Type of study	Outcomes of treatment	No. of patients assessed
Acitretin	(Cooper 2006)	Prospective case series	Poor	4
	(Eisen 1994)	Retrospective case series	Partial	4
Colchicine	(Cooper 2006)	Part of prospective cohort	Poor	1

Dapsone	(Eisen 1994)	Retrospective case series	Poor	4
	(Pelisse 1989)	Part of retrospective case series	Poor	1
	(Edwards 1988)	Case report	Poor	1
Etretinate	(Pelisse 1989)	Retrospective case series	Poor	3
Griseofulvin	(Eisen 1994)	Retrospective case series	Poor	4
	(Pelisse 1989)	Part of retrospective case series	Poor	1
	(Edwards 1988)	Case report	Partial	1
Hydroxychloroquine	(Cooper 2006)	Prospective cohort	Poor	2
	(Hubbard 2003)	Retrospective case series	Good	15
Rituximab	(McAleer 2010)	Case series	Good	1
Sulpiride	(Pelisse 1989)	Part of retrospective case series	Complete Resolution	1

Thalidomide	(Cooper 2006)	Part of prospective cohort	Poor	1
	(Borrego 1993)	Case report	No benefit	1

Combined Treatments

Table 11: Combined topical therapy in the treatment of ELPV

Treatment	Author	Type of study	Outcomes of treatment	No. of patients assessed
Topical ciclosporin plus topical corticosteroids	(Eisen 1994)	Retrospective case series	Partial	5
Clobetasone butyrate 0.05%, 3% oxytetracycline plus nystatin	(Cooper 2006)	Prospective cohort study	Good	14
Topical corticosteroid plus topical tacrolimus (preparations not specified)	(Bradford 2013)	Retrospective case series	Response not specified	2

Table 12: Combined topical and systemic therapy for the treatment of ELPV

Treatment	Author	Type of study	Outcomes of treatment	No. of patients assessed
Topical corticosteroids (superpotent or potent) and systemic immunosuppressant (prednisolone)	(Bradford 2013)	Retrospective case series	Response not specified	31
Topical corticosteroids (Clobetasol), immnosuppressants (Tacrolimus) and systemic immunosuppressant (Methotrexate)	(Jang 2008)	Case report	Good	4

Topical corticosteroids (regimen not stated) and systemic immunosuppressant (Methotrexate)	(Nylander Lundqvist 2002)	Case report	Good	3
Topical corticosteroid (superpotent or potent) and systemic immunosuppressant (methotrexate)	(Bradford 2013)	Retrospective case series	Response not specified	1
Hydroxychloroquine , 25mg hydrocortisone suppositories , mycophenolate mofetil 1g BD	(Genadry 2006)	Case report	Good	1

Methotrexate, hydroxychloroquine , 25mg hydrocortisone suppositories	(Genadry 2006)	Case report	Good	1
Mild topical steroids and oral corticosteroids	(Mann 1991)	Case series	Good	9
Griseofulvin and clobetasol	(Edwards 1988)	Case report	Good	1
Dapsone and topical hydrocortisone	(Edwards 1988)	Case report	Good	2

Table 13: Combined systemic treatment for ELPV

Treatment	Author	Type of study	Outcomes of treatment	No. of patients assessed
Oral prednisolone plus oral methotrexate	(Bradford 2013)	Retrospective case series	Response not specified	1

Table 14: Combined medical and surgical intervention for the treatment of ELPV

Treatment	Author	Type of study	Outcomes of treatment	No. of patients assessed
Topical corticosteroids (+/- oral prednisolone) plus surgical division of adhesions	(Bradford 2013)	Retrospective case series	Adequate	8
Topical corticosteroids (preparation not specified) plus surgical division of adhesions	(Santegoets 2010)	Retrospective case series	Not commented	9
Topical steroids plus dilatation	(Helgesen 2010)	Retrospective case series	Partial response	17
Topical steroids (diflucortolone valerate 0.3%, prednisolone foam) and surgical division of adhesions	(Panagiotopoulou 2010)	Case report	Good	1

Topical corticosteroids (Clobetasol), immunosuppressants (Tacrolimus), oral Methotrexate (7.5mg weekly) and surgical dilation	(Kortekangas-Savolainen 2007)	Case series	Good	5

1.10 Complications of vulval erosive lichen planus

1.10.1 The risk of malignant transformation with ELPV

The risk that ELPV lesions increase the risk of squamous cell carcinoma (SCC) in the vulval area has been reported in case series (Lewis 1994, Dwyer 1995, Franck 1995, Ramos-e-Silva 2010), but larger-scale studies are lacking. A recently published critically appraised topic to evaluate whether ELPV is associated with an increased risk of vulval SCC did not find conclusive evidence to confirm or refute these reports (Simpson 2012). The critically appraised topic analysed case series with five or more consecutive patients to reduce reporting bias.

Identified were 4 case series (Kirtschig 2005, Cooper 2006, Kennedy 2008, Santegoets 2010) that described the long-term follow up of a total of 366 patients with ELPV. A further 2 case series (Zaki 1996, Derrick 2000) of patients with anogenital carcinoma were found whereby the authors investigated the underlying aetiology of the malignancy. Combining findings from the 4 case series, vulval SCC occurred in 5 of 366 patients. The overall duration of ELPV was only reported for 1 of these incident cases (3 years)(Kennedy 2008). Mean follow up time was only documented by 2 studies (60 months (Kennedy 2008) and 72 months (Cooper 2006)). There were 3 retrospective and 1 prospective studies. These studies are summarized in Table 15, page 95.

Squamous cell carcinoma may also occur in other sites affected by ELP. Studies included in the review also documented SCC developing in the oral mucosa and the oesophagus (Table 15, page 95). Vulval intraepithelial neoplasia (VIN) was documented in a total of 6 women. It is not clear from the reports whether these cases were due to ELP or not. The most common cause of VIN is known to be preceding infection with the human papilloma virus but viral status was not discussed in the patients who developed VIN.

Other malignancies that occurred within the case series of patients discussed were cervical adenocarcinoma and rectal adenocarcinoma. These are unlikely related to ELP itself as the cell type of the tumour is different to what would be seen with ELP. Therefore, it is most likely that an alternative aetiology was underlying these cases.

There is clear evidence that certain vulval inflammatory disorders, such as lichen sclerosis predispose to the development of malignancy. However, at present there is only a *suggested* increased prevalence of vulval SCC in patients with ELPV. The only way to clarify whether there is a *real* risk is for long-term follow up data of the disease and its complications to be recorded in a multi-centre registry.

1.10.1.1 Malignant transformation of ELP affecting other sites

The development of SCC has been described most commonly in oral LP. The World Health Organisation considers oral LP as a

premalignant condition, however, there remains controversy whether oral LP is an intrinsically premalignant condition, a facilitator of the action of carcinogenic agents, or simply a coincidental (and therefore confounding) factor (Ramos-e-Silva 2010). Two analyses of the literature, one including 223 cases (reported between 1950 and 1977) (Krutchkoff 1978) and the other 98 cases (reported between 1977 and 1999) (van der Meij 1999) of SCC arising in oral LP concluded that there was not enough evidence to settle the debate. These reviews have been subject to criticism, particularly due to the selection criteria used for included cases and it is felt that bias has influenced their findings (Lodi 2005).

There have been isolated case reports of SCC developing within oesophageal LP (Moncarz 1993, Shenfine 2006, Zvidi 2012), but no case series or longitudinal studies.

Malignant transformation of cutaneous LP (non-erosive) is rare and tends to be in longstanding hypertrophic lesions located on the lower limbs (Sigurgeirsson 1991, Singh 2006).

Therefore, as for vulval LP, long-term prospective studies are required to determine whether lichen planus is a truly pre-malignant condition, or not.

Author	Study type (Level of evidence)	Study period	No. of patients	Mean follow up period (months)	No. of patients with malignancy (duration of preceding ELPV if known)
Santegoets (2010)	Retrospective case series	May 1995- Dec 2002	95	?	2 (unclear)
Kennedy (2008)	Retrospective case series	Jan 1995 – Dec 2002	113	60	Vulvar SCC - 1 (3 years after diagnosis of ELPV; 1 yr after treatment for cervical carcinoma) Oral SCC -1 (2 years) Oesophageal SCC - 1 (7 years) Cervical adenoca - 1 (5 years) Rectal adenoca -1 (14 years)
Cooper (2006)	Prospective cohort study	5-year study period, unclear timeline	114	72	Oral SCC – 1 Perianal SCC – 1 Vulval SCC – 1 (on background of VIN 3) VIN in further 6 patients Duration of ELPV preceding malignancy not stated in this study
Kirtschig (2005)	Retrospective case series	1997-2000	44	?	1 (not stated)

Table 15: Summary of included studies for critically appraised topic performed to assess the relationship between ELPV and the development of SCC

1.10.2 Scarring

Scarring is frequently observed in patients with ELPV (Table 2, page 57). Cooper et al, in their prospective study of 114 females with ELPV specifically commented that 'some degree of scarring was present in almost all women (95%), with 73% having moderate or severe scarring' (Cooper 2006).

The degree of and location of scarring can be variable, however, it seems to typically affect the vaginal introitus (to cause a fused/semi-fused vagina), the labia (causing loss of the labia minora) and the clitoral hood (to cause burying of the clitoris). The resulting physical morbidity from vulvovaginal scarring includes urinary outflow obstruction and loss of ability for sexual activity. Psychological effects due to this loss of function, not to mention the altered anatomical appearance can be profound. In advanced cases, scarring needs to be treated with division of adhesions, either manually or under general anaesthesia, depending upon the level of scarring that is to be addressed.

It is logical to presume that early effective treatment of ELPV would prevent progression to scarring, however, data demonstrating this are lacking. Interestingly though, Cooper et al found that a delay in diagnosis of ELPV (and therefore delay in treatment) was not associated with worse scarring at the time of presentation.

1.10.3 The development of neuropathic pain

Vulvodynia is the term given to vulval discomfort, most often described as a burning pain, occurring in the absence of relevant visible findings or a specific, clinically identifiable, neurological disorder. It is a form of neuropathic pain. Similar symptoms of vulval pain may develop as a result of inflammatory skin disease, such as ELPV. In this context it may be either an acute, or a chronic symptom. In one study, 89 patients who had vulval pain that was either unresponsive to initial treatment or who had an unclear initial diagnosis, underwent biopsy of the vulval area (Bowen 2008). Lichen planus was found to be present in four of these cases. Therefore, clinicians should be mindful of this potential complication in patients with ELPV whose symptoms appear out of keeping with the clinical severity of ELPV. In particular, point tenderness on examination with a Q-tip in a patient with ELPV may represent secondary vulvodynia and this should be managed appropriately. Amitriptyline, a tricyclic antidepressant, is the treatment of choice in these patients (Nunns 2010).

Study	N in series	Anatomical Site							
		Oral mucosa (%)	Skin (%)	Perianal skin/mucosa (%)	Scalp (%)	Nails (%)	Oesophagus (%)	External Auditory meatus (%)	Lacrimal duct (%)
Lewis 1996	37	54	68	-	-	-	-	-	-
Anderson 2002	60	40	7	-	-	-	-	-	-
Byrd 2004	16	-	31	12	-	-	12	19	-
Cooper 2006	114	59	-	28	8	4	3	2	1
Kennedy 2007	113	17	-	-	-	-	-	-	-
Cooper 2008	161	48	14	17	1	2	2	-	-
Ebrahimi 2012	120	80	30	-	-	-	5% (symptoms only- not confirmed by OGD)	-	-

Table 16: Frequency of concomitant sites affected by lichen planus as reported by published studies- = Site not commented upon in paper

1.11 Measuring the clinical severity of vulval erosive lichen planus

Accurate assessment of disease severity is essential to enable clinicians to deliver optimal patient care. However, there are no tests of clinical significance that are available to measure the severity of erosive lichen planus or indeed, other vulval skin conditions. A clinician managing ELPV must take into account both objective (clinician assessed) and subjective (patient reported) outcomes when measuring severity and response to treatment.

1.11.1 Clinician assessed outcomes in vulval erosive lichen planus

A scoring system has been validated for the clinical assessment of *oral* LP (Escudier 2007), which is a composite score taking into account extent of site involvement, disease activity at each site and an overall pain level as reported by the patient. This score provides an *objective* view of disease severity and is used in both clinical practice and clinical trials. However, this outcome measure tool has been relatively recently devised, and heterogeneity for outcome measures in oral LP still exists (Cheng 2012).

The same is true for vulval ELP, in which there are *no* published or validated outcome measure scales to document its severity.

Reported case series of ELPV patients have used a heterogeneous selection of methods to assess the disease.

1.12 Measuring the impact of vulval erosive lichen planus on the patient

1.12.1 Impact of vulval erosive lichen planus on the patient

Patients with chronic skin diseases – in line with other chronic physical conditions- report lower levels of psychological and social well-being (Evers 2008). Vulval skin disorders are no exception as they cause significant distress and can affect both physical and psychological well-being. Previous qualitative studies have demonstrated how genital skin disease causes a reduction in quality of life (QoL) (Sargeant 2007, Hickey 2010). The existing literature has tended to focus on gynaecologic malignancies and their treatment, with little having been published on inflammatory vulval conditions. A systematic review of health related QoL measurement for patients with benign gynaecologic conditions (Jones 2002) concluded that few questionnaires have been used to evaluate treatment outcomes in terms of subjective health status.

A study of patients with oral and genital LP (Lundqvist 2006) has demonstrated that depression, anxiety and increased levels of stress are distinctly more prominent compared to a matched group of

healthy controls. Furthermore, the loss of function caused by ELPV (due to pain and scarring) interferes with patients' personal and working lives. It is likely that involvement of increasing number of mucocutaneous sites will have proportionally greater effect on QoL.

A number of outcome measure tools exist within dermatology to assess the impact of disease on QoL, however, none have been specifically devised with vulval skin conditions in mind. Therefore, the instruments used in studies and clinical practice tend to be a combination tools which are perceived to 'best-fit' the condition. In a world where QoL and consideration of the patient's perspective plays a major role in the provision of services, current methods of assessing vulval skin disease seem inadequate. This dissertation will detail later the results of a systematic review analysing published outcome measures for patients with vulval disease.

1.13 Economic consequences of vulval erosive lichen planus

The economic consequences of ELPV, although never formally assessed, are likely to have considerable impact on those affected, their families and the health system as a whole.

The only work to look at the economic evaluation of ELP was a study from an Italian group comparing topical clobetasol proprionate against topical ciclosporin in the treatment of oral lichen planus

(Conrotto 2006). This study was summarised by the Cochrane centre for reviews and dissemination as a 'Critically Appraised Economic Evaluation.

In this study both drugs were mixed separately with 4% hydroxyethyl cellulose gel to obtain a final concentration of 0.025% for clobetasol and 1.5% for ciclosporin. Forty patients were enrolled in the study, 20 being allocated to each group. There was a statistically significant difference in improvement of clinical signs (95% improvement in clobetasol-treated patients versus 65% of ciclosporin-treated patients) after 2 months of therapy, but there was not a statistically significant improvement in symptoms, with both groups showing high levels of improvement (95% clobetasol group versus 85% ciclosporin group). Ciclosporin seemed to produce a statistically significant improvement of stability in clinical scores.

No total costs of the interventions were reported but the daily cost of ciclosporin treatment was EUR 1.82 compared with EUR 0.35 for clobetasol therapy. Therefore the cost of topical ciclosporin was 5.2 times greater than clobetasol. The authors concluded that clobetasol propionate in 4% hydroxyethyl cellulose gel was to be more cost-effective than topical 1.5% ciclosporin in the same medium for the treatment of oral lichen planus. The main drawback of using ciclosporin routinely was its high cost.

The sources of the cost data were not fully reported and the price year was also not reported. Even though this study is a start to estimating the economic burden of ELP it does not investigate the vulval subset and it is not possible to directly extrapolate the findings to a genital population. Therefore these data in the literature are lacking and steps should be taken to rectify this.

1.14 Chapter 1 Summary

Vulval erosive lichen planus (ELPV) is a rarer variant of lichen planus and is an inflammatory dermatosis causing painful erythema and/or erosions of the vulva and vagina. Scarring can cause burying of the clitoris and narrowing of the vaginal introitus/vaginal canal, which may alter sexual function and make intercourse impossible. ELPV has a significant negative impact on QoL as it affects day to day function and there is a reported risk of malignant progression.

There is no randomised controlled trial evidence (RCT) on which to base treatment for ELPV, including no evidence for the efficacy of very potent topical steroids, which are used by most clinicians as standard first-line therapy. Approximately 25% of patients with ELPV are resistant to the accepted first-line therapeutic agents as defined by crudely reported patient and clinician outcome measures, and there is considerable variation in second-line agents used. Since the condition is chronic, any therapies used need to be safe for long term use.

There is a general lack of standardisation of management in terms of diagnostic criteria, methods of assessing disease severity and treatment. To improve the care pathway for patients with this distressing condition, these issues need to be addressed.

This PhD will outline a number of steps that have been taken to reduce these uncertainties to improve understanding about how the how the disease is currently defined and treated and to review the evidence for the best outcome measures to use when assessing the condition. This will lead to the design of randomised controlled trial protocol for a study that is designed to identify interventions that are effective in improving disease control in patients with ELPV who have failed first-line therapy. The structure of this thesis and aims of each chapter are outlined below:

Overview of Chapters	Aims
1 - Introduction	Background to project, clinical features and impact of vulval erosive lichen planus plus description of the problems in management and gaps in knowledge which need to be addressed.
2 – Determining current clinical practice in the management of vulval erosive lichen planus	A retrospective study to assess current clinical management in the UK. Variation in practice was found and a number of uncertainties were highlighted, including methods of diagnosing the condition, outcome measures used to assess severity and impact of the disease and therapeutic choices.
3 – A qualitative investigation into UK clinician views and principles of management of vulval erosive lichen planus	This qualitative study involving interviews with 25 UK clinicians aimed to clarify the uncertainties identified by the retrospective case note study. Subsequent chapters are aimed at reducing the identified uncertainties.
4 – Diagnostic criteria for erosive lichen planus affecting the vulva : An international electronic-Delphi exercise	An international consensus exercise to agree a set of diagnostic criteria that are acceptable to the clinical community. The resulting diagnostic dataset can be applied to clinical practice and future studies.
5 – Outcome measures for vulval skin disorders	A systematic review of the literature to assess outcome measure tools that have been used in randomised controlled trials of vulval skin disorders. The findings were subsequently discussed with patients to ascertain which measures are most appropriate to use in the context of vulval erosive lichen planus.
6. Patients views on vulval erosive lichen planus	A survey of a national patient group, the UK Lichen Planus Society identified early information about living with the disease from the patient's perspective. These themes, plus findings from the systematic review of outcome measures described in Chapter 5, were then explored in greater detail through focus group work with patients.
7–A randomised controlled trial of adjunctive systemic therapy for vulval erosive lichen planus – The hELP Trial.	Information from the previous chapters was brought together to design a randomised controlled trial that aims to improve practice by identifying effective treatments for patients with severe disease. The chapter concludes with a fully developed multi-centre randomised controlled trial protocol for the 'hELP' (systemic tHerapy for vulval Erosive Lichen Planus) Trial.

2 Determining current clinical practice in the management of vulval erosive lichen planus: A case-based review and UK multi-centre case note audit.

2.1 Introduction

Chapter 1 outlined current knowledge about the epidemiology, aetiology, clinical presentation and outcome of erosive lichen planus. It also reviewed the treatment options that are presently available to offer patients with the condition. The 2012 Cochrane systematic review of interventions for mucosal lichen planus, and subsequent search of case series of ELPV patients discussed in Chapter 1 identified a significant lack of evidence for the management of ELPV, poor consensus upon disease definition and diagnostic criteria, and deficiencies in methods of assessment of the condition (outcome measures).

In order to progress this work in the light of these deficiencies, it was important to investigate and define what 'normal' care that is followed in day to day clinical practice. This was achieved through collaborating with UK physicians to perform a multi-centre case-based audit and review of practice. The process of this audit and review study is described in Chapter 2.

The work in this thesis is building towards a randomised controlled trial. For the findings from a clinical trial to be adopted into clinical practice it is imperative that the trial design resembles 'usual' care as closely as possible. A trial using treatments or demanding follow up arrangements that are not practical in 'real life' is not relevant

and not going to be followed by the clinical community. The development of a pragmatic study which reflects usual practice will be the end point of this thesis.

Until this point, it was not clear how ELPV was managed by different centres. The goal of this exercise was to ascertain 'usual' clinical practice and determine current standards of care.

2.2 Aims

The aims of this national multi-centre audit were to compare real-life clinical practice to a proposed standard of optimal care for ELPV, as well as collecting additional data about the condition. In the absence of national/international guidance, audit standards were set following agreement with expert clinicians from the British Society for the Study of Vulval Disease (BSSVD), a multi-disciplinary national specialist group (See Section 1.7.2, p2).

2.3 Materials and Methods

This study was coordinated centrally from the Centre of Evidence Based Dermatology, University of Nottingham. Proposed audit standards were set following communication with experts from the British Society for the Study of Vulval Disease in the context of a questionnaire survey and subsequent discussion at the society's biennial meeting. Derived standards are detailed in Figure 18, p112,

and were circulated to the involved clinicians for approval prior to conducting the audit.

A data abstraction form (Appendix 2) was used for data to be extracted from casenotes to compare current UK practise as against the agreed audit standards(Figure 18, p112) for the management of ELPV. Data that were also collected in addition to the audit standards included:

- Co-morbidities
- Concurrent medications
- Disease duration
- Result of biopsy
- Documentation of other affected sites
- Duration and side effects of therapy

Lead consultants from multiple UK centres were identified through the BSSVD. These included nine dermatologists and one gynaecologist. Each centre identified consecutive patients with a clinical diagnosis of ELPV who were seen in the outpatient clinic over a six-month period. For each patient the notes were reviewed back to the time of presentation to secondary care. Since the histology of ELPV is variable (Pelisse 1989), histological confirmation of ELPV was not considered mandatory, for inclusion to the study patients only required a clinical diagnosis of ELPV to have been made.

To maintain anonymity, each patient was assigned a study identity code number and participating centres were asked to maintain a separate confidential list of participants to permit identification of all included patients in case additional follow-up should be later required.

Data were inputted it into an Excel spread sheet for analysis. Data were of mixed type; categorical data were summarized as percentages with numerator and denominator indicated. Numerical results were summarized by the mean and median values.

Diagnosis of ELPV:

- Biopsy should be performed in cases of diagnostic uncertainty to exclude other pathology
- Other skin sites and the oral cavity should be examined for evidence of lichen planus

Documentation of severity and impact of ELPV:

- Assessment of disease should include:
    - Documented evidence of disease severity and disease extent as assessed by the clinician
    - Impact of disease on quality of life as completed by patient (e.g. visual analogue scale for pain, Dermatology Life Quality Index)
    - Consideration of interference with functional activity such as sexual activity

Provision of care:

- Patients with multi-site **or** complex disease should be managed by a multidisciplinary approach involving the relevant specialties

Treatment for ELPV:

- A very potent topical steroid should be used as first-line treatment
- Patients who fail first-line treatments should be changed to an alternative agent (although there is no evidence to determine optimum second-line therapy)

Figure 18: Multi-centre case note audit: Agreed audit standards for the management of vulval erosive lichen planus

2.4 Results

Participating clinicians included nine dermatologists and one gynaecologist. A total of 172 case notes were reviewed by the ten participating centres. The number of patient notes reviewed by the centres ranged from 4 to 37. Data were recorded from under 10 patients in three centres, 10-20 patients in four centres and over 20 patients in three centres.

All patients were female and their ages ranged from 34-94 years (mean 66.5 years, median 68 years). Duration of disease ranged from six months to more than 20 years (median range 1-5 years) with nearly half, 49% (85/172) having disease documented for more than five years (Table 17, page 113).

Duration of ELPV (years)	Number of patients
<1	10
1-5	77
6-10	45
11-15	19
16-20	11
>20	7
Unclear	3
TOTAL	172

Table 17: Multi-centre case note audit results: Duration of vulval erosive lichen planus

The individual audit standards set for this study (Figure 18, p112) were assessed individually and a summary of how well the standards were met is detailed at the end of the results section (Table 21, page 124).

2.4.1 Diagnosis

Biopsy of the vulval region was taken as part of the initial diagnosis in 77% of patients (132/172); oral mucosal biopsy had been performed in a further 2% (3/172). It was recommended in the audit standards that biopsy should be performed in cases of diagnostic uncertainty or resistant disease; this did not occur in 5 such cases. These cases were all patients with disease that was resistant to first line therapy.

The majority of histology results reported were consistent with a diagnosis of erosive lichen planus (71%, 96/135). The remainder either ruled out any other significant pathology (10%, 14/135) or were inconclusive (16%, 22/135). The result could not be located in two cases, and one was not answered.

Since erosive lichen planus may occur at other sites it was recommended as a standard that clinicians examine other areas that might be affected. Documentation of examination of other skin sites occurred in 60% (104/172) of patients and 62% (106/172) had recorded oral cavity examination.

2.4.2 Documentation of disease severity/impact

A description of symptoms and clinical findings were documented for nearly all of the patients whose data contributed to this study. Severity of disease was documented in 99% (170/172) of notes and 87% (150/172) displayed a schematic diagram of the vulva indicating disease location and scarring. However, less than half of patients (42%, 72/172) had evidence about ability for sexual function documented. Assessment of disease impact using the Dermatology Life Quality Index (DLQI) was performed in 3% (6/172) and only 1% (2/172) had pain/discomfort recorded by a visual analogue scale.

2.4.3 Affected sites and provision of care

The vulva was affected exclusively in 44% (75/172) of patients. The most commonly affected other sites were oral mucosa, skin and vagina, with anal and oesophageal mucosa being affected least frequently (Table 18, p117). One patient had lacrimal duct involvement.

In considering provision of care, nearly all patients with skin involvement had input from a dermatologist (95%, 35/37), which reflected the speciality of recruiting clinicians. Of patients with oral disease, only 54% (40/74) were also managed by oral medicine or maxillofacial surgery. Half of patients with vaginal disease (51%, 18/35) were under the care of a gynaecologist. All patients with

unusual site involvement (oesophagus, lacrimal duct) received input from the relevant specialities.

Site	Number of patients (%)
Vulva only	75 (44)
Vulva plus:	
Oral mucosa	74 (43)
Skin/scalp	37 (22)
Vagina	35 (20)
Anus	9 (5)
Oesophageal mucosa	2 (1)
Lacrimal duct	1 (0.6)

Table 18: Multi-centre case note audit results: Anatomical sites affected by lichen planus

2.4.4 Treatment

Topical treatment alone was received by 78% (134/172) and additional systemic treatment was used in 21% (37/172) of patients. One patient did not receive any treatment as their condition improved spontaneously.

As recommended by the audit standard, first-line treatment with a very potent topical steroid was received in 75% (129/172) with the remainder being given alternative topical or systemic treatments (Table 19, page 121). The most common alternative first-line therapies were potent topical steroids (i.e. one class of potentcy down from the recommendation) or topical immunomodulators.

Of the patients who received first-line therapy with a very potent topical steroid, 66% (85/129) were documented to have responded but it was unclear what methods had been used to assess response. First-line treatment failure occurred in 11% (14/129) and it was unclear how well the patient responded in 10% (13/129) of cases. A number of cases (13% (17/129)) who were new referrals to the clinic had recently commenced treatment and were awaiting further follow up.

Of those who failed first-line very potent topical steroids (n=14), second-line agents used were topical tacrolimus (4/14), intravaginal steroids (enemas 2/14, suppositories 2/14), oral hydroxychloroquine (2/14) and less-potent topical steroids (3/14). One patient continued on the same very potent topical steroid. Therefore 71% (10/14) of this group were appropriately given a more potent therapy.

In 24 patients who had initially responded to a very potent topical steroid, intra-vaginal steroid enemas or systemic agents were required at a later stage due to relapsing-remitting disease.

A total of 66 treatment episodes (in 37 patients) with systemic agents were recorded and 16 different systemic agents had been used (Table 20, p122). There was no demonstrable consistency in approach. The most frequently used agents were oral corticosteroids (15 patients) and, hydroxychloroquine (11 patients). These agents

were given simultaneously in one further patient. Acitretin, methotrexate, mycophenolate mofetil and minocycline were each used a total of six times. A number of other agents were used less frequently (Table 3).

Prednisolone (13/37) and hydroxychloroquine (8/37) were the most frequently used *initial* systemic agents after failure of topical treatment. The systemic therapies recorded as being most effective were oral prednisolone (7/15), which was withdrawn once disease remission was obtained and hydroxychloroquine (4/11) which tended to be used longer-term to maintain disease control. Though again, as with the topical agents, there was no clear methodology though for recording disease severity or induction of remission.

Reported side effects varied according to the therapy used. The most frequent was burning/irritation secondary to topical immunomodulators (21/45). Irritation occurred infrequently from very potent topical steroids (4/229), potent topical steroids (2/60), topical lidocaine (1/8), zinc (1/1) and topical isotretinoin (1/1). Skin atrophy or local steroid effect on the skin was only documented in 2 cases.

Intravaginal steroid enemas caused bleeding in 2 cases. Side effects from systemic agents were seen most commonly with hydroxychloroquine (4/11 – rash in three patients, joint pain/headache in one patient) and oral prednisolone (4/15 – weight

gain and low mood in two patients, hypertension in one patient and agitation in one patient).

Treatment	Number of patients	Outcome
Mild potency topical steroid /antimicrobial preparation	2	2 successful for >12 months then failed
Moderate potency topical steroids /antimicrobial preparation	5	4 successful 1 failed
Potent Topical steroid	10	7 successful 2 successful for > 12 months then failed 1 failed: non-compliance
Potent Topical steroids/ antimicrobial preparation	4	1 successful for > 12 months then failed 3 failed
Topical immunomodulators	6	3 Stopped as side effects 1 successful 1 failed 1 unclear
Intravaginal steroid enemas	5	2 successful 2 stopped due to patient choice 1 Failed
Topical antibiotics	1	Successful
Topical oestrogens	3	3 failed
Oral antibiotics	2	1 Stopped as side effects 1 Successful
Oral corticosteroids	1	Successful
Dapsone	1	Unknown
No treatment	1	N/A
Unclear	2	N/A
TOTAL	43	

Table 19: Multi-centre case note audit results: Other first-line treatments if super-potent topical steroid not initially used to treat vulval erosive lichen planus.

Systemic agent	Total times used*	Total used as *first* systemic agent[$]	Patients on treatment currently (duration of treatment in months)	Patients failed treatment	Patients successfully responded to treatment
Prednisolone	15	13	3 (1,6,12)	5	7
Hydroxychloroquine	11	8	4 (1, 12, 36,240)	5	2
Acitretin	6	3	0	4	2
Methotrexate	6	2	3 (1,3,18)	3	0
Minocycline	6	4	2 (6, 6)	2	2
Mycophenolate	6	1	4 (1,7, 12,13)	2	0
Ciclosporin	3	0	0	1	2
Erythromycin	3	1	1 (3)	1	1
Azathioprine	1	0	1 (96)	0	0
Dapsone	1	0	0	1	0
Efalizumab	1	0	0	Drug withdrawn	0
Imipramine	2	2	0	2	0
Isotretinoin	1	0	0	1	0
Metronidazole	1	0	0	1	0
Prednisolone + HCQ	1	1	0	1	0
Sulfasalazine	1	0	0	1	0
Thalidomide	1	0	0	1	0

Table 20: Multi-centre case note audit results: Systemic agents used (+/- concomitant topical steroids) when other first-line treatments failed to provide adequate disease control.

Key: * - number of times agent used in total accounting *all* treatment episodes with systemic agents; [$] - number of times agent was used as the *first* systemic treatment after failure of topical treatments

2.4.5 Complications of disease

Additional information about long term sequelae of ELPV was collected. Vulval squamous cell carcinoma (SCC) occurred in two patients, both of whom had preceding vulval intraepithelial neoplasia (VIN). One of these patients was documented to have differentiated VIN and had been under the care of vulval dermatology for one year with the disease. She had been managed by maxillofacial surgery for a number of years due to oral ELP with associated dysplasia. The second patient had been diagnosed with grade 3 VIN, (this was prior to publication of the updated International Society for the Study of Vulvovaginal Disease classification system for VIN (Heller 2007) in which terminology was changed from to 'usual' or differentiated' VIN, rather than grading the severity of dysplasia on a scale of 1, 2 or 3) and had been under the care of vulval dermatology for over 10 years with ELPV.

A histological diagnosis of 'usual' VIN was seen in two further patients. Oral SCC occurred in two patients; it is unknown whether these had dysplastic changes diagnosed histologically before the diagnosis of SCC was made.

Agreed Standard	Number of patients in category	Number of patients meeting standard n (%)
Biopsy to exclude other diagnoses	55	5 (19)
Evidence of other affected sites examined?	172	104 (60)
Oral cavity examined?	172	106 (62)
Evidence of documentation of disease severity?	172	170 (99)
Evidence of disease extent using schematic diagram documented?	172	150 (87)
Evidence of documentation of disease impact? (e.g. DLQI and VAS)	172	6 (3)
Interference with functional activity documented (e.g. sexual activity)?	172	72 (42)
Evidence of multiple site/complex disease managed by multidisciplinary approach?	155	101 (65)
Documentation of first line treatment super-potent topical steroid	172	129 (75)
Evidence of second-line treatment given very potent topical steroid not effective?	14	10 (71)

Table 21: Multi-centre case note audit results: Summary of compliance against agreed audit standards

N.B. Diagnostic uncertainty was defined as complicated disease (atypical presentation or features suggesting neoplasia), or disease resistant to very potent topical steroids/requiring systemic treatment defined as no documented response over a three-month period. DLQI = Dermatology Life Quality Index; VAS = Visual Analogue Scale

2.5 Discussion

This audit provided a comprehensive insight into current UK dermatological practice for the management and treatment response of a large cohort of patients with ELPV. Patient demographics were consistent with previous studies that have found that ELPV is most common in women of menopausal age (Mann 1991, Eisen 1999, Cooper 2006) and follows a chronic course (Bidarra 2008), with half of our patient cohort experiencing disease lasting five years or longer.

2.5.1 Main findings

The findings were particularly relevant to further work in this field as a *number of uncertainties were highlighted*; these are considered in the discussion section and mainly include assessment of appropriate outcomes, treatment algorithms and methods of diagnosis.

2.5.1.1 Outcome measures

When taking into account the method of assessing and documentating outcomes, it was found that although clinicians were thorough in taking a description (99%) and recording severity with a diagram (87%), a measure of disease impact to assess how the condition affects the patient, such as assessment of quality of life, was performed in fewer than 50% cases. In even fewer

circumstances was the patient asked about impact on sexual functioning.

2.5.1.2 Diagnosis of the disease

In terms of accurately diagnosing ELP, it has been recognised that definite histological evidence of the disease in mucosal sites is more difficult to confirm than it is for classical cutaneous lichen planus (Pelisse 1989). The majority of patients in this study (79%) had a diagnostic biopsy and histological findings consistent with ELPV were present in 71% of these. An alternative diagnosis was ruled out in a further 10%. This indicates that diagnostic biopsy is a worthwhile investigation and appears to be part of normal care for most clinicians.

2.5.1.3 Other involved mucocutaneous sites

Mucocutaneous sites were frequently affected in addition to the vulva. Vaginal disease was present in 20% of patients with ELPV, which is in keeping with the results of Cooper (26%) (Cooper 2006), but lower than in other published series (58% (Pelisse 1989); 100% (Bermejo 1990)). The findings for skin/scalp involvement (22%) were similar to previously published data (17% (Eisen 1999)), but may be an underestimate as not all patients received formal cutaneous examination. Anal mucosal, oesophageal and lacrimal duct involvement were found to be present in 5%, 1% and 0.5% of patients respectively.

2.5.1.4 Complications of the disease

Malignancy developed in four (2.3 %) patients; two patients had vulval SCC (both occurred on a background of VIN and one also had oral dysplasia) and two patients had developed oral SCC. Three further patients developed VIN. We know that vulval SCC developed after disease duration of >10 years in one patient and after several years in the other, although this study was not designed to elucidate the exact timings.

2.5.1.5 Treatment algorithms

A very potent topical steroid was received as first-line treatment in 75% (129/172) of patients, which was successful in 66% (85/129) of these cases. Although there was no consensus as to how this was determined.Treatment regimens were variable, although a reducing regimen over 3 months was most frequent.

The 66% success rate of very potent topical steroids as determined retrospectively in this audit was lower than the 75% improvement in a previous report (Cooper 2006). One quarter of patients (24/ 85) who experienced initial good symptomatic response to treatment required *further* treatment with a second line agent. This demonstrates the relapsing, remitting nature of the disease.

For the remaining 25% (43/172) of patients who did not receive very potent topical steroids, a wide range of other first-line topical

treatments were used with varying success. Due to the small numbers that were treated in each category we do not feel that it is possible to draw any conclusions regarding efficacy. One patient did not require any specific treatment for their disease and received only physiotherapy; this is an unusual finding and is not typical for ELPV.

For patients with severe recalcitrant disease requiring systemic treatment, a variety of agents had been used. Although oral corticosteroids were the most frequently used agent, they are not the treatment of choice for long-term control of a chronic disease due to the potential side effect profile. In some centres it is standard practice to initially use oral corticosteroids to induce remission, or 'switch off' the inflammatory process before moving to a more long-term systemic treatment, but this is not the case in all centres. Hydroxychloroquine was the second most frequently used first systemic agent after failure of topical treatment, however, side effects were seen in four patients resulting on discontinuation of the drug in three of these.

The numbers of patients on other systemic agents - immunosuppressants (e.g. mycophenolate mofetil, methotrexate), anti-inflammatory antibiotics (e.g. minocycline, erythromycin) or other agents (e.g. acitretin, dapsone) were relatively few, and varied responses were documented. A small number of patients had been treated with methotrexate, mycophenolate mofetil or

azathioprine for over 12 months, but in other cases these agents were unhelpful indicating the need for more therapeutic evidence in this area (Table 20, page 122).

2.5.1.6 Side effects of therapies

The greatest frequency of side effects, in nearly half with documented use, was seen with the topical immunomodulators - tacrolimus and pimecrolimus. Reports have been published regarding the efficacy of these in ELPV (Kirtschig 2002, Lonsdale-Eccles 2005, Cooper 2006) and oral LP (Volz 2008), although no comparative studies between topical immunomodulators and topical steroids have been reported. The frequency of side effects found by this audit therefore suggests that these may not be a suitable second-line agent for ELPV due to their poor tolerance. Surprisingly few side effects were seen with the potent and very potent topical steroids despite being by far the most frequently used agents. This is reassuring, especially for non-dermatologists managing ELPV patients who may feel less confident in prescribing topical steroids.

2.5.2 Implications for clinical and research practice

Health-related QoL measures as scored by the patient (known as 'Patient Reported Outcome Measures') are important for therapeutic decision-making. They are also fundamental in developing service provision, particularly in smaller subspecialty areas such as vulval dermatology. As vulval diseases cause a reduction in QoL (Sargeant

2007, Hickey 2010) it is necessary that clinicians use patient based assessment tools as part of their monitoring of ELPV.

The fact that ELP is a multisystem disease demonstrates the importance of the managing clinician having a good understanding of its effects so that management of other affected sites is considered where necessary. Although vulval disease is rarely asymptomatic (Cooper 2006), oral and oesophageal involvement (Dickens 1990, Eisen 1999) may be. It is therefore pertinent that physicians perform an oral examination and ask screening questions about dysphagia in all patients.

The development of SCC secondary to LP has been previously documented (Ruocco 1989, Lewis 1994, Dwyer 1995, Cooper 2006, Kennedy 2008) although a formal consensus on whether ELPV is a premalignant condition does not yet exist (Ramos-e-Silva 2010). None the less, these previous reports in conjunction with our findings reinforce the need to discuss potential complications of ELP with patients and their primary health care practitioners.

There is considerable variation in second-line therapy if a patient fails superpotent topical steroids. The findings for the types of systemic agent used are similar to a previously published international survey of ELPV treatments where data were collected in 2004 (Cooper 2008). That survey prospectively collected data from 161 patients by nine physicians in three countries; the United

States (n=106), UK (n=48) and Brazil (n=7). They found that oral prednisolone (12/161) and hydroxychloroquine (7/161) were the most frequently used systemic agents with others such as ciclosporin, methotrexate, doxycycline and minocycline only being used each in 4 patients. The use of systemic treatments was much more common in the USA (29%) than in the UK (8%) and Brazil (0%).

These audit data suggests that clinicians in the UK may now be treating ELPV more aggressively than previously as higher numbers of systemic agents were used. An alternative explanation would be that we have a more representative sample of UK practice by auditing multiple centres.

2.6 Chapter 2 Summary

This audit has provided a comprehensive overview with respect to the current management of ELPV in the UK; results of usual care against the agreed standards are summarized in Table 21 (p124). A wide variation in practice reflected the shortage of published evidence, and subsequent absence of guidance for clinicians when treating ELPV. Although the majority of clinicians used very potent topical steroids as first-line treatment, there was no clear consensus for which second-line treatment was best to use. There was a lack of appropriate documentation of outcome measures in ELPV (and

likely vulval disease in general) and impact of disease on the patient did not appear to be adequately addressed.

Following on from this work, these findings can be used to help the design of a multi-centre randomised controlled trial of treatments for ELPV. A clinical trial is required to addresses the lack of evidence in this neglected area. However, the issue of appropriate outcome measures, participant inclusion criteria and medications to use in a future trial need to be formally addressed prior to protocol preparation.

3 Reducing uncertainties in the management of vulval erosive lichen planus: A qualitative investigation into UK clinician views and principles of management of erosive lichen planus affecting the vulva

3.1 Introduction

Early feasibility work through the multi-centre case note audit described in Chapter 2 showed general agreement on appropriate first-line therapy and recording of clinical findings in ELPV, but there were shortfalls in assessing disease impact, inconsistencies in determining response to treatment and variation in choice of second-line therapies.

The qualitative work described in this chapter involved structured interviews with clinicians. This work sought to reduce treatment uncertainties and was also an opportunity to engage with UK clinicians to increase awareness of this project and assess potential willingness to participate in a future trial. This qualitative work involved collaboration with clinicians from a variety of different settings, ranging from tertiary referral centres to district general hospitals. The reason for this was to determine whether the case note audit findings were representative of UK management as a whole and to obtain further information to inform the design a pragmatic RCT protocol.

3.2 Aims

To assess how clinicians make the diagnosis of ELPV, prescribe therapies, record therapeutic responses and make the decision to escalate therapy.

The overall purpose was to assess feasibility and inform the design and conduct of a future RCT of treatments for ELPV.

The structured interviews were designed to assess the diagnostic criteria and outcome measures that other clinicians employ in usual practice and to help define which treatments should be assessed in the planned RCT. Furthermore, engaging with other UK clinicians was a method to improve collaborative links and identify potential recruitment sites for the eventual trial.

The objectives of the study were to ascertain:

- How clinicians make the diagnosis of ELPV;
- Which outcome measures (Clinical and patient oriented) are perceived as important for use in a clinical trial;
- Which first and second-line treatment approach do the clinicians take for ELPV;
- Which factors make a clinician move to a second line therapy;
- Which doses of systemic agents tend to be used;
- Which, if any, restrictions are there in individual centres for using certain systemic agents.
- Which medications clinicians feel comfortable in prescribing for patients with ELPV;

- Would clinicians be willing to randomise patients to a trial where that includes a control arm?

3.3 Materials and methods

This was a multi-centre study involving clinicians from secondary care settings who regularly treat patients with vulval disease. Participants were asked to take part in a one-off structured telephone interview lasting 15-20 minutes. Interviews were recorded manually. The questionnaire proforma is in Appendix 3.

Research participants were all members of NHS staff, and so ethical approval was not required as participation in research is considered part of their professional role. Interviews specifically did not discuss any personal or identifiable patient information and only theoretical issues regarding management of ELPV were covered.

3.3.1 Recruitment

Clinicians were recruited from secondary care settings. As ELPV is a rare condition that requires specialist management, patients with ELPV are predominantly managed in secondary care. The initial approach was through the departmental secretary where information about the study was verbally communicated. A subsequent email/fax documenting the purpose of the study and inviting the clinician to participate was then sent.

Clinicians who have dedicated outpatient services, as well as those who treat vulval patients as part of their general outpatient practice were approached. Participants were identified from multiple disciplines including dermatology, gynaecology and genitourinary medicine.

3.3.2 Interview conduct

An appropriate date and time was arranged and the telephone interview was performed using a structured method with a standardised proforma to ensure that all relevant areas were covered. The interviewer asked a range of open and closed questions that explored clinicians' background, beliefs, experiences and opinions regarding aspects of ELPV and its management.

3.3.2.1 Analysis

Recorded notes were transcribed. Transcriptions of open questions were typed in full and analysed thematically. Questions with a choice of answers were inputted into an Excel spreadsheet and analysed quantitatively.

3.4 Results

The telephone numbers of 80 departments were identified using the NHS choices website (Figure 19, page 138). Thirty of these numbers were either incorrect or not answered, despite leaving answer phone messages where possible. Of the remaining 50 centres that were

successfully contacted, 44 agreed for an explanatory email/facsimile to be sent to the relevant consultant. Of these, 25 agreed to participate in the study, which represented a wide geographical area (Figure 20, p139). Interviews were carried out from December 2011-March 2012.

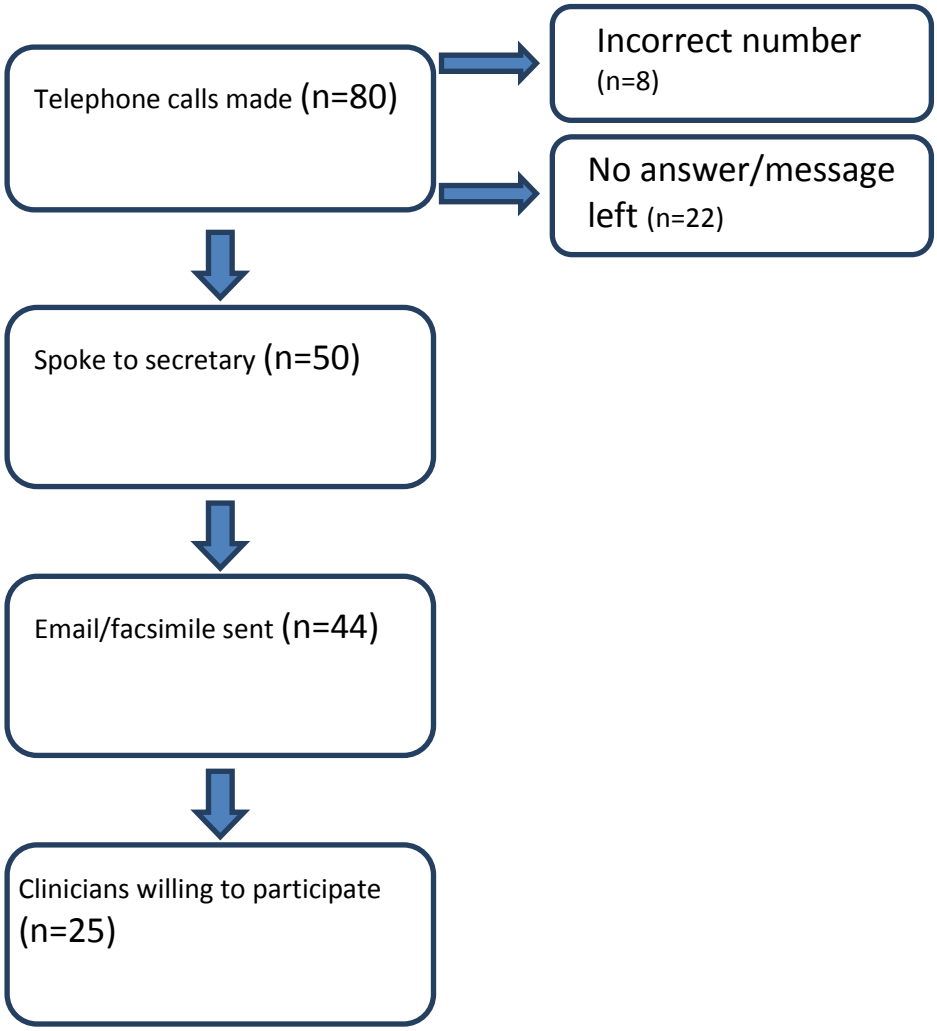

Figure 19: Structured interview Results: Flow chart demonstrating recruitment process

Figure 20: Structured interview Results: Map of United Kingdom demonstrating location of participating centres.

3.4.1 Demographic details

Respondents were dermatologists (22/25, 88%) and gynaecologists (3/25, 12%). Of these, 15/25 (60%) were members of the British Society for the Study of Vulval Disease (BSSVD) and 3/25 (12%) were also International Society for the Study of Vulvovaginal Disease (ISSVD) members. There was a combination of those who worked in Teaching (14/25, 56%) and in District General Hospitals (11/25, 44%). The majority of participants worked in specialist vulval disease clinics (19/25, 74%. Four of these were multidisciplinary clinics). Most participants saw more than 20 patients per month with vulval skin disease (Table 22, page 141) although the number of patients with ELPV varied (Table 23, p141).

Vulval patients seen/month	Number of centres
0-10	1
11-20	4
21-30	6
31-40	2
>40	5
Unsure	7

Table 22: Structured interview Results: Number of vulval patients seen per month by participants (estimate)

ELPV patients (approx. total number)	Number of centres
0-5	5
6-10	3
11-15	0
16-20	4
>20	1
Unsure	12

Table 23: Structured interview Results: Number of ELPV patients managed by participants (estimate)

3.4.2 Initial thoughts on treating ELPV

The overwhelming theme was that ELPV is a difficult disease to treat and patients are often resistant to therapy.

Other themes that emerged were regarding the **poor prognosis**, **difficulty in making a diagnosis** and **potential complications** from the disease, including scarring and sensory problems such as vulval pain syndromes.

3.4.3 Follow up arrangements

The majority of clinicians followed up patients long-term (18/25, 72%). The reasons for this were that this is a chronic disease which is often difficult to control (8/18, 44%), risk of malignancy (1/18, 6%), and a combination of poor treatment response/concerns about malignancy (9/18, 50%).

The remainder of clinicians would only follow up long-term if control was poor and the patient required ongoing support (6/25, 24%). One respondent did *not* follow up long-term as they believed the disease responded to treatment given and therefore follow up was not required.

3.4.4 Clinical and histological features required to make the diagnosis

A number of clinical criteria were given with most respondents wanting to see a combination of diagnostic features to make a clinical diagnosis. The most commonly sought characteristics were erosions (10/25, 40%), specifically vaginal introital erosions (5/25, 20%), scarring/architectural change (7/25, 28%) and presence of a white hyperkeratotic edge to lesions or Wickham's striae (5/25, 20%). Other clinical features cited were a glazed appearance to the vaginal mucosa (3/25, 12%), excruciating pain (3/25, 12%) and vaginal involvement (2/25, 8%). Two respondents were not willing to commit to specific clinical criteria.

A biopsy was performed as part of routine practice by 16/25 (56%) of clinicians and in cases of diagnostic doubt/poor treatment response by 9/25 (36%). In addition some clinicians recommended that a specimen should be sent for direct immunofluorescence (3/25, 12%).

Respondents were more hesitant to commit to specific pathological criteria. Over half (13/25, 52%) commented that typical features are not often seen on biopsy and felt that clinical findings are the most important factor in making a diagnosis. The most common diagnostic histological feature sought was the presence of a lichenoid infiltrate on biopsy (10/25, 40%). The role of a

multidisciplinary approach with specific pathology review was highlighted by 4 clinicians. Three respondents were not willing to commit to histopathological features.

3.4.5 Assessment of severity in clinical practice

None of the respondents used a specific tool for assessing severity in clinical practice. The most common *clinical* method was through drawing a diagram in the notes (9/25, 36%). A broad physician assessment of severity using a global measure (mild/moderate/severe) was used by 20% (5/25) and clinical images by a further 20%. In addition a further four clinicians would preferably use medical photography if they had access to this resource in their department.

Only 5/25 (20%), used a specific tool to assess impact of disease on the patient (Dermatology Life Quality Index (DLQI) 3/25, Hospital Anxiety and Depression Scale (HADS) 2/25). The main focus of management was to preserve an acceptable level of functioning (18/25, 72%) and respondents specifically identified sexual function, micturition, defecation and ability to wash as important outcomes to assess. Disease impact was not routinely assessed by 8/25 respondents (32%).

3.4.6 Assessment of severity for clinical trial purposes

The majority of respondents felt that the most important clinical trial outcome (Table 24, page 146) should be an assessment of function (13/25, 52%) and the most popular tool to measure this was suggested as the DLQI (11/25, 44%). An objective clinical outcome was suggested by 28% (7/25) and a combination of function/clinical signs was suggested by 16% (4/25). A variety of other outcomes were suggested. In particular two clinicians stated that they 'would like to see a specific vulval outcome scale' developed.

Table 24: Structured interview Results: Outcomes considered to be measured as a minimum requirement for patients with vulval erosive lichen planus.

Outcome measures	**N**
Clinician-assessed:	
Reproducible objective clinical outcome measures e.g. Physician Global Assessment, Clinical Images	8
Topical steroid usage	2
Number of other sites involved by lichen planus e.g. oral cavity	2
Time to heal	1
Presence of malignant/pre-malignant change	1
Patient-assessed:	
Functional ability e.g. sexual function	13
Specific validated scales suggested:	
Dermatology Life Quality Index	11
Visual Analogue Scale of symptoms	6
Hospital Anxiety and Depression Scale	3
Female Sexual Function Index	2

3.4.7 Treatment approach

3.4.7.1 First-line therapy

In keeping with the case note audit results, the majority of respondents used super-potent topical steroids as first-line therapy (96%, 24/25). One used an alternating regimen of a super-potent topical steroid with a less potent topical steroid/antimicrobial preparation. Intravaginal steroids were specifically used by 44% (11/25) for vaginal disease and 4% (1/25) additionally used topical anaesthetic as part of their standard practice.

3.4.7.2 Second-line therapy

Considerable variation occurred with the use of second-line therapies. A change of topical steroid preparation was suggested by 8/25 (32%) before moving onto a systemic treatment. Prednisolone was used by 8/25 (32%) to achieve remission before converting to an alternative systemic agent, whereas 4 /25 (16%) used an alternative systemic agent immediately post topical treatment. One stated that they had 'no set regimen' and one stated that systemic treatment was not effective or required in ELPV as topical therapy always gave success.

Gynaecology respondents (3/25) all stated they would refer onto their dermatology colleagues following failure of first-line therapy.

3.4.7.3 Follow up arrangements

Follow up arrangements were variable depending upon severity of disease and the treatments being used. In general, initial follow up between 2-3 months was acceptable for 16/25 (56%) clinicians. One hospital used a telephone follow up two weeks after commencing therapy which was followed up by an outpatient appointment at the three-month time point. 4/25 (16%) followed up at one month and 4/25 (16%) stated it depended entirely on the treatment being prescribed. One respondent made no comment.

3.4.7.4 Factors for escalating treatment

The main reason for escalating treatment was based on symptoms alone (14/25, 56%) and a combination of symptoms and appearance in 5/25 (20%). No comment was made by 3/25 (12%), and a further 2/25 (8%) stated that they 'do not escalate care' .The final participant stated that escalation was due to a 'clear lack of response'. Since the second-line medical treatment for EVLP is usually prescribed by physicians it is unlikely that gynaecologists would escalate care and it is possible there is also some reluctance with GUM physicians.

3.4.7.5 Systemic treatments for potential use in RCT

The multi-centre case note audit (Chapter 2) identified a number of systemic treatments that were used more frequently than others in ELPV resistant to topical therapy. These were prednisolone,

hydroxychloroquine, methotrexate, mycophenolate mofetil, acitretin and minocycline (+/- nicotinamide). It is important to reiterate that prednisolone is not appropriate for long term management of a chronic disease due to its side effect profile.

Gynaecologists were not comfortable prescribing any of the systemic agents as they do not use these in day to day practice. Of the remaining 22 respondents who were dermatologists, 10 did not use minocycline/minocycline and nicotinamide in their usual dermatological practice due to potential side effects.

None of the clinicians had witnessed patients with *unexpected* adverse effects from any medications on the list; all had been predictable due to the drugs' documented side effect profile. All respondents prescribed these treatments according to national guidelines (British Association of Dermatologists or British National Formulary). The only restrictions in usage of the systemic treatments were of mycophenolate mofetil (n=1) and minocycline (n=1) in individual centres.

For the treatment of ELPV, respondents would not routinely use acitretin (6/25, 24%), hydroxychloroquine (1/25, 4%) or minocycline (2/25, 8%)) as a treatment. For clinical trial purposes, four respondents would be put off recruiting patients into a RCT if acitretin was one of the trial arms and one would be put off if hydroxychloroquine was being used. One clinician commented that

the costs of the trial treatments would be a potential barrier for recruitment and one stated that they would not participate into a trial using systemic treatments for ELPV.

All clinicians prescribed the relevant systemic medications according to national guidelines from the British Association of Dermatologists and the British National Formulary. The only variation was with Acitretin, which was often commenced at a low dose due to its potential mucocutaneous side effects.

3.4.7.6 Washout period for systemic therapy

In practice, 15/22 (65%) dermatologists did not leave a specific washout period when transitioning between systemic agents. 17% (4/22) stated that the washout would depend upon the specific agent. The remaining respondents stated they leave a period of 4 weeks (1/22, 5%) or made no comment (2/22, 9%).

For clinical trial purposes, there was no agreement on the optimum washout period required, however five respondents stated that to be pragmatic, treatment should be transitioned as quickly as possible. Many (11/22, 50%) were not willing to give a definite answer, 6/22 (27%) felt it depended entirely upon the drug, 2/22 (9%) stated one-month should be left and 1/22 (5%) stated that three-months should be left as washout period.

3.4.7.7 Vulval skin care regimen

All clinicians agreed that topical and systemic therapy should be administered in conjunction with a vulval skin care regimen. There were a range of emollient and soap substitute regimens adopted by the respondents in their normal practice. The majority (18/25, 72%) felt that the specific regimen should not be prescribed for a trial and the recommended agent should be at the discretion of the managing consultant.

3.4.7.8 Trial design and participation

Almost all respondents (21/25, 84%) were willing to be consulted regarding a RCT protocol. If one of the trial arms was placebo (but continuing topical steroids), 17/25 (68%) would be willing to recruit to such a trial. A further three stated that their decision would depend upon the overall trial design. However, three stated that they would not be willing to recruit if this were the case. One participant gave no comment and one would not consider recruiting to a trial involving systemic therapy at all.

3.5 Discussion

3.5.1 Main findings

Most physicians diagnosed ELPV based upon clinicopathological correlation. Features including vaginal introital erosions with a white edge, scarring and architectural change, were frequently sought

clinical features. Most physicians in this sample performed a biopsy as part of routine clinical practice, although there was recognition that pathognomonic histological findings are not always found. Those who did not perform biopsy as routine practice did so to exclude other vulval pathology. Since the histology is often non-specific, it may be beneficial for clinicians to discuss their cases with a histopathologist in a multidisciplinary setting, as was described by several participants.

In the absence of vulval-specific outcome measure tools, methods of recording severity vary. One third of participants did not formally assess the impact of disease on the patient, although the patient symptoms were reported to drive the escalation of treatment. This suggests that physicians are thinking about impact of disease, even if it is not formally documented. Of those who did assess impact, the most common method was to assess functional impairment with a DLQI (Finlay 1994, www.dermatology.org.uk/quality/dlqi). Although the DLQI is a commonly used and convenient dermatological health-related QoL tool, recent studies have suggested it is suboptimal in assessing individuals with mild disease (Fernandez-Penas 2012, Twiss 2012) and in comparing different diseases and different patient populations (Twiss 2012). Furthermore, the DLQI does not assess micturition, defecation or washing ability, all items that were identified as important functional outcomes by respondents.

Overall, patient-reported outcomes were a popular method for assessing disease severity. This is most likely because anecdotally, clinical signs lag behind symptomatic recovery. Hence, the main driver for escalation of therapy is patient-reported symptoms, not clinical appearance.

The use of super-potent topical steroids as first-line therapy and lack of agreement for second-line therapy was in keeping with the published literature (Cooper 2006, Simpson 2012). For patients resistant to super-potent topical steroids, some clinicians use an alternative topical agent, some attempt remission with oral corticosteroids and some move straight to longer term anti-inflammatory/ immunosuppressant systemic medications.

3.5.2 Strengths and weaknesses

This study takes into account the views of 22 dermatologists and three gynaecologists working in UK secondary care. These numbers are only a small sample of the total number of physicians who make up these groups. In order to obtain a broad idea of whether practice was the same in different environments, physicians from different specialties and settings were invited to participate. Three quarters of those who responded managed patients in a specialist vulval disease clinic. Therefore, data obtained are likely representative of those who feel confident in managing vulval skin disease and see such patients on a regular basis, rather than representing the wider

clinical community. Gynaecology participant numbers were small, but their practice was similar to that of dermatologists in that they were confident in diagnosing ELPV clinically and commencing therapy, however, patients who did not respond to initial therapy were referred onto dermatology colleagues.

3.5.3 Implications for clinical practice

As it is a chronic disease with poor response to treatment and perceived risk of malignant transformation, most clinicians follow up their patients long-term. Therefore, clusters of patients with ELPV are likely to be found at centres across the UK.

Pitfalls in managing difficult cases were highlighted, in particular, the need to look out for secondary vulvodynia as a cause of ongoing pain in patients whose clinical signs are improving. This should clearly be managed in a different way to ELPV.

3.5.4 Implications for this research project

For clinical trial purposes, patient-related outcomes were the most favoured method of assessment with an objective method of clinical assessment being rated less important. This is most likely because clinical signs do not always match symptoms, and improvement of visual appearance often lags behind symptomatic recovery. Of interest, the main driver for escalation of treatment was described as patient-reported symptoms, not clinical appearance. However,

thorough clinical assessment to exclude secondary infection, allergy and malignant transformation, and exclusion of secondary vulvodynia are always needed before there is any escalation of treatment.

It is important that when determining appropriate outcome measures for this condition this is taken into account.

3.6 Chapter 3 Summary

Having engaged with clinicians from a variety of different clinical settings, it was clear that treating ELPV is difficult, but there was a collective sense of enthusiasm to provide good quality RCT evidence for treating resistant cases.

To further knowledge about treatment of ELPV, a collaborative approach will be required to run multicentre studies. It is apparent that management differs between centres, and a pragmatic approach needs to be adopted for studies to be successfully run amongst busy outpatient clinics.

A set of diagnostic criteria acceptable to the clinical community for inclusion into a trial and outcome measures that are relevant to patient and clinician needs should be devised before definitive therapeutic randomised controlled trials can be performed.

4 Diagnostic Criteria for Erosive Lichen Planus Affecting the Vulva: An international electronic-Delphi Consensus Exercise.

4.1 Introduction

Published literature suggests that most clinicians managing vulval diseases would diagnose ELP affecting the vulva (ELPV) following careful clinico-pathological correlation (Ball 1998). This was reinforced by findings from the structured interview process described in Chapter 3.

Oral lichen planus, has a defined set of diagnostic criteria that was set out by the World Health Organisation in 1978 (and subsequently modified in 2003 (van der Meij 2002)), but the same does not exist for vulval erosive lichen planus.

ELPV may mimic other conditions such as lichen sclerosus (for which it may overlap clinically and histopathologically (Marren 1994, Niamh 2009, McPherson 2010)), autoimmune bullous disorders and intraepithelial carcinoma (McPherson 2010). The diagnosis can therefore be challenging (see section 1.5.2, page 36).

Early recognition of ELPV is important to minimise unnecessary medical or surgical procedures and to instigate prompt treatment and alleviation of symptoms (Pelisse 1989, Eisen 1999). However, ELPV may present to a range of specialties such as general dermatology, gynaecology and genitourinary medicine, where variation in diagnosis and management exists (Simpson 2012). An agreed diagnostic dataset would be valuable to standardise practice,

assist non-experts in making a correct diagnosis and to regulate inclusion into clinical trials.

4.2 Aims

The purpose of this international, multiperspective, electronic-Delphi (e-Delphi) consensus exercise was to reach agreement on a diagnostic dataset for ELPV that is acceptable to the international clinical community.

4.3 Materials and methods

4.3.1 Study type

This was a three-stage, international electronic-Delphi exercise that was conducted between October 2012 and December 2012. A formal feedback process was undertaken and results generated from the process were circulated to participants for comments. All communication occurred electronically and the process was moderated by a single central coordinator (RS).

The Delphi process is widely used in clinical and health services research (Vernon 2009); it is an iterative technique based upon the scoring of a series of structured statements which are revised and repeated until consensus has been reached amongst a panel of expert participants (Murphy 1998). It is a method that has been used for establishing diagnostic criteria (Turoff 1970, Graham

2003). This study was conducted as an electronic-Delphi (e-Delphi) process.

4.3.2 Participants

A letter of invitation was emailed to all members of the International Society for the Study of Vulvovaginal Disease (ISSVD, see section 1.7.1, page 47) and members of the British Society for the Study of Vulval Disease (BSSVD, see section 1.7.2, page 47). These multidisciplinary societies enabled international collaboration with experts from different stakeholder groups who manage vulvovaginal disorders. Members of these societies were identified as ideal participants of this e-Delphi study as they represent professionals with a specialist interest in vulval skin conditions who would adopt the outcomes of the Delphi study in their daily practice and they were capable of making an insightful, well-informed contribution to the exercise.

4.3.3 Study procedures

Findings from the literature review (Chapter 1) and structured interviews (Chapter 3) were used to provide an evidence base for the consensus process. Results from the two exercises were collated to form a structured questionnaire that contained a list of 12 potential diagnostic criteria required for the diagnosis of ELPV. The study protocol was finalised in September 2012.

An invitation letter containing background information, study aims and an explanation of how to participate was sent out via email to all members of the ISSVD and BSSVD. Recipients were asked to declare an expression of interest, via email, to the study coordinator. No inconvenience allowance was offered and response to the initial invitation was taken as implied consent to participate in the study. The coordinator was required to know participants' details for administrative purposes. The exercise was otherwise conducted anonymously. Participants were asked specifically for their consent to be acknowledged in future presentation or publication.

Questionnaires were completed using the online tool 'Survey Monkey' (www.surveymonkey.com). A two-week period for each round was given in which participants could submit their responses (Hsu 2007). Reminders for each round were sent at seven, 10 and 14 days to those that had not responded to the surveys.

4.3.3.1 Round 1

In the first round of the e-Delphi exercise (Appendix 4), participants were asked to rate the importance of the selected 12 diagnostic criteria on a five-point Likert scale. The scale's five categories consisted of *'very important';' important'; 'less important'; 'not important' and 'not sure*'. When discussing histological criteria, it was specified that biopsy samples should be taken from the edge of an erosion where more representative histology would more likely

be present. Contributors were then asked to list any additional diagnostic features that they considered relevant that were not in the original list.

4.3.3.2 Round 2

Following analysis of round one, the survey instrument was amended to create the round two questionnaire (Appendix 5). Diagnostic items that were rated by consensus as '*not important*' were removed and additional diagnostic items were incorporated into the questionnaire. Due to a number of comments regarding nomenclature of the condition, a question on disease terminology was also included in round two. Participants received feedback on the group's overall scores from the previous round. In the second round, respondents could submit new answers, or leave their original responses unchanged. The same process of analysis and amendment of survey instrument occurred to create the round three questionnaire (Appendix 6).

4.3.3.3 Round 3

In the third round participants were asked to rate the diagnostic criteria that had reached consensus as important as '*essential'*, '*supportive'* or '*neither*'. '*Essential'* was defined as a diagnostic feature that must be present to make a diagnosis of ELPV. '*Supportive'* was defined as a feature that does not have to be present, but adds weight to other diagnostic features that are

present. Participants were also asked how many essential and/or supportive diagnostic criteria should be present to make a diagnosis of ELPV.

It was made clear throughout all rounds if questions had been amended, added or excluded following analysis of previous rounds. Participants were given the opportunity to comment on any of these amendments.

4.3.3.4 Feedback

After completion and analysis of all three rounds, the findings were circulated for formal feedback and comments from the participants (Appendix 7). The feedback round was not mandatory although participants were encouraged to complete the questionnaire.

4.3.4 Definition of consensus

Consensus was defined as being where 75% of participants agreed on the importance of an item i.e. rated '*very important'* or '*important*' on the Likert scale, or agreed whether an item should be '*essential'* or *supportive'* . As a soft measure of consensus to avoid premature exclusion of diagnostic items, we also carried through items that less than 25% participants rated '*not important'* or *'unsure'*. Diagnostic criteria that did not achieve consensus in this way were excluded from subsequent rounds of the exercise.

4.4 Results

4.4.1 Demographic data

The letter of invitation was circulated to 283 members of the International Society for the Study of Vulvovaginal Disease and 175 members of the British Society for the Study of Vulval Disease. Some physicians were members of both societies but for confidentiality reasons these data are unknown. An expression of interest was received by 87 physicians; a total of 73 individuals participated in the first round. Of these, 71 (97.2%) completed the second round and 69 (95%) completed the final round. The formal feedback survey, which was optional, was completed by a total of 54 participants.

Participants represented four distinct stakeholder groups and were from 14 different countries. Characteristics of participants are in Table 25, p166. The majority had over ten years' experience in managing patients with vulval skin disease and 88% respondents were either Professors or Consultants in their field.

	No. participated in Round 1 (%)	No. participated in Round 2 (% response rate)	No. participated in Round 3 (% response rate)
Total participants in round	**73**	**71**	**69**
Stakeholder group			
Dermatology	30 (41.7)	30 (42.3)	30 (43.5)
Gynaecology (+/- Obstetrics)	30 (41.7)	28 (39.4)	26 (37.7)
Histopathology/ Dermatopathology	7 (9.7)	7 (9.9)	7 (10.1)
Genitourinary medicine/venereology	6 (8%)	6 (8.5)	6 (8.7)
Grade			
Professor/Associate Professor	19 (26)	18 (25.3)	17 (24.6)
Consultant	45 (61.6)	45 (63.3)	45 (65.2)
Associate Specialist	6 (8.2)	5 (7)	4 (5.8)
Resident/Specialist Registrar	2 (2.7)	2 (2.8)	2 (2.9)
Specialist Nurse	1 (1.4)	1 (1.4)	1 (1.4)
Country			
Argentina	2	2	2
Australia	7	7	7
Canada	3	3	3
Denmark	1	1	1
France	2	2	1
Germany	1	1	1
Israel	1	1	1
Italy	2	2	2

Netherlands	3	3	3
New Zealand	1	1	1
Portugal	1	1	1
UK	34	33	32
US	14	13	12
Uruguay	1	1	1
Duration of Experience			
< 5 years	11 (15.3)	8 (11.3)	7 (10.1)
6-10 years	12 (16.7)	13 (18.3)	12 (17.4)
11-15 years	15 (20.8)	15 (21.1)	14 (20.3)
16-20 years	18 (25)	18 (25.4)	22 (31.9)
> 20 years	17 (23.6)	17 (23.9)	14 (20.3)

Table 25: Characteristics of participants in the e-Delphi exercise

4.4.2 Refinement of diagnostic criteria

Following the first round, two additional clinical and three additional histopathological items were added to the second round questionnaire. In addition, the wordings of four questions needed to be amended for clarity.

After the first and second rounds, six potential diagnostic criteria were removed from the final dataset as participants answers indicated these were not important features in diagnosing ELPV (Table 26, p169).

There were ten diagnostic features (six clinical and four histopathological) that reached consensus, or soft consensus, and were carried through for final approval in the third round (Table 27, p171).

In the third and final round, participants were asked to rank items as 'essential' or 'supportive' diagnostic criteria, or neither (Table 28, p172). No diagnostic indicator reached consensus as being 'essential'. There were three definite 'supportive' criteria, where >75% respondents agreed on the same answer. One item was not favoured as being in the final diagnostic dataset; this was '*the absence of dermal hyalinisation*' on histopathological examination, where 29.4% of respondents classified it as neither an 'essential' nor a 'supportive' diagnostic feature. The remaining five diagnostic

items were recommended as being supportive diagnostic criteria (Table 28, p172). The resulting diagnostic dataset therefore consisted of nine criteria that represent the clinicopathological features of erosive lichen planus. Of the 54 participants who provided feedback 92.6% were in agreement with this dataset.

When asked how many diagnostic features should be present to diagnose ELPV, consensus was reached for three supportive features needing to be present. However, results from participant feedback were not so decisive and opinion was divided between three or four of the nine supportive features being required (Table 29, page 173). Some participants also suggested that clinical and histological criteria should be separate, or that criteria should be weighted as some are considered more important than others.

Diagnostic item	Responses Number of responses (%)				
	Very important	Important	Less important	Not important	Not sure
Excluded after Round 1					
Presence of symmetrical lesions	2 (2.7)	9 (12.3)	30(41.1)	30 (41.1)	2 (2.7)
Presence of vaginal discharge	1 (1.4)	10 (13.7)	30 (41.1)	30 (41.1)	2 (2.7)
Presence of pain on Q-tip pressure	2 (2.7)	8 (11)	21 (28.8)	38 (52.1)	4 (5.5)
Excluded after Round 2					
Findings on wet mount preparation	2 (2.8)	5 (7)	27 (38)	28 (39.4)	9 (12.7)
Presence of epidermal changes on histopathological examination	5 (7)	20 (28.2)	25 (35.2)	8 (11.3)	13(18.3)
Direct immunofluorescence	3 (4.2)	12 (16.9)	29 (40.8)	20 (28.2)	7 (9.9)

Table 26: Diagnostic criteria excluded after the first and second e-Delphi rounds.

N.B Criteria were excluded if >25% participants considered them as 'not important' or 'not sure'

Diagnostic item	Responses				
	Very important	Important	Less important	Not important	Not sure
Clinical					
Presence of well demarcated erosions or glazed erythema at the vaginal introitus	41 (57.7)	26 (36.6)	0 (0)	1 (1.4)	3 (4.2)
Scarring/loss of normal architecture	13 (18.3)	46 (64.8)	10 (14.1)	0 (0)	2 (2.8)
Presence of a hyperkeratotic white border to erythematous areas/erosions +/- Wickham's striae in surrounding skin	9 (12.7%)	37 (52.1)	21 (29.6)	2 (2.8)	2 (2.8)
Presence of vaginal inflammation +/- vaginal scarring	7 (9.9)	20 (28.2)	34 (47.9)	8 (11.3)	2 (2.8)
Involvement of other mucosal sites e.g. mouth, oesophagus	13 (18.3)	31 (43.7)	21 (29.6)	4 (5.6)	2 (2.8)
Symptoms of pain/burning	16 (22.5)	32 (45.1)	18(25.4)	28 (39.4)	9 (12.7)
Findings on wet mount preparation	2 (2.8)	5 (7)	27 (38)	28 (39.4)	9 (12.7)
Histopathological					
Presence of a well-defined inflammatory band in the superficial connective tissue that involves the dermo-epidermo junction	27 (38)	40 (56.3)	3 (4.2)	0 (0)	1 (1.4)
Presence of an inflammatory band that consists	6 (8.5)	60 (84.5)	3 (4.2)	0 (0)	2 (2.8)

predominantly of lymphocytes					
Signs of basal cell layer degeneration e.g. Civatte bodies, abnormal keratinocytes or basal apoptosis	13 (18.3)	47 (66.2)	7 (9.9)	0 (0)	4 (5.6)
Absence of dermal hyalinisation	8 (11.3)	17 (23.9)	29 (40.8)	3(4.2)	14 (19.7)
Epidermal changes e.g. wedge shaped hypergranulosis, saw toothed acanthosis	5 (7)	20 (28.2)	25 (35.2)	8 (11.3)	13 (18.3)
Findings on direct immunofluorescence	3 (4.2)	12 (16.9)	29 (40.8)	20 (28.2)	7 (9.9)

Table 27: e-Delphi round two results.

N.B Items that reached consensus as important (i.e. where >75% participants rated 'very important' or 'important') were carried through into the final round (white background). Items which did not meet this cut-off, but where <25% participants rated 'not important', or 'not sure', were also carried through as a measure of 'soft consensus' (blue background). The remaining items were dropped following round 2 (red background).

Diagnostic item	Essential	Supportive	Neither
Presence of well demarcated erosions or glazed erythema at the vaginal introitus	44 (63.8)	24 (34.8)	1 (1.4)
Presence of a hyperkeratotic white border to erythematous areas/erosions +/- Wickham's striae in surrounding skin	8 (11.6)	57 (82.6)	4 (5.8)
Symptoms of pain/burning	13 (18.8)	47 (68.1)	9 (13)
Scarring/loss of normal architecture	10 (14.5)	55 (79.7)	4 (5.8)
Presence of vaginal inflammation	7 (10.1)	48 (69.6)	14 (20.3)
Involvement of other mucosal sites	1 (1.4)	66 (95.7)	2 (2.9)
Presence of a well-defined inflammatory band in the superficial connective tissue that involves the dermo-epidermo junction	37(53.6)	32 (46.4)	0(0)
Presence of an inflammatory band that consists predominantly of lymphocytes	30 (43.5)	37 (53.6)	2 (2.9)
Signs of basal cell layer degeneration e.g. Civatte bodies, abnormal keratinocytes or basal apoptosis	24 (34.8)	43 (62.3)	2 (2.9)
Absence of dermal hyalinization	11 (15.9)	38 (55.1)	20 (29)

Table 28: e-Delphi round three results - essential and supportive diagnostic criteria and final diagnostic dataset.

N.B. Items that reached agreement to be in the final diagnostic dataset are with a white background. The item that did not reach consensus and was subsequently has a red background.

Number of criteria from final diagnostic dataset	Response count	Response percent (%)
≥ 1	3	5.8
≥ 2	3	5.8
≥ 3	15	**28.8**
≥ 4	17	**32.7**
≥ 5	7	13.5
≥ 6	5	9.6
≥ 7	1	1.9
≥ 8	0	0
9	1	1.9
TOTAL	**52**	**100**

Table 29: e-Delphi feedback survey – number of diagnostic criteria needed to confirm vulval erosive lichen planus

Categories with the greatest number of responses were ≥ 3 and ≥ 4 and are highlighted in red

4.4.3 Requirement for histopathological examination of affected tissue

During the exercise, participants were also asked about the importance of performing a diagnostic biopsy for ELPV. The majority (36/69, 52.2%) responded that a diagnosis of ELPV does *not* always have to satisfy clinical and histopathological criteria. However, 63/69 (93.1%) acknowledged that a biopsy should be performed if there was diagnostic uncertainty or concern of neoplastic change. During group feedback, the main differential diagnoses that could potentially cause diagnostic difficulty were identified as lichen sclerosus and mucosal autoimmune bullous disorders (Table 30, p175).

Differential Diagnosis	Number of participants
Lichen Sclerosus	27
Autoimmune blistering diseases (MMP, PV, BP)	22
Plasma Cell Vulvitis/Zoon's vulvitis	9
Eczema/contact dermatitis	6
Atrophic vaginitis	5
Cancer/VIN	5
Desquamitive Inflammatory Vaginitis	5
Drugs/Fixed Drug Eruption	5
'Vulvovaginitis'	3
Infection	3
SLE	3
HSV infection	2
Psoriasis	2
Vulvodynia	2
Amyloidosis	1
Behcets disease	1
Crohns disease	1
Extramammary Paget's Disease	1
GVHD	1
Lichen Simplex chronicus	1
Pyoderma Gangrenosum	1

Table 30: Differential diagnoses for ELPV that were offered by the 54 participants in the e-Delphi Feedback Round.

N.B. 47 participants offered more than one differential. MMP = mucous membrane pemphigoid; PV = pemphigus vulgaris; BP = bullous pemphigoid

4.4.4 Nomenclature

Anxiety regarding nomenclature of the condition was expressed in the first round. This led to the addition in the second round of a specific question about terminology. Participants were asked "*what is the best nomenclature for the finding of painful erosions/glazed erythematous lesions at the vaginal introitus (+/- vaginal involvement)".* Based upon comments from the first round, three options were given: i) Vulval erosive lichen planus; ii) vulvovaginal erosive lichen planus and iii) vulvovaginal lichen planus. These scored 29.6%, 52.1% and 18.3% of responses respectively. Therefore consensus was not reached and many commented that the nomenclature should depend upon the individual clinical context. For the purposes of the exercise the original phrase '*erosive lichen planus of the vulva* (*ELPV*)' was used, although it was acknowledged that not all patients have true erosions and some may have more extensive mucosal involvement. In practice it seems that physicians will use the diagnostic expression 'erosive lichen planus of the affected sites e.g. '*Erosive lichen planus of the vulva and vagina'* or '*erosive lichen planus of the vulva and gingiva*' etc.

4.5 Discussion

4.5.1 Main findings

This exercise enabled the collation of a set of nine diagnostic criteria defined by experts as supportive of the diagnosis of ELPV (Figure

21, p183). It was agreed at the third round that *three or more* of these supportive features were required to diagnose ELPV and these can be a combination of both histological and clinical features. However, feedback from participants suggested that more focused work is required to determine whether this is the optimum number of features and whether the individual features should be weighted.

The consensus exercise did not identify any essential diagnostic criteria. The term 'essential' is a powerful word and may have been interpreted by participants as being synonymous with 'always'. The diagnostic feature that was closest to reaching consensus as 'essential', with 63.8% of responses, was well-demarcated erosions/glazed erythema at the vaginal introitus. In some cases patients may have only vaginal disease without any external signs. It was commented by some physicians that this was the reason they did not rate introital erosions as essential.

As ELP can affect a variety of mucosal surfaces one nomenclature does not necessarily fit all presentations of the disease. Furthermore, erosions are secondary to intense inflammation and in some cases only glazed erythematous areas are seen (Kirtschig 2005). This caused debate amongst participants as to whether the term 'erosive' was technically correct. The final dataset took this discrepancy into account by wording the relevant diagnostic criteria as *'well demarcated erosions **or** glazed erythema'.*

The nomenclature of this condition is likely to remain controversial; although the term '*erosive lichen planus*' was considered inaccurate by some, '*lichen planus'* as a standalone saying is usually reserved for disease affecting keratinising epithelium, which has a very different natural history and response to therapy than the mucosal variant (as described in section 1.2.1, page 12).

4.5.2 Strengths and limitations of the study

The 'e-Delphi' method was used to answer a research question that required specialist input from the clinical community as these data were not available in the existing literature. This was a modification of the original description of the Delphi method that was first used in the 1950s (Murphy 1998). The present study involved communication with participants electronically rather than by post.

The Delphi technique is characterised by four core features: involvement of an expert panel, multiple iterations, feedback between rounds and anonymity (Holloway 2012). The latter is particularly important as in face to face group-based processes, the presence of dominant individuals can have a large influence on the results (Hsu 2007). Each of these features were embodied by this study.

Due to the study conduct being via web-based communication, geographical constraints were overcome and anonymity of participants was maintained. There was a high degree of experience

and skill level within the recruited group, with the majority of those who completed all three rounds practicing as a Professor or Consultant having greater than ten years of experience in their field. All participants were members of specialist societies with a specific interest in vulvovaginal disease. The demographics of the group indicate that respondents had the necessary skills and experience to contribute to the derived diagnostic dataset.

Three rounds of the Delphi exercise were performed which enabled the study to be completed in a timely manner without participants developing survey 'fatigue'. Feedback indicated that three rounds were sufficient to formulate a list of clinicopathological features that are suggestive of ELPV but further work is needed to determine the exact number of these criteria required.

Important considerations when interpreting the results of this exercise are that two of the stakeholder groups, dermatopathology and genitourinary medicine were underrepresented. Reliability of responses from individual groups diminishes with numbers of less than 12 and are considered to be unreliable with 6 or less (Murphy 1998). Whilst dermatology and gynaecology expertise was adequately represented by respondents (Table 25, p166), histological opinion was not as only seven dermatopathologists took part. Individual histopathologists did comment that epidermal changes such as saw toothed acanthosis and hypergranulosis, and dermal changes of lack of hyalinisation, were important. These

comments were not sufficient to alter the results, however, it is possible that the views of the seven dermatopathologists were not representative of the profession as a whole, and findings may be different with larger numbers. Unfortunately it was beyond the scope of this exercise to investigate further.

4.5.3 Implications for clinical and research practice

It was important to do this exercise for two reasons, firstly to improve the diagnosis of an uncommon condition and improve patient care, and secondly to define stringent diagnostic criteria so that robust clinical trials can be carried out to improve current patient management (Simpson 2012). This is particularly crucial as patients with ELPV may present to various specialty groups.

Participants agreed that ELPV can be diagnosed clinically and a biopsy does not always need to be taken. Biopsy should however, be performed in cases of diagnostic doubt or if there is suspicion of malignancy.

The site of biopsy is important as histological features described in the diagnostic dataset are more likely to be present at the edge of an erosion than centrally. Classical lichenoid features are most likely to be found when taken from the white margin of erosions (Pelisse 1989). Assessment of vulval biopsies should be by a specific dermatological or gynaecological pathologist as changes of LP are often subtle and there is a possibility of an incorrect diagnosis being

made by pathologists who are inexperienced in this field (Bowen 2008).

The interest and high fidelity demonstrated in all three rounds shows that physicians internationally are motivated to advance practice in this area of vulvovaginal disease; 73 experts participated in the first round and only four dropped out during the nine-week study period.

It should be realised that this is just one utility of the Delphi process and the methodology can be translated to other areas of healthcare where information in the scientific literature is lacking and therefore needs to be generated using expert opinion, for example in establishing core outcome sets (Schmitt 2011).

4.6 Chapter 4 Summary

The result of this consensus exercise represents the views of a group of experts and provides a list of supportive features that they consider important to diagnosing ELPV. The next steps are to validate the diagnostic criteria in the clinical setting by applying them to patients managed during normal practice. It is anticipated that the diagnostic criteria will guide physicians in their daily practice but more importantly, this dataset can be utilized in the conduct of my future clinical trial criteria to ensure inclusion of comparable participants. As practicing clinicians were participants in

the e-Delphi exercise, a trial protocol incorporating the results should provide a sense of ownership for those who participate in the main study.

- Presence of well demarcated erosions or glazed erythema at the vaginal introitus
- Presence of a hyperkeratotic white border to erythematous areas/erosions +/- Wickham's striae in surrounding skin
- Symptoms of pain/burning
- Scarring/loss of normal architecture
- Presence of vaginal inflammation
- Involvement of other mucosal sites
- Presence of a well-defined inflammatory band in the superficial connective tissue that involves the dermo-epidermo junction
- Presence of an inflammatory band that consists predominantly of lymphocytes
- Signs of basal cell layer degeneration e.g. Civatte bodies, abnormal keratinocytes or basal apoptosis

Figure 21: Final diagnostic dataset agreed through the e-Delphi consensus process. Diagnosis of erosive lichen planus affecting the vulva requires three out of the nine criteria listed in this table.

5 Outcome measures for vulval skin disorders: A systematic review of randomised controlled trials

5.1 Introduction

5.1.1 The concept of an outcome measure

The concept of an outcome measure is important for patient care. It is a way of assessing the health status (or disease-specific aspect of health) of a defined population, or a method to measure the effects of disease before and after an intervention to determine the effectiveness of that intervention.

In many areas of medicine, bedside or laboratory tests are available to determine response to an intervention. For example, the use of a sphygmomanometer in primary care to assess hypertension. However, it is more difficult to assess disease severity for conditions where adequate laboratory tests are not available. Specific tools that serve the purpose of an outcome measure in these circumstances are available and can be categorized as demonstrated in Figure 22, below.

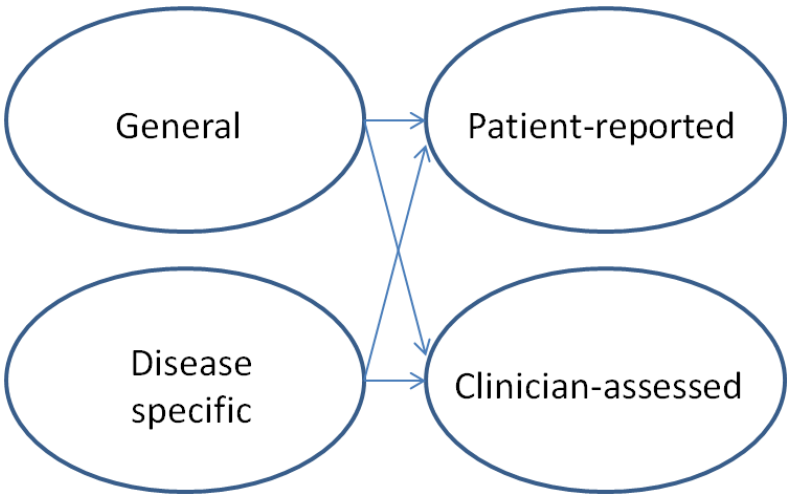

Figure 22: Different categories of outcome measure

'General' outcome measures are those that have been designed for use in patients with any type of condition. They are useful in comparing different populations and diseases, particularly for health economic purposes. An example of a general outcome measure tool is the Short Form-36 questionnaire, which is a patient-reported health related quality of life, (HRQoL) measure.

'Disease specific' outcome measures are designed to assess certain aspects of named conditions and cannot be translated to other conditions. An example of a disease specific measure is the 'POEM' (Patient Oriented Eczema Measure) which is a patient-reported eczema severity measure.

Clinician-rated outcome measures tend to assess impairments, whereas patient-rated measures evaluate the impact of disease on a patient's daily activities, work, and recreation.

5.1.2 Outcome measures for vulval skin conditions

The work described in Chapter 1 (literature review), Chapter 2 (multicentre case note audit and review of current clinical practice) and Chapter 3 (structured interviews with clinicians) of this thesis have all indicated that there are no outcome measures specifically designed for use in ELPV, or vulval skin disorders as a whole.

The work in this chapter aimed to elucidate outcome measures that were already being used in for vulval skin conditions through a systematic review of the literature.

5.2 Aims

The aim of this systematic review was to identify the outcome measures reported in published RCTs that had investigated the treatment of vulval diseases, and to determine whether any vulval-specific scales existed.

As it had been established that there were no RCTs and only a few large case series for ELPV, it was decided that RCTs of *all* vulval skin conditions should be included in the review. The rationale for this was that the goal of therapy for vulval dermatoses, regardless of underlying aetiology, is similar. Physicians aim to i) reduce symptoms that are of most importance to affected patients and ii) prevent secondary complications such as scarring or malignancy.

5.3 Materials and methods

The study protocol was finalised in July 2012 and published on the COMET Initiative database ("COMET Initiative" 2013). The protocol was also available in the public domain through the Centre of Evidence Based Dermatology website ("CEBD" 2012).

The Medline, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched from the time of inception to the 17th July 2012, to identify all interventional RCTs of vulval skin conditions where the full text was available in English. The search strategy combined the free text terms *'vulval', 'vulvar'*

and 'vulv'* with the medical subject headings '*Vulvitis'*, *'Extramammary Paget Disease', 'Vulvar Neoplasms', 'Vulvodynia'* and *'Vulvar Vestibulitis'*. The Cochrane Collaboration's search filter for RCTs was then applied to select all RCTs categorised under those search terms. The full search strategy for the Medline database is in Appendix 8. There was no time limit on the searches. All types of topical, systemic, surgical and psychological intervention were considered.

5.3.1 Inclusion criteria for studies assessed in systematic review

i. RCTs of vulval skin conditions that included a clinical assessment of disease impact and severity of disease.

5.3.2 Exclusion criteria for studies assessed in systematic review

i. Non-randomised studies;
ii. Papers where the outcomes were
    a. determined wholly by laboratory tests (e.g. histopathological specimens, microbiological tests)
    b. determined by survival rates
    c. pertaining to cervical disease
    d. pertaining to menopausal symptoms
    e. pertaining to infective conditions.
iii. Reports that did not have clinically assessed or patient-reported outcomes in the title or abstract

5.3.3 Data extraction

Data were double-extracted by two researchers (RS and RM). All of the papers were reviewed independently by the data extractors. Data were entered onto a standardised proforma that was designed specifically for this study. Any difference in opinion was adjudicated by a third researcher (KT).

Data collected included:

i. The vulval condition being investigated
ii. The study interventions
iii. Whether the primary outcome measure was specified in the abstract or main text
iv. Which primary and secondary outcomes were measured
v. Which scales were used to assess the outcome
vi. The method of assessment (i.e. assessed by physician, patient or other means). N.B. When the primary outcome was not specified, the first reported outcome in the results section was taken to be the primary outcome measure.

A Microsoft Access 2007 database was designed to enter and process data from the paper extraction forms.

5.4 Results

5.4.1 Included studies

A total of 1,613 articles were retrieved by the search strategy. The full texts of 67 articles were reviewed, of which 28 were eligible for inclusion into the study in line with selection criteria stated in the

eligibility criteria. A flow chart of included articles is shown in Figure 23, page 193.

The disorders reported by the included studies were vulvodynia (localised provoked, n=12 (Bornstein 1995, Weijmar Schultz 1996, Bornstein 1997, Bornstein 2000, Bergeron 2001, Nyirjesy 2001, Munday 2004, Danielsson 2006, Murina 2008, Petersen 2009, Bornstein 2010, Foster 2010); generalised provoked, n=1 (Brown 2009); type not specified, n=1 (Masheb 2009)), lichen sclerosus (n=9) (Paslin 1991, Bracco 1993, Sideri 1994, Cattaneo 1996, Origoni 1996, Paslin 1996, Burrows 2011, D'Antuono 2011, Goldstein 2011), vulval intraepithelial neoplasia (VIN, n=2) (Naik 2006, van Seters 2008), vulval pruritus (n=2) (Origoni 1990, Lagro-Janssen 2009) and lichen planus (n=1) (Rajar 2008).

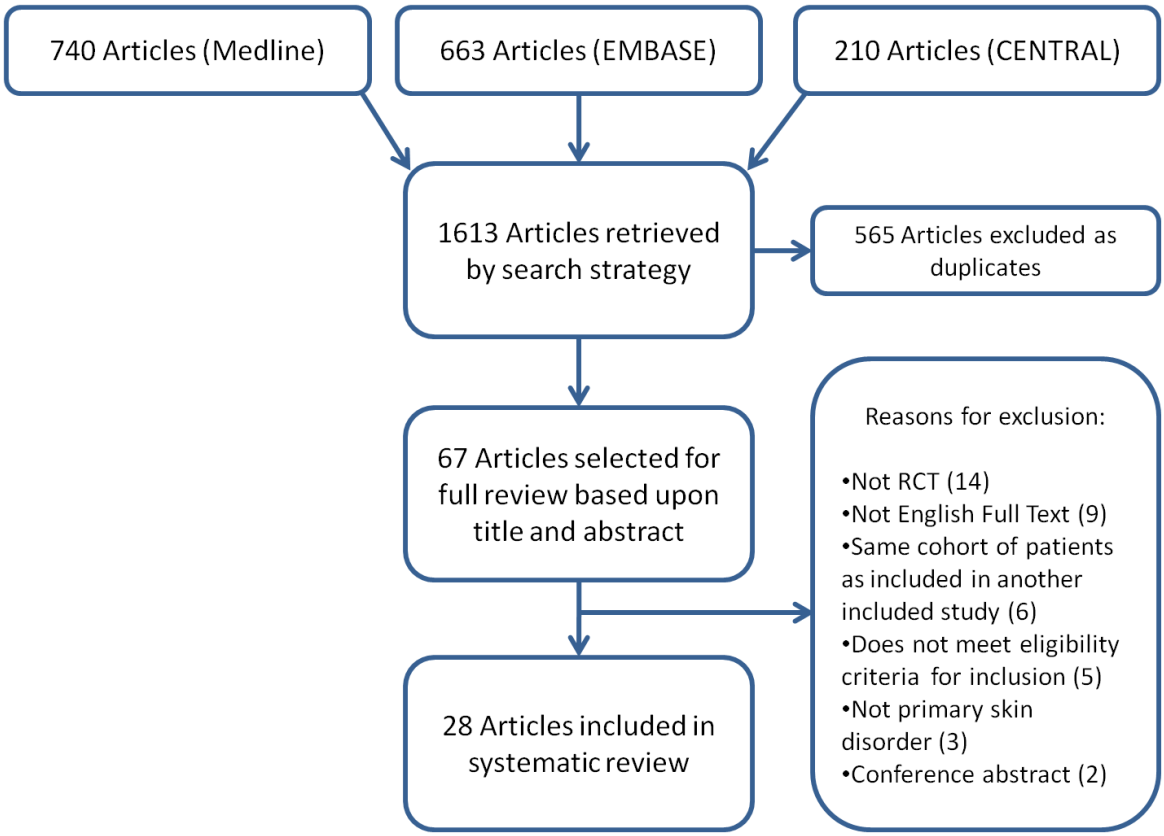

Figure 23: Articles identified for systematic review of outcome measures used in RCTs of vulval skin disorders

5.4.2 Outcomes identified from included studies

The 28 studies measured 25 different types of outcome using 49 different scales (Table 31, page 201). One study reported as many as 13 outcomes in their results. Only 6/28 (21%) studies clearly stated the primary outcome measures in the abstract or in the main text (Bornstein 1995, van Seters 2008, Bornstein 2010, Foster 2010, Burrows 2011, Goldstein 2011).

Of the total number of outcomes measured by the studies, those reported by patients were most common (69/103, 67%), followed by physician-reported outcomes (21/103, 20%). Histological assessment was used on eight occasions and digital images on four. The histological assessments identified were secondary outcomes and were always measured in conjunction with either physician or patient-reported outcome measures, or both.

Some studies measured an outcome type more than once using different methods of assessment. The most commonly assessed outcomes were patient-rated improvement in pain (15/103, 15%), clinician-rated improvement in appearance (13/103, 13%) and patient-rated improvement in overall symptoms (11/103, 11%).

Of the 49 different scales listed in Table 31, only one-third of these referenced previously used methods. Very few of these were specific to vulval disease; four were relevant to vulvodynia and five were

relevant to sexual functioning. The remaining eight were general QoL scales that were not specific to vulval disease.

5.4.2.1 Patient reported symptoms

Patient-reported improvement in pain was the most commonly reported outcome (n=15). It was almost exclusively used in the context of vulvodynia with only one study reporting its utility in lichen sclerosus. The McGill pain questionnaire (n=7) and a visual analogue scale (VAS, n=6) were the tools most commonly used to assess pain. The VAS was used with scales of 0-10 and 0-100.

Improvement in overall symptoms was assessed by 11 studies investigating several different disorders, lichen sclerosus (n=5), vulvodynia (n=3), VIN (n=2) and pruritus (n=1). Of these, there were three different ways of measuring 'patient global assessment' (PGA). As with the investigator-reported outcome measures, no two PGA scales were the same. Scales for PGA included 0-3 scale of severity, a 1-5 scale of severity and a scale of complete/partial/no response compared to baseline

A composite scale of patient-assessed severity was used by five studies. Each study asked the patient to score the severity of various symptoms on a pre-defined scale. Symptoms included a combination of itch, burning, pain, dyspareunia (painful sexual intercourse), dryness and dysuria (pain on passing urine). These varied depending on the condition under investigation. They all used

a scale of 0-3 for a variety of symptoms. A VAS was used to measure overall symptoms by three studies, two of which measured on a 0-10 (Naik 2006, van Seters 2008) scale and one on a 0-100 scale (Nyirjesy 2001).

5.4.2.2 Clinician reported measures

Clinician-rated improvement in appearance was reported in 13 studies; these were investigating lichen sclerosus (n=8), vulvodynia (n=2), lichen planus (n=1), vulval pruritus (n=1) and vulval intraepithelial neoplasia (n=1). Of these, six used an 'investigator global assessment' (IGA), that is, clinician assessed overall severity of disease. However, the specific IGA scales varied with no concordance between the different investigators and studies.

A composite score of clinician-assessed severity was used in five studies, various component parts were used to form the composite score. For example, one study investigating lichen sclerosus (Cattaneo 1996) scored clinical features of hyperkeratosis, atrophy and sclerosis in terms of severity (0-3), summed these scores and then adjusted depending upon the extent of disease. Another study investigating lichen sclerosus (Munday 2004) scored pain, tenderness and erythema on a 0-3 scale and summated these; the total score was used as the outcome.

A single study investigating vulval lichen planus (Rajar 2008) scored clinical severity according to criteria used by Thongprasom

(Thongprasom 1992), which assesses the disease severity on a scale of 0-5. However, Thongprasom originally described this scale for *oral* lichen planus and it has never been validated in the assessment of vulval disease.

5.4.2.3 Measures to assess disease impact on function and quality of life

Sexual function was specifically addressed by 61% of studies (17/28). The different aspects of sexual function measured were i) the presence of dyspareunia (n=7); ii) improvement in sexual function (n=6); iii) severity of dyspareunia (n=5); iv) frequency of intercourse (n=3); v) sexual distress (n=2); vi) capability of completing intercourse (n=1) and vii) sexual satisfaction (n=1).

A large number of different scales were used to assess these aspects of sexual function, as outlined in Table 31, page 201. Otherwise, other than one study that assessed dysuria as part of a composite assessment (Origoni 1990), day to day functioning including passing urine, defecation and washing was not assessed by the studies.

Only 14% (4/28) of studies reported QoL or general health state (Danielsson 2006, van Seters 2008, Lagro-Janssen 2009, Petersen 2009). The scales used to assess these were the Short Form 36 (SF36, n=3) and the 'Dartmouth Primary Care Cooperative and

World Organisation of Family Doctors' (COOP/WONCA) questionnaire (n=1).

5.4.2.4 Other outcomes

Side effects of treatment were only measured by one study (Origoni 1990), treatment satisfaction by two (Masheb 2009, Bornstein 2010) and treatment acceptability by two studies (Origoni 1990, Masheb 2009).

Method of outcome assessment	Outcome measured	Times outcome measured by the studies (n)	Scales used to measure the outcome type (number of times scale used)	References *
Patient-rated	Pain reduction	15	McGill Pain Questionnaire (7) VAS (6) Brief Symptom Inventory (1) Neuropathic Pain Index (1)	(Bergeron 2001, Murina 2008, Brown 2009, Masheb 2009, Petersen 2009, Bornstein 2010, Foster 2010, Goldstein 2011)
	Improvement in overall symptoms	11	Composite score, comprising various components (5) PGA (various scales) (3) VAS (3)	(Origoni 1990, Bracco 1993, Sideri 1994, Cattaneo 1996, Origoni 1996, Weijmar Schultz 1996, Nyirjesy 2001, Naik 2006, van Seters 2008, D'Antuono 2011)
	Dyspareunia	7	Yes/no (1) Satisfactory/Unsatisfactory (1) Complete/partial/no response (1) 0-4 scale (1) Marinoff Dyspareunia scale (1)	(Paslin 1991, Bornstein 1995, Bornstein 1997, Bornstein 2000, Murina 2008, Bornstein 2010, Foster 2010)
	Improvement in itch	6	PGA, various scales (3) Frequency, intensity and duration of itch (1)	(Origoni 1990, Paslin 1991, Origoni 1996, Paslin 1996, Lagro-Janssen 2009, Goldstein 2011)
	Improvement in sexual function	6	FSFI (3) Sexual History Form (1) Derogatis Sexual Functioning Index (1)	(Paslin 1996, Bergeron 2001, Murina 2008, Masheb 2009, Petersen 2009)
	Psychological impact of disease	5	Beck Depression Inventory (2) Profile of Mood States (1) Brief Symptom Inventory (1) Structured Questionnaire (1)	(Bergeron 2001, Danielsson 2006, Masheb 2009, Foster 2010)
	Frequency of intercourse	3	Frequency/week or month (2) Once weekly yes/no (1)	(Bergeron 2001, Bornstein 2010, Foster 2010)

	Treatment acceptability	3	VAS (1) 0-5 Scale (1) Consistency/absorbance/skin colour (1)	(Origoni 1990, Masheb 2009)
	General health state	2	SF 36 (1) COOP/WONCA (1)	(Lagro-Janssen 2009, Petersen 2009)
	Sexual distress	2	FSDS (2)	(Petersen 2009, Burrows 2011)
	Treatment satisfaction	2	VAS (1) Excellent/Good/Low (1)	(Masheb 2009, Bornstein 2010)
	Quality of life	2	SF 36 (1)	(Danielsson 2006, van Seters 2008)
	Capability of completing intercourse	1	Yes/No (1)	(Bornstein 2010)
	Relationship with partner	1	Excellent/Good/Mediocre/Poor (1)	(Bornstein 2010)
	Side effects of treatment	1	No description given (1)	(Origoni 1990)
	Sexual satisfaction	1	Index Sexual satisfaction (1)	(Foster 2010)
	Tampon test	1	Tampon Test (1)	(Foster 2010)
Clinician-rated	Global assessment of appearance	13	IGA, various scales used (6) Composite score, comprising various components (5) Thongprasom score (1) No description given (1)	(Origoni 1990, Paslin 1991, Bracco 1993, Sideri 1994, Cattaneo 1996, Origoni 1996, Nyirjesy 2001, Munday 2004, Naik 2006, Rajar 2008, Masheb 2009, D'Antuono 2011, Goldstein 2011)
	Improvement/reduction in pain	6	Vulval algesiometer, pain rated on VAS (1) Vulval algesiometer (1) Speculum rating (1) Cotton swab test (2)	(Bergeron 2001, Danielsson 2006, Masheb 2009, Foster 2010)

			Digital palpation of muscle groups (1) Vestibular pain index (1)	
	Ulceration	1	IGA (1)	(Goldstein 2011)
	Lichenification	1	IGA (1)	(Goldstein 2011)
Histological assessment	Pathological-reported changes in histology	8	No description given (3) Complete/partial/no response (1) Yes/no (1) Improvement in elastic fibres (1) Atrophy/Fibrosis/Oedema/Inflammatory infiltrate on 0-3 scale (1) Inflammation 0-4 scale (1)	(Paslin 1991, Bracco 1993, Sideri 1994, Cattaneo 1996, Paslin 1996, Naik 2006, van Seters 2008)
Digital image	Improvement in appearance (photograph)	2	No specific description of how images used (2)	(Paslin 1996, Goldstein 2011)
	Lesion size	2	Method of measuring not given (1) Lesion measured with calipers and calculated by computer program (1)	(Naik 2006, van Seters 2008)
Assessment unclear	Vestibular pressure sensitivity	1	No description given (1)	
TOTAL	25 different outcome types	103 outcomes were measured by the included studies	49 different outcome measure scales	

Table 31: Outcome measures used in the 28 studies included in the systematic review of interventional trials for vulval skin conditions

*N.B some studies measured an outcome type more than once (using different assessment methods); COOP/WONCA- Dartmouth Primary Care Cooperative and World Organisation of Family Doctors questionnaire; FSFI – Female Sexual Function Index; FSDS – Female Sexual Dysfunction Scale; PGA – Patient Global Assessment; IGA – Investigator Global Assessment; SF36 – Short Form 36; VAS – Visual Analogue Scale.

5.5 Discussion

5.5.1 Main findings

There was little consistency in the way that studies assessed outcomes in trials of vulval skin conditions. Although outcome measure tools for the assessment of sexual function and pain were identified we did not find any global vulval-specific outcome measures.

Symptoms and signs of disease were most commonly assessed using composite scores, physician or patient global assessments or visual analogue scales. However, scales and categories of assessment varied widely. The studies that measured pain were almost exclusively those investigating vulvodynia despite the fact that many vulval disorders are considered painful, such as erosive lichen planus.

Outcome measures can be categorised into patient and physician-reported measures which may be either *general* or *disease-specific* (Figure 22, page 187). The review identified eight measures that were *specific* to vulval pain – the vestibular pain index (Bergeron 2001), the vulval algesiometer (Curnow 1996) and the Marinoff dyspareunia scale (Marinoff 1992). There were five measures *specific* to sexual function – the Female Sexual Functioning Scale (Rosen 2000), the Sexual History Form (Nowinski 1979), the

Derogatis Sexual Function Index (Derogatis 1979), the Female sexual Distress Scale (Derogatis 2002) and the Index of Sexual Satisfaction (Hudson 1998). There was only one *disease-specific* measure, the Thongprasom score (Thongprasom 1992), which is specific to lichen planus. However, this has previously been described for oral, not vulval lichen planus and has not undergone validation in either subtype. There were no disease-specific measures for lichen sclerosus or premalignant disease.

Studies were inconsistent in terms of measuring impact of disease on day to day function and on QoL. Whereby nearly two thirds of the included studies specifically asked about sexual function, other functional aspects of daily life were not considered, with the exception of one study reporting dysuria (Origoni 1990). We did not find any specific reference to bowel habit, washing, wearing specific clothing, walking, sitting or physical activity, despite patients with vulval problems commonly describing an impact on all these functions. Furthermore, only five studies specifically evaluated psychological impact of the vulval skin condition, which is an important factor when considering overall quality of life (Chen 2007).

It is disappointing that only four studies assessed quality of life since the majority of the conditions studied were chronic and clinically are known to affect daily life in affected individuals (Hickey 2010, Lawton 2013).

5.5.2 Strengths and weaknesses of the study

The strengths of this review were that it identified RCTs involving a range of vulval conditions – vulvodynia, lichen sclerosus, pre-malignant disease, lichen planus and 'pruritus'. Even though the aetiology of these conditions is different, their symptoms and effect on quality of life are comparable, as is the general clinical approach to initial disease assessment and response to therapy. It was therefore possible to collate the outcome measures that had been used in a range of clinical and research environments in the context of vulval disease.

Potential limitations are that non-RCTs and trials without full text available in English were excluded. It is possible that some studies were not identified due to the latter, however, there are many hundreds of case series and pragmatically it would not have been possible to include all of these.

A formal critical assessment of the quality of included studies was not undertaken as this was not the primary aim of the review. Overall, it appeared that many studies were poorly reported. Details about randomisation, blinding and concealment of allocation were frequently omitted. These factors are important in assessing risk of bias in a study design (Moher 2010). Stringency of disease definition was also a problem in some cases, and two studies investigated 'pruritus', which is a symptom rather than a diagnosis and can be

the result of varying pathologies, rather than specific diagnoses. However, it was beyond the scope of this review to examine these issues in greater detail.

5.5.3 Clinical and research implications

For most skin conditions it is not possible to assess disease response on the basis of laboratory tests. Therefore, monitoring disease in RCTs and in clinical practice requires the use of reliable and relevant tools to assess *clinical* outcomes. Such measures are a necessary prerequisite for good evidence-based practice (Chren 2000) and are paramount in clinical trial research.

The most commonly reported outcomes in the included studies were patient-led, which fits with standard clinical practice as described in Chapter 3 following structured interviews with clinicians. Therapeutic decision making for disease management is predominantly driven by patients' symptom response to therapy (Simpson 2013). This is because with many vulval skin conditions, the appearance of vulval skin does not necessarily mirror the patient symptoms and the clinicians treating them are aware that adequate treatment must reflect the aspects of disease that particularly affect the patient.

There is currently a movement towards core outcome sets for trials of specific conditions, as detailed by the COMET Initiative, which aims to standardise practice and enable comparison of the results of different treatment modalities in meta-analyses. Groups such as

OMERACT (outcomes in rheumatologic conditions) (Tugwell 2007), HOME (outcomes in eczema) (Schmitt 2011) and IMMPACT (outcomes in chronic pain) (Turk 2003), are disease or specialty-specific projects striving to reach concordance so that the same disease specific outcome measures are adopted in therapeutic intervention studies .

As vulval skin conditions affect patients in a multidimensional manner, outcome measures used in trials and clinical practice need to provide a holistic assessment of disease status encompassing emotional and social interactions, symptoms and functional impairment. Further work is required to identify what aspects of vulval disease are most important to patients, and to establish which aspects they would most like to see improved by therapy.

5.6 Chapter 5 Summary

This systematic review has highlighted the lack of outcome measures for chronic inflammatory vulval skin diseases and in particular, for erosive lichen planus. Patient and physician global assessments and visual analogue scales were commonly used to measure symptoms and signs, but there was no standardization in the scales used. Assessment of sexual function is clearly important when managing vulval skin conditions, however, a variety of scales had been used without agreement on which one(s) are most

appropriate. Finally, quality of life was poorly assessed and limited validated tools were used to assess this aspect of vulval skin disease.

However, this is evidence on which to base further work with patients and clinicians. The most relevant outcomes to be measured in a randomised controlled trial of ELPV should be established and the following chapter (chapter 6) will describe qualitative work which was carried out to identify the treatment outcomes which patients consider most important.

6 Patients’ views on vulval erosive lichen planus

6.1 Introduction

Having established clinicians' perspectives on treating ELPV (Chapter 3) and subsequently demonstrating the lack of clinically appropriate outcome measures for the condition (Chapter 5), it was important to ascertain patients' views on ELPV and assess which outcomes were most relevant from their perspective. For any clinical research patient involvement is paramount to ensure that the work and end results are relevant and important to the population affected. This chapter aimed to provide evidence through patient input that would build upon the work described in the previous chapters.

6.2 UK Lichen Planus Society Survey

6.2.1 Aims

In order to supplement the systematic review of outcome measures in Chapter 4, members of the UK Lichen Planus Society (UKLP, see section 1.7.3.1, p48) were approached to obtain qualitative information about the aspects of ELPV and its treatment that are important from a patient's perspective. Specifically investigated were aspects of disease that have the greatest impact upon quality of life, and patients' priorities for treatment

6.2.2 Materials and methods

The UKLP society membership consists of people who suffer from lichen planus. Members were contacted by electronic mail and invited to complete a questionnaire that was posted on the website. Forms were completed anonymously and returned electronically to the study coordinator (RS) via the UKLP website lead. As this was a voluntary survey which was completed anonymously without any information to link back to an individual, ethical approval was not required.

The questionnaire was devised to obtain the following information:

- basic demographic data;
- medical care received for treating lichen planus
- specific details about the disease itself (i.e. site, duration);
- aspects of disease that 'bother' patients the most;
- priorities for treatment.

To ascertain impact on quality of life caused by ELP, patients were asked to complete a Dermatology Life Quality Index questionnaire (Finlay 1994).

The term 'bother' was used as it has been shown to be easily understood by patients when developing symptom-based outcome measures in other disease areas, such as eczema (Charman 2004).

Data from forms received were entered data entered into a Microsoft Excel spreadsheet for qualitative and quantitative analysis.

6.2.3 Results

6.2.3.1 Demographic data

At the time of the survey 234 people were a member of the UKLP support group, but it was not possible to identify how many of these were active website users. There was an 18% (42/234) response rate. Of these, 35/42 had genital or oral disease, or both; the remainder did not have LP affecting mucosal surfaces. Respondents with mucosal LP consisted of 26 females and 9 males.

The mean duration of disease was 5.2 years (range 0.5-20 years). The majority of respondents were aged between 35 and 65 years.

Patients were asked to indicate which anatomical sites were affected by lichen planus (Figure 24, p213); most had more than one site affected. The oral cavity was most commonly involved, followed by the vulva and vagina. Other mucosal sites such as the anus and penis were affected, but much less commonly. These are demonstrated in the bar chart below.

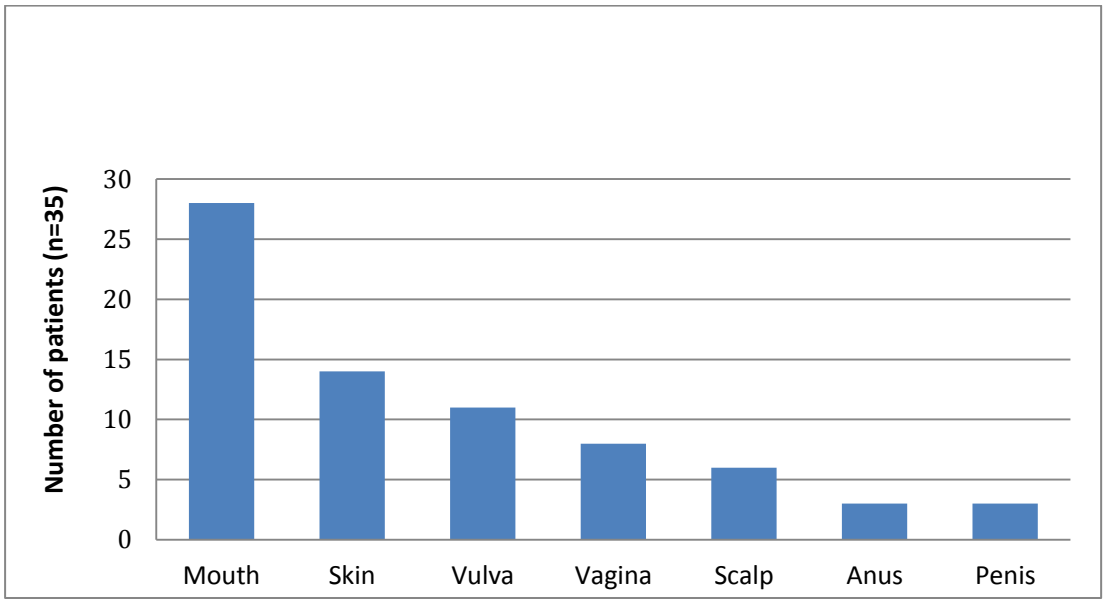

Figure 24: Bar chart showing the results of UKLP survey - body sites affected by lichen planus

More than one anatomical site was involved in the majority of respondents; 71% (25/35) patients having two or more sites and 43% (15/35) had over 3 different anatomical sites affected by LP.

6.2.3.2 Effect of ELPV of quality of life

Results for female respondents with ELPV were separated from the remainder of the group as these were of greatest relevance to this project. Dermatology life quality index scores (DLQI) ranged from 0-22 (Figure 25, page 215). It has been shown that a score of 10 or more on the DLQI represents the disease as having a 'large effect' on quality of life (Basra 2008). For this group of females, 44% scored 10 or more on the DLQI scale. Furthermore, when mapped to

number of anatomical sites affected by LP, there was a directly proportional relationship with the DLQI score (Figure 26, page 215).

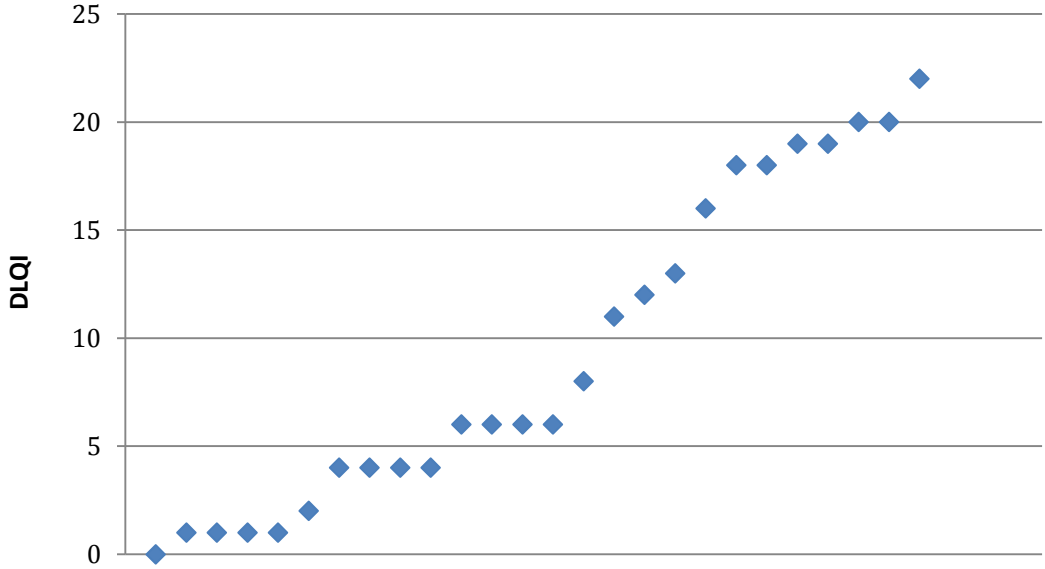

Figure 25: Scatter plot from the UKLP survey showing the dermatology life quality index scores of participants.

N.B DLQI scores are for females with orogenital erosive lichen planus (n=26)

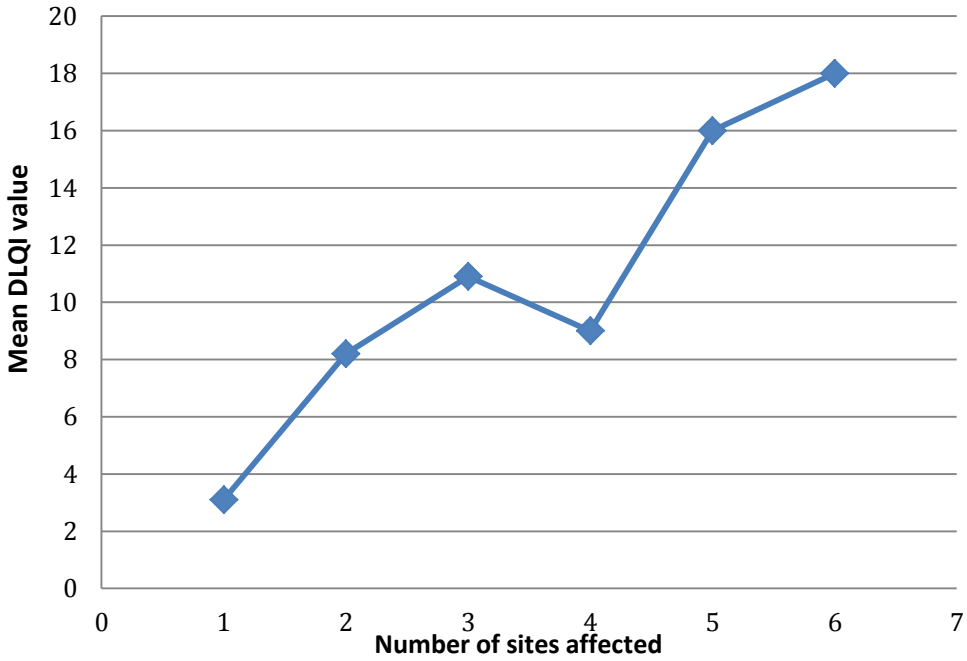

Figure 26: Scatter plot from the UKLP survey showing the correlation between numbers of sites affected with lichen planus and dermatology life quality index.

6.2.3.3 Symptoms of ELPV that bother people the most

Patients were asked to list the top two aspects of disease that bothered them the most and were therefore priorities for treatment (Table 32, 217), not all patients filled in two answers. **Symptoms** (pain/discomfort/itch) were the most common response, followed by **functional impairment** (sexual problems/difficulty in passing urine). 'Other' responses were a heterogeneous group with no distinct themes, ranging from the possibility of malignant transformation to having a smear test under general anaesthetic.

Disease aspect that bothers the most	N (%)
Pain/discomfort	12
Sexual problems	8
Appearance	5
Difficulty eating	3
Itch	2
Scarring	2
Other	12

Table 32: UKLP survey - Aspects of mucosal lichen planus that bother patients the most

Other themes that emerged from the questionnaire were that:

- there is a lack of understanding of ELP and its management amongst primary care practitioners;
- definitive treatment pathways are not currently available and therefore management of ELP is suboptimal;
- existing quality of life assessment tools were not specific enough to meet the patients' needs.

6.2.4 Discussion

Despite the relatively low number of resonses, this questionnaire survey of patients with lichen planus demonstrated that when the disease affected mucosal surfaces, it has a considerable effect on quality of life. This was evidenced by the fact that nearly half of patients scored greater than 10 on the DLQI, indicating that the condition has a large impact upon quality of life. Furthermore, this study showed a convincing positive correlation between number of sites affected and DLQI value.

The emphasis of patients' concerns were symptoms, functional impairment and the physical appearance of lesions. However, there was also dissatisfaction with current treatment, disease specific outcome measures and level of understanding of the disease from the wider medical community.

To explore these themes further and to demonstrate their validity, patient-oriented focus groups that were subsequently performed (Section 6.3).

6.3 Erosive Lichen Planus Focus Groups

6.3.1 Introduction

Following on from the questionnaire work described in section 6.1 the next natural step was to engage directly with patients to verify and consider in more details some of the findings of these studies.

It was felt that interaction on a group level using focus groups, rather than individual structured interviews, would provide a more appropriate environment and peer support to explore this sensitive and potentially difficult topic. In addition, it was felt that this group setting would help individuals to verbalise feelings that they might find difficult to express alone.

This type of interaction was also intended to obtain patient input into the design of the future trial, for which the work in previous chapters has been building towards.

As has already been alluded, in order to design an RCT for patients with ELPV a number of steps need to be taken to ensure the trial is pragmatic, answers clinical questions that are important to patients and doctors, and measures clinically relevant outcomes. The primary aims of these focus groups were to obtain this information,

however, they were also an opportunity to perform an exploratory evaluation of how ELPV affects peoples lives.

6.3.2 Aims

This study had a number of aims relating to patients' experiences of living with ELPV and to obtaining patient input into the RCT design.

- To identify the most important aspects of ELPV from the patients' perspective.
- To ascertain outcome measures that might be appropriate for use in a future RCT
- To determine whether the overall design of the planned RCT is acceptable to patients with ELPV and if they would be willing to take part;
- To understand the potential barriers to recruitment and consider ways to overcome these;
- To explore factors that will make the RCT attractive to participants including: content of patient information sheets, discussing the potential treatments/regimens to be used, willingness to be randomised to a new treatment, follow up timings and monitoring investigations.
- To explore the effects of ELPV on peoples' lives and ascertain specific problems encountered from the patients' perspective.

6.3.3 Materials and methods

6.3.3.1 Ethical approval

The focus group study proposal underwent a full ethical review and was approved by the Nottingham Research Ethics Committee on 27th December 2012 (REC Reference 12/EM/0462).

6.3.3.2 Participants

Participants were enrolled from a single centre. Focus groups were held on two occasions two weeks apart. The same participants were involved in both sessions. As there was a considerable amount of information to process and understand it was decided that two sessions would be preferable to one. The first session covered the concept of outcome measures and most bothersome symptoms with the second session covering trial design. Participants therefore had the opportunity to reflect upon issues brought up in the initial discussion prior to attending the second session.

Each participant's involvement was limited to the two focus groups. The study duration, from time of sending out invitation letters to completing the second focus group was three months from January 2013 to March 2013.

All participants provided written informed consent for their involvement in this study.

6.3.3.3 Recruitment

Participants were recruited from Nottingham University Hospitals, which runs a dedicated vulval dermatology clinic.

Participants were identified through outpatient clinic lists and invited to join through a letter from by their usual treating clinician. A full patient information sheet (PIS) was enclosed with the invite letter. Patients who were interested in taking part were asked to contact the study co-ordinator by either return of a response slip or by telephone. A follow-up telephone call subsequently took place to discuss the PIS prior to attending the focus group. The patients were counselled on all aspects relating to participation in the study and given the opportunity to ask questions before deciding whether to participate or not.

6.3.3.4 Moderators

Two moderators were present to lead the sessions and each had distinct roles. A clinical researcher (RS) provided clinical input into the discussion, introduced the concept of a future trial and its design and explained the concept of 'outcome measures'. An independent moderator was present to facilitate the discussion in a non-biased manner (CL).

6.3.3.5 Inclusion criteria

- Clinical diagnosis of ELPV as made by a Dermatologist;

- Capability to give informed consent and to attend focus group meetings;
- Fluent in written and spoken English language;
- Age >18 years.

6.3.3.6 Exclusion criteria

- Age < 18 years;
- Not willing/ unable to give informed consent/unable to attend focus group meetings;
- Alternative/unclear clinical diagnosis.

6.3.3.7 Focus group session 1 format

At the beginning of Focus Group 1, introductions took place and the function of the day was reiterated. Consent forms were signed prior to starting of recording of the first session.

Participants were encouraged to discuss their experiences of living with ELPV and the impact it has had on their lives. After this initial open discussion the session focused on assessing what might be important outcomes for patients being treated for ELPV as well as exploring the appropriateness of outcome measure tools that are commonly used in clinical practice. Patients were asked specifically to comment upon the tools that had been identified by the systematic review (section 5.4.2, page 194). Prompts used for this part of the session can be seen in appendix 9.

The concept of an 'outcome measure' was introduced before patients were asked to give their opinion on the relevance of the tools. These had been identified by the systematic review and are outlined in Table 33, page 225.

Aspect of disease measured	Tools discussed
Health related quality of life	COOP/WONCA questionnaire
	Short Form-36 questionnaire
Overall disease score (e.g. bother)	Visual Analogue Scale
	Likert Scale (3- and 5-point scales presented)
Pain	Visual analogue scale (0-10)
	McGill pain Questionnaire
Psychological effects	Hospital Anxiety and Depression Scale
Sexual function	Female Sexual Functioning Index
	Female Sexual Distress Scale
	Derogatis Sexual Function score
Skin related quality of life	DLQI
	Skindex-29 (vulval specific version)

Table 33: Outcome measure tools discussed in Erosive Lichen Planus Focus Groups

Patients were asked which of the tools they felt were relevant to their needs and accurately provide a reflection of their disease severity. Discussion also took place around other aspects of disease (or its treatment) that the patients felt should be asked about as an outcome.

Participants were then given a 2-week period in which to reflect upon the discussion and to complete some example questionnaires at home, before attending Focus Group 2.

6.3.3.8 Focus group session 2 format

A summary of findings from the first session was given in order to reiterate and clarify the important points that had been identified from the first focus group.

The proposed future RCT plan was subsequently presented, focusing on aspects of the study that have most impact on patients. Participants were encouraged to give their honest opinion on the overall study concept i.e. proposed trial medications, timing of follow up visits, and were asked to highlight any aspects that would prevent or discourage them from entering the study, as well as aspects that they particularly liked.

Focus group sessions one and two each lasted two hours. This included a refreshment break and the sessions were followed by lunch.

6.3.3.9 Data management

The sessions were audio-recorded using two devices (one for backup). The recordings were copied onto DVD and transcription occurred within two weeks of the second session. The recordings and their transcriptions were stored securely on a password-protected computer and the recordings were deleted once transcription was complete. The resulting documentation did not contain any identifiable patient information. Formal analysis (section 6.3.3.10, page 227) was performed using NVivo 10 software.

6.3.3.10 Analysis

Although the focus groups were carried out at two different time points, data were considered as one set as the same group of participants were involved in both. There were two main aims to the analysis:

1. to obtain information relevant to designing a future randomised controlled trial;
2. to perform an exploratory analysis and identify key features of patients' experiences of ELPV.

Data were analysed thematically using a multi-stage process as described by Braun and Clarke in 2006 (Braun 2006). Thematic analysis is a method of identifying, analysing and reporting patterns (themes) within data. A 'theme' captures something that is

important about the data in relation to the research question and represents a degree of patterned response or meaning within a dataset (Braun 2006). Researcher judgement and discretion is necessary to define and determine what themes exist within the dataset. Thematic analysis is a flexible and organic process that evolves as data is repeatedly analysed and greater familiarisation with the content occurs (Braun 2006).

The steps taken to analyse data resulting from the ELPV focus groups were as follows:

Stage 1: Familiarising with the data

This stage was performed to generate preliminary thoughts on what *might be* interesting or important about the data. Firstly, recordings from the sessions were listened to in order to understand the breadth and content of the data. Brief notes of initial thoughts and ideas were recorded as well as postulating broad categories of how the data could later be organised.

As data were transcribed by an external typist, it was important to check the transcript against the original audio recording for accuracy and become more familiar with the data.

Stage 2: Generation of initial broad codes

The full dataset was then assessed and sections of text were systematically coded; a code represents the most basic segment of

the raw data that at a later stage can be organised to find meaning within the data (Boyatzis 1998). Coded data were in much broader categories than postulated in phase one of analysis resulting in a larger number of codes being generated. It was important in this stage to code for as many potential themes and patterns as possible and to keep the data in context. Therefore coded sections of text were taken with relevant surrounding data to maintain the full meaning of the selection. It was possible that an individual extract of data could fit into more than one category if the content was relevant to a number of different issues. Furthermore, as this was a fluid process, data could be un-coded if it later became apparent that it was not important or if it did not fit within its initial designated category.

Finer analysis of the coding then took place and items that had been broadly coded were considered in greater detail with the initial codes being broken down into smaller subcategories.

Stage 3: Organising codes and searching for themes

During this stage coded data were organised so that the original raw data took on a more structured format. The codes were then used to find themes, which is a way that the codes are organised in a systematic fashion. In this stage an early look at the relationship between the codes and the themes took place.

Stage 4: Rationalising and refining themes

Themes were then rationalised through assessing the data contained within each category. It became evident if there was not enough data to support a theme that it should not be a feature of the end results whereas other themes were too diverse and needed to be restructured.

Following this process it was then possible to organise the themes into a hierarchical model, to assess links and associations between the themes and to create a thematic 'map' that adequately represents the original data set (Appendices 9 and 10).

Stage 5:

This final stage was to identify the key themes and features resulting from the data, these are presented as the main findings of this work. This is the information which will help us to understand women's experiences of living with and being treated for erosive lichen planus affecting the vulva.

6.3.4 Results

Invitation letters were sent out to 31 patients identified from the specialist vulval clinic at Nottingham University Hospitals. Responses were received from 14/31 (45%) with 11/14 agreeing to participate in the sessions. Due to various reasons, six participants were able to attend both sessions. In addition, one patient who was unable to be

present at the focus groups attended a structured interview to discuss the focus group findings. Participants were aged 42-76 (mean 64.1) years, with six being in the post-menopausal range. All were white British females.

The total study period from sending out invitation letters to completing the two focus groups and structured interview lasted from January 2013 to March 2013.

As discussed in the methods (section 6.3.3, page 221), these focus groups were analysed with two different purposes -practical considerations for a future trial design and thematic analysis of patients' experiences. These will be presented separately. The structured interview was analysed in a similar way and any findings additional to the focus group data were incorporated into the main results.

6.3.4.1 Practical consideration for a future randomised controlled trial

6.3.4.1.1 Outcome measures

The outcomes that are most important to assess from the patients perspective are overall 'bother' of disease, soreness, psychological impact, impact on quality of life and sexual function. People were keen for all of these to be assessed in some way as ELPV has a greater impact than on just physical symptoms as discussed in the

thematic analysis of these data. Through assessing these different effects of the disease on peoples' lives, they feel that doctors are considering them as a whole person, not just a condition affecting one part of them.

Having discussed the tools that can be used to measure the outcome domains there were some clear preferences. These are tabulated alongside the reasons for patients preferring these to the other options (Table 33 and Table 34 pages 225 and 233 respectively). Examples of the questionnaires described in Table 33 are in appendix 10.

Outcome measure to assess	Preferred tool	Comments
Overall disease control	'Bother' score on 5 point Likert scale	The word 'bother' was considered the most appropriate term to assess overall control. A Likert scale was preferable to a VAS
Symptoms	Soreness measured by 10-point VAS	VAS preferred to a Likert scale as people felt it gave them the greatest flexibility given that their symptoms are variable day to day
Psychological impact	HADS	People felt this was a very good way of considering them as a whole person and liked the questions asked
Quality of life (Skin specific)	Vulval Skindex-29 scale	This was preferred over the DLQI as it was in greater depth and asked questions of more relevance to their condition
Quality of life (General)	SF-36	This was the preferred tool, although people were not particularly supportive of a general QoL tool and preferred the skin-specific measures
Sexual function	Derogatis sexual functioning scale	Although people did not mind the more in depth scales (FSFI and FSDS) they felt the Derogatis scale was simpler to complete and was in sufficient detail for their needs

Table 34: Outcome measure tools preferred by patients in focus groups.

DLQI- Dermatology Life Quality Index; FSDS- Female Sexual Distress Scale; FSFI – Female Sexual Functioning Index; HADS – Hospital Anxiety and Depression Scale; SF-36 – Short Form-36; VAS – Visual analogue scale

6.3.4.1.2 Trial design

The focus group participants were extremely supportive of a future RCT, despite two of them already having taken the proposed trial medications with resulting poor effects. People were positive about the fact that the study would improve knowledge about treatments for ELPV and would help patients to understand that there are other people out there with the same condition. Although the monitoring and follow up schedule proposed is the same for any patient on a systemic therapy, people felt that clinic visits being increased slightly from when on topical therapy alone were reassuring and would encourage their participation in a trial.

The main concerns expressed about the study were the fact that people with ELPV are likely to be on other medications and that there is a risk of drug interactions. There was some worry about taking medications for six-months in case the disease worsened, or the treatment caused side effects or was intolerable. Furthermore, comments were made about the potential size of tablets and the fact that they may be difficult to take.

These are all understandable fears, particularly from a slightly older age group who may have previously experienced adverse effects from medications. Such responses are witnessed in the clinical environment and are an indication that extra time will need to be spent to allay these fears before the randomisation process.

Furthermore, a telephone help line to discuss any problems related to the medication was suggested by the participants.

Hypothetically, five of the seven participants were willing to take part in the proposed trial. The remaining two had well-controlled disease and therefore would not have been eligible for the trial, they were therefore more hesitant. However, if their condition did get significantly worse, they would be willing to consider entering into a trial of systemic therapy.

6.3.4.2 Thematic analysis of the exploratory data generated by the focus groups

Thematic analysis of data from these exploratory focus groups was broken down into an hierarchical structure consisting of a number of categories with numerous subcategories. These are demonstrated in Appendix 11. It became apparent that there were interlinking themes between all of these categories and none were mutually exclusive. The categories and subcategories were used to create a thematic map, which demonstrates the complexity of issues identified during the focus groups (Appendix 12).

This thematic map was reduced down into four main themes that from this early work appeared to underpin the experiences faced by patients with ELPV. These themes can be broken down further to give a fuller understanding of why they are important (Table 35, page 237). These four main themes have been interpreted as areas

in which healthcare professionals need to work to improve management, increase awareness of the condition and develop opportunities for supporting patients.

Main theme	Major category within theme	Effect on management/patient
Symptoms	Soreness	Profound effect on daily activities and function
	Psychological effect	Low mood Anxiety Distress Fear Guilt Stigma Embarrassment
	Effect on relationships	Impact on other people
Negative experiences	Community management	Time taken to diagnosis Lack of understanding/lack of faith in non-specialists
	Secondary care	Inconsistency in care received Poor handling of clinical examination and diagnostic tests Lack of communication between doctors Lack of understanding
	Misunderstandings	Patient misunderstandings Health care professional misunderstandings
	Treatments	Feeling unsupported when on systemic treatment Difficulty in using treatments as requested by the clinician
Support networks	Poor information available	Dearth of information available on the internet and from doctors
	Value of reassurance	Patients needing someone to talk to
Positive outcomes	Stoicism	Coping mechanism
	Trust in specialist doctors	Improves perception of management

Table 35: Four main themes identified by the ELP focus groups

6.3.4.2.1 Symptoms

Symptoms caused by ELPV are the main factor that seems to lead to a number of secondary problems.

The predominant symptom caused by ELPV is soreness. Although patients described the unbearable sensation of itch in the early stages, this quickly turned into soreness, which has significant sequelae. Doctors often ask patients about the level of *pain* that they are experiencing from their condition; a term that doesn't always accurately describe the symptom that people face. From these focus groups people talked predominantly about soreness:

"For me it is the soreness that gets me down. It is not as itchy now as it was. Even just sitting causes it."

Symptoms of soreness have an impact in the following ways; there is considerable interlinking between these categories:

6.3.4.2.1.1 Soreness

Soreness and discomfort caused by ELPV has a substantial effect upon performing day to day activities and should not be underestimated. It causes difficulty in most routine tasks that are otherwise taken for granted. The most notable effects seemed to be upon mobility, sitting, urination, choice of clothing and eating. Even those without oral ELP found that certain food types they ate impacted on their *vulval* symptoms due to changes in their urine.

The following comments demonstrate the ways in which people are affected:

"I know it sounds so silly but just getting into a car, if you imagine just getting into a car, you open your legs and you sit down and then it hits you then when you out the other leg in, it hurts."

"Sometimes even just walking is so uncomfortable. You just get so sore and then you try to sit down thinking, 'well I won't do that', but sitting can be as bad."

"I sit on the toilet and bend forward in the hope it won't touch it and won't hurt."

"If you go out for a meal, if it is slightly spicy I still try and get more and more water because the spice can also affect urinating so (I try to) dilute it again."

"I cannot wear trousers very often. If I do it has to be cotton or loose fitting. In the summer time I cannot wear shorts because I find in the summer I can get really sore."

6.3.4.2.1.2 Psychological effects

The symptoms of ELPV and its effects on daily activities contribute extensively towards a range of psychological consequences. All of the patients had experienced a variety of emotions when coming to terms with dealing with the condition. Predominantly people feel low in mood, distressed or anxious, fearful, guilty and embarrassed or ashamed by their condition. In particular, one participant described the psychological side of things as the worst aspect of disease. This

is important as doctors often do not spend much, if any, time exploring the emotional impact of disease.

"I find it all very distressing. It just makes you feel completely miserable."

"I worry because of the psychological side where it may get worse."

"I feel guilty as it is my problem. Well it is my problem but I cannot do anything about it."

"I do not like to even look at it ……"

6.3.4.2.1.3 Effects on relationships

ELPV has a significant effect on relationships with other people, particularly intimate relationships and has subsequent impact upon partners as well as the patient. This is a particular problem for patients as ELPV is a chronic disease and the situation is unlikely to improve much over time. Many people developed ELPV in their perimenopausal years and feel that the condition has 'robbed them' of their ability to have a relationship with their partner. This is again contributory to the psychological consequences of the disease.

"…if my husband now, I mean god bless him he is so good, if he suddenly started showing an interest in everything else I think I would be mad because I am so scared."

"You know this business of intimacy that plays on your mind, it plays on my mind. Don't get me wrong I am not waiting to jump on my husband at all but just the sheer fact that you know there is nothing you can do about it plays on my mind."

"A lot of my problem is that… my husband tells me I am just silly…. but it is the guilt of not being able to do anything, as in general personal things with my husband."

However, some people felt that it had taken the pressure off their relationships, particularly if their partners had problems of their own that prevented them from sexual activity:

"I mean the physical side of marriage has gone a long while ago but I am sure he won't mind me telling you at the time that he had a few problems so having my problem took the pressure off him."

6.3.4.2.2 Negative experiences

There were numerous occasions on which people felt subject to negative medical experiences. These meant that overall care was often considered unsatisfactory and was contributory towards the psychological effects of ELPV. These negative experiences were witnessed at all stages of care and are attributable to both community and hospital environments.

6.3.4.2.2.1 Community management

People experienced numerous incidences of misdiagnosis and a subsequent delay in referral to secondary care. Most common was the misdiagnosis of thrush. It took several years for most participants' condition to be correctly diagnosed but even then they

found that there was poor understanding from the wider medical community about ELPV. This led to a lack of faith in non-specialists.

"I don't find that your General Doctor quite understands because there are that many different ones at our practice."

"I used to have thrush quite a bit and so you go to the Doctor and I had a spate of not having it for quite a while and then I went back again and the Doctor said well it's thrush so I felt pretty silly about that but anyway I got some creams and then I was getting some other creams and then it got to the stage where it was getting worse and I went back to the Doctors, broke down in the room and I said it is not working…."

"I had been to my GP for 8 years and every time I was told it was thrush and it was a fluke there was a lady Doctor just standing in who said to me I do not think this is thrush…."

"They put me on HRT for about 5 years which seemed to help at one time but then got very sore and I looked one day and there was this little red spot about the size of a 5p, it got bigger and so I went to the Doctor and was given various creams and it was a long while before it was diagnosed."

6.3.4.2.2.2 Secondary care

Within the hospital environment there was also inconsistency in care received with incidences of misdiagnosis and poor continuity and communication between specialties. It seems that other specialties didn't necessarily manage ELP as a multisystem disease, which led to patients visiting numerous different departments. Once the

correct diagnosis was made, patients felt that on occasion there was lack of consideration of the severity of symptoms by doctors, particularly when it came to clinical examination and invasive diagnostic procedures. This again contributed towards psychological effects particularly those of fear and anxiety.

"I have started to count how many people I have seen when I got to 30 and that was years ago and I must have seen at least 30 since. All different people were looking at different bits of me and it wasn't until I got to Dr X and I saw her that was for the vulva I thought and then I was there one day and I said there is some in my mouth but I don't think you want to hear that and she said 'yes I do'. Her just saying yes I want to hear about everything was such a relief."

"I even had a D and C and I thought the Gynaecologist would surely notice things…. he did not say anything and nothing ever happened so I thought it must be alright…. "

"You can't touch a certain area. I mean Dr Y did a swab a time or two ago and I nearly shot off the table…"

"At the moment I have got a thing to go for a cancer smear. I just dread the thought. It is like being tortured."

"Dr X sent me for a biopsy a couple of times previously to me seeing her and I was absolutely distraught because it was so painful."

"He cut into me and he had not numbed me and…. I got tears rolling down my face and the nurse was apologizing because he had not checked."

6.3.4.2.2.3 Misunderstandings

A number of factors seemed responsible for patients misunderstanding certain aspects of their condition, its management and pathways that they have followed. Predominantly, the psychological effects of anxiety, distress, fear and stigmatisation seem to feed into patient misunderstanding, which in turn links back to the lack of information and support that is available.

"I had got it into my head, that when they first told me it was lichen planus that I had not been clean enough and I had passed it to my mouth."

"That is why I did not want to go (to the Genitourinary Medicine clinic) because I did not have a problem in that area…..at my age that I had got it into my head that I did not want to go to a clinic like that."

"…and whether you would still be able to wee. Will that bit close up? Does it close up? I don't know enough about it really."

6.3.4.2.2.4 Treatments

People found that they often had difficulty in managing their condition in the way that their specialist doctor had advised, and when on systemic therapy felt quite frightened and unsupported. This led to non-compliance and stopping therapy early on some occasions.

"As the entrance to the vagina had narrowed and then when she gave me these…these…… dilators, as soon as I started to use them it was just as if I was on a period and it tore."

"It was Dr X that prescribed it (Mycophenolate) for me and then I never saw them again and I was having blood tests here and I thought……. I was a bit afraid of what the tablets were doing to me, you know what I mean, because you go to the clinic and it is very rare that you see the same Doctor twice."

"I will be very honest because the last one I took (Mycophenolate) it wasn't so much they were very large hard… much larger than a Paracetamol and I had to take 3 at night, 3 at lunch and 3 at bedtime and I just could not cope with it, I just could not get them down at all."

6.3.4.2.3 Support networks

All of the participants expressed the need for reassurance about their condition and expressed comfort in being able to talk to about their experiences. They were all appreciative of the opportunity to take part in the focus groups as this was a way of sharing their experiences and voicing their feelings in a way which had not been possible previously. This seemed to stem from information being poorly available from doctors, a lack of support groups in the community and little patient information being available on the internet.

6.3.4.2.3.1 Poor information available to patients

People felt that even when the correct diagnosis had been made their General Practitioners did not have the knowledge to provide them with any information and although they had confidence in vulval disease specialists, they still found that information available was limited. When people used the internet they were unable to find reputable sources and found themselves frightened by what they read. Furthermore, lack of information had led to uncertainty and misunderstandings about the condition with people showing concern that they developed the disease due to something they have done.

"I see somebody different rather than my own Doctor because I do not think your own Doctor knows enough about the condition."

"I am scared and I made the mistake of going on the Internet when I first got it about the fusion of the labia and things like that and it really scared me when I read that."

"Another thing I wanted to ask is, I have had everything in my head - is it catching?"

6.3.4.2.3.2 The need for reassurance

It became clear that in dealing with this chronic condition, people require reassurance from vulval disease specialists, particularly in terms of checking for malignant progression. They value follow up appointments even if these are only 6 monthly so that they remain 'in the system', have a point of contact and receive continuity of care. People also appeared reassured by talking with others in the

group and sharing their experiences, which were all relatively similar. To this end, the group exchanged contact details so that they could keep in touch after the focus groups had ended.

"I think it is good to know that you are not the only one with the condition…"

"'The fact also is that when you start to read about it there is always this possibility of cancer later on. At least with the six monthly check ups you are in the system and so things can be kept an eye on."

"…every time I go (to the clinic) I think of its fine but there might be something so it is that kind of fear. That is why it is so reassuring to be able to see someone every six months"

"I think it is nice to be able to offload it all … to discuss it with people who understand it and you all understand each others' problems."

6.3.4.2.4 Positive experiences

Although negative experiences did seem to predominate in the discussions, there were positive aspects that came apparent during the focus groups.

6.3.4.2.4.1 Stoicism

All participants showed an enormous level of stoicism that had developed as a coping mechanism to dealing with the condition. Whilst the psychological aspect of disease was critical for the patients and they found this difficult to come to terms with, people

were able to accept and carry on with their symptoms, no matter how uncomfortable. This is a real testament to these patients and should not go unmentioned. Examples of people demonstrating stoicism are:

"You just get on with it – you have to don't you and I have been living with it for 24 years now."

"Because we have been through all the initial awfulness of it haven't we, we have all done that and been frightened and then passed from pillar to post, then getting a bit of treatment which helps a bit and then you look at other people who cannot walk or have other disabilities, well you think, at least I am...."

"In a way as things are at the moment with no cure it is good that we have accepted it."

"I mean years ago before all this I had it and I did really suffer trying to have sex."

6.3.4.2.4.2 Trust in doctors

Whilst there was an apparent lack of faith in generalists and non-specialist doctors, patients were extremely loyal to the Consultants who managed their condition in the specialist vulval clinic. It appears that patients feel they can trust a doctor who is confident in managing the condition and this reduces their fear and anxiety.

"Dr X and Dr Y have been so good. You feel confident so you are not anticipating the pain so much."

"You go to all these places and she was interested in the whole thing (erosive lichen planus at all sites), it was just amazing."

6.3.5 Discussion

6.3.5.1 Main Findings

The key areas highlighted by these focus groups were the effects of the disease on patients' lives, particularly the psychological and functional impact, which for most of the participants were marked. These problems were further compounded by perceived substandard care with poor understanding and lack of communication between primary and secondary care professionals. Support networks were lacking and sources of information available to patients were difficult to identify.

The findings of the focus groups confirmed the results of the UKLP survey described in Section 6.2 with the themes identified being extremely similar.

6.3.5.2 Strengths and weaknesses of the study

Whilst it is important to remember these qualitative findings from this early exploratory exercise are preliminary as they represent the views of a small group of patients, some provisional lessons can still be learnt. Furthermore, the findings corroborate those from the earlier work involving UKLP society members (section 6.2). Patient experience needs to be improved and although these patients were

all from one geographic area, given the lack of national guidance for ELPV and in context with the UKLP society survey findings, it is possible that experiences are similar across the country.

6.3.5.3 Clinical and research practice implications

Symptom control is extremely important but there are currently no randomised controlled trials to guide treatment, particularly for those patients with severe disease. Therefore the planned RCT for second-line therapy will address this.

As psychological effects were identified as being significant, it would be appropriate if all patients (and potentially their partners) should be offered links to psychological support. The British Association of Dermatologists is currently setting up an online support system for people with chronic skin conditions, which may be of interest to ELPV patients; however, as this is a particularly sensitive and specialised area psychological support should be integrated into the vulval multidisciplinary team clinic where possible.

There are a number of ways in which management of ELPV can be improved. Education is paramount as are the introduction of management pathways including national guidelines for the management of ELPV. Communication between specialties needs to be enhanced; this can be achieved through the use of a multidisciplinary team.

Finally, existing support and information available to patients needs to be highlighted (e.g up to date information leaflet on the ISSVD website, the UK Lichen Planus support group) and developed. Better information sheets should be available in clinic, support groups that are not necessarily web-based could be set up (bearing in mind the demographic of patients means that many are not comfortable internet users) and potentially short educational videos could be made (although these would most likely be web-based).

6.4 Chapter 6 Summary

This chapter has addressed a number of concepts that are important for clinical practice and research into erosive lichen planus affecting the vulva.

The aspects of disease that matter the most to patients were identified by the by the UKLP survey as discomfort and functional difficulty, including sexual problems. The survey also demonstrated that the quality of life of patients with orogenital erosive lichen planus is significantly affected. In-depth discussion in the focus groups reinforced these findings and also suggested that psychological aspects of disease are often neglected.

These studies have provided information to inform a RCT protocol. That is, a list of suitable outcome measure tools and an idea of what the primary outcome in a future study should measure.

Furthermore, aspects of study design were discussed with patients and areas which will need specific attention, such as reassurance about taking systemic medications and potential side effects, have been highlighted. Patients were supportive of a future RCT in this area and showed enthusiasm to take part if eligible.

The focus groups highlighted that there seem to be shortfalls in the management of ELPV in primary and secondary care. It is likely that these experiences will be shared by patients with other vulval diseases. These findings are a basis on which clinicians can start to build and improve the patient journey for what is a distressing, chronic disease. However, it should be realized that further focus group sessions are required to draw more evidenced based conclusions.

7 A Randomised Controlled Trial of Adjunctive Systemic Therapy for Vulval Erosive Lichen Planus: The ‘hELP’ Trial

7.1 Introduction

Chapters 1 to 6 of this thesis describe what is known about the epidemiology, aetiology, clinical presentation effects on patients' lives and treatment of erosive lichen planus affecting the vulval area (ELPV).

There is no high quality randomised controlled trial evidence on which to base treatments for ELPV. The only RCTs identified (Rajar 2008, Helgesen 2013) were of poor quality with inadequate information on included patients, weak description of study methodology and inappropriate outcome measures.

As demonstrated in Chapters 2 and 3, first-line therapy is usually with a super-potent topical steroid, usually clobetasol propionate 0.05% (Simpson 2012, Simpson 2013). Non-randomised studies, mainly retrospective case series, have suggested that these can be an effective first-line therapy (Lewis 1996, Cooper 2006, Helgesen 2010, Bradford 2013, Maor 2013). Therefore, evidence to date suggests that super-potent topical steroids are a reasonable first-line therapeutic choice and the qualitative and quantitative work demonstrated in Chapters 2 and 3 has shown that they are ingrained into clinical practice as an initial therapy for ELPV.

However, the only prospective published case series (Cooper 2006) identified in this field showed that up to one-third of patients had

unsatisfactory response to super-potent topical steroids. The case note review (Chapter 2) and structured interviews with clinicians (Chapter 3) indicated that there is no agreement for which second-line agents should be used (Simpson 2012, Simpson 2013),

Most second-line therapies are used based upon expert opinion. In Chapter 1, a wide range of systemic agents were identified from the literature for treating ELPV, although these were described by case series and case reports rather than randomised controlled trials. The Cochrane Systematic review of interventions for mucosal lichen planus confirmed that there were no quality RCTs in this field.

Providing an evidence base for the treatment of ELPV has been prioritised by the British and International Societies for the Study of Vulval Disease and the most important question clinically is to determine the most effective second-line therapy for ELPV. Patients with disease that does not respond to standard first-line therapy with a super potent topical corticosteroid undergo the most suffering and are in the greatest need of help.

Collaboration with expert clinicians throughout the duration of this PhD has indicated that the systemic treatments with the greatest success rates (anecdotally) when used in clinical practice are hydroxychloroquine, methotrexate, mycophenolate mofetil and prednisolone. It is these agents that clinicians have prioritised to compare in a randomised controlled trial.

7.2 Aims

This chapter describes the agreed protocol for the 'hELP' (systemic tHerapy for vulval Erosive Lichen Planus) Trial. This is to be a four-armed, open label, multi-centre, pragmatic randomised controlled trial to compare three systemic treatments (hydroxychloroquine, methotrexate and mycophenolate mofetil) against a control group who will receive clobetasol proprionate 0.05% in conjunction with an initial short course of oral corticosteroids.

This methodology will allow information about the four treatments that are favoured by clinicians to be acquired more quickly compared with separate trials and will require smaller patient numbers than three separate placebo controlled RCTs. This approach is important to maximise information about ELPV which is a rare disease.

This RCT of second-line therapy for ELPV will contribute towards future evidence-based management guidelines and will help to standardise practice.

7.2.1 Purpose

The RCT is designed to identify interventions that are effective in improving disease control in patients with erosive lichen planus affecting the vulva (ELPV).

7.2.2 Primary Objective

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

7.2.3 Secondary Objective

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

7.3 Materials and Methods

7.3.1 Trial configuration

A four-armed, open label, multi-centre, pragmatic randomised controlled trial.

7.3.2 Participants, settings and outcomes

7.3.2.1 Recruitment

Up to 96 female participants will be recruited from secondary care clinics. The trial will aim to recruit up to a maximum of 96 participants into the trial in order to have a clinically relevant outcome.

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

If a participant is believed to be eligible a patient information sheet (PIS) will be provided and any questions answered by the investigator or their designated nominee.

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

It will be explained to the potential participant that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time but attempts will be made to avoid this occurrence. In the event of their withdrawal it will be explained that

their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate.

7.3.2.2 Participants

Participants will be patients with ELPV who satisfy the following criteria. Eligibility criteria have been determined through collaboration with expert clinicians in the structured interviews (Chapter 3), the e-Delphi consensus exercise (Chapter 4) and through personal communication with future recruiting clinicians.

7.3.2.2.1 Inclusion criteria

- Clinical diagnosis of erosive lichen planus affecting the vulvovaginal region;
- Histological examination within the past 12 months to exclude malignant/pre-malignant disease;
- Inadequate disease control despite first-line therapy with clobetasol propionate 0.05%;
- Disease severity of moderate-severe on Investigator Global Assessment
- Negative microbiological swabs at study entry;
- Willing and capable of giving informed consent;
- Willing to have clinical images taken;
- Female aged 18 years or over (there is no upper age limit);

- Use of effective contraceptive methods in females of childbearing age for the duration of treatment and for 6 weeks following the end of treatment.

7.3.2.2.2 Exclusion criteria

- Cases of lichen sclerosus/lichen planus overlap;
- Patients taking Beta Blockers or non-steroidal anti-inflammatory medications;
- Received one or more of the trial drugs within the last one month (excluding clobetasol propionate 0.05%);
- Previous/current diagnosis of malignant disease (skin or internal);
- Pre-malignant vulval skin or cervical disease;
- Receiving concurrent medications (as listed in the BNF) that would preclude the use of any of the trial medications in normal practice;
- History of clinically significant renal or liver impairment or other pre-existing medical conditions that would preclude the use of any of the trial medications in normal practice;
- Administration of a live vaccine (BCG, Measles, Mumps, Rubella, Yellow Fever, Oral Polio, Oral Typhoid) within the last 2 weeks;
- Pregnancy (to be confirmed by testing) or breast-feeding;

- Known sensitivity to any of the trial medications.

7.3.2.3 Informed consent

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

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

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

7.3.3 Outcome measures

The outcomes for this study have been discussed at length by the trial development group taking into consideration the information

obtained from earlier work (Structured Interviews, Chapter 3, Systematic review, Chapter 5, Patients' views, Chapter 6).

7.3.3.1 Primary outcome measure

The proportion of patients achieving treatment success at 6 months. Treatment should be classed as successful if both Patient Global Assessment and Investigator Global Assessments are met (for definitions of scales see Figure 27, page 263):

- **Patient Global Assessment** of disease severity of 0 or 1 on a 4-point scale
- **Assessment** of improvement from baseline using **blinded** clinical images

As identified in the systematic review (Chapter 5), these outcomes are not validated. Following discussion with clinicians (Chapter 3) it was apparent that the primary driver for therapeutic decision making in ELPV is patient reported symptoms. However, in the clinical setting the clinician's judgment will also form part of that assessment. Furthermore, as this is an open-labelled trial, there is a possibility of bias being introduced if the patient global assessment only was used as the primary outcome.

Therefore, this composite primary outcome measure was devised to take into consideration both patient and clinician judgment of disease severity. It is intended that the investigator global assessment is performed using blinded clinical images taken at

baseline and at the end of the treatment period. This way, any bias from the patient-reported outcome should be minimised as both patient and clinician outcomes have to have shown improvement to confirm treatment success.

Figure 27: Patient and Investigator Global Assessment categories or hELP trial primary outcome

Patient Global Assessment: How much bother is the erosive lichen planus causing the patient **TODAY**?	0 -No bother at all/not much bother 1 - A little 2 - A lot 3 - Very much
Investigator Assessment of vulval disease: How do you clinically rate this patient's VULVAL erosive lichen planus at THIS visit?	0 - Clear/almost clear 1 - Mild 2 - Moderate 3 - Severe

7.3.3.2 Secondary outcome measures

1. **Reduction in soreness** throughout the 6 month treatment period compared with baseline using a visual analogue scale.
2. **Global assessment of disease** assessed by:
    a. Patient Global Assessment at baseline, 3, 6 and 12 months
    b. Investigator Assessment by treating clinician at baseline, 3 and 6 months
3. Assessment by blinded assessor using clinical images at baseline and 6 months

4. **Assessment of severity of other oral and vaginal sites if affected –** Investigator assessment by physician at baseline, 3 and 6 months.
5. **Psychological assessment** using the Hospital Anxiety and Depression Scale at baseline, 6 and 12 months.
6. **Assessment of sexual function** at baseline, 6 and 12 months**.**
7. Impact on **health-related quality of life** –using a dermatology specific tool 'Skindex-29' (Ponte 2009) and a general utility measure, the 'Short Form 36'(Brazier 1992) at baseline, 6 and 12 months.
8. **Days of topical steroid use** (as a surrogate marker of control in each of the groups) as documented in patient diary.
9. **Overall treatment satisfaction** assessed by
    a. overall satisfaction
    b. number of patients continuing treatment post the primary endpoint
10. **Economic considerations**: Average cost of intervention in each treatment group per participant based on prescribed medication.

As with the primary outcome measure, the secondary outcome measures are not standardised. These assessments have been derived from the systematic review for all outcome measures used

for vulval disease (Chapter 5), the UK Lichen Planus Society survey and the subsequent patient focus group sessions (Chapter 6). Outcomes 1-6 in the list reflect patients' views on living with ELPV and assess the main aspects of life that are affected by the disease.

Outcome 9 is important as the economic impact of ELPV has not previously been investigated.

7.3.3.3 Safety endpoints

All of the investigational medications are familiar to Dermatology and have been used as part of routine clinical practice for years. It is not anticipated that these agents will have any greater side-effects in this population. Structured interviews (Chapter 3) showed that clinicians were confident in prescribing the proposed medications and had not encountered any unexpected adverse events n their daily practice.

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

7.4 Trial procedures

Participants will undergo 5 study visits in the clinic environment over a six-month treatment period. There will subsequently be a long-term follow up communication 12 months after entering the trial. A

summary of assessments to be made at each trial visit is summarized in Table 37, page 275. A flow diagram of the trial is shown in Figure 28, page 276.

Trial visits are to be as follows:

7.4.1 Pre-screening

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

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

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

- That a biopsy has been performed within the last 12 months to rule out any other pathology that would make non-response to treatment more likely (It may be clinically indicated to repeat the biopsy if unusual clinical features are present for example if the diagnosis was in doubt before commencing immunosuppressive therapy due to the risk of

malignant transformation. This will be a decision made by the clinician on a case by case basis as part of normal care);

- That microbiological swabs are negative (as infection can worsen disease severity). Swabs would only be repeated if there was a clinical need to do so as part of normal care.

The rationale for 3 months duration of clobetasol proprionate 0.05% is based upon the practice described by Cooper et al in their prospective case series of treatment for patients with ELPV (Cooper 2006). Furthermore, it the recognised standard for patients with lichen sclerosus, which is managed similarly in the initial stages (Neill 2010).

A screening visit appointment will be made for all potentially eligible participants. The screening visit may be on the same day as pre-screening depending upon individual circumstances.

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

7.4.2 Baseline visit (Study visit 1)

It may be possible to combine the baseline and safety screening visits (visits I and 2) for participants who have already had the relevant screening investigations done within the past month (this

could be the case for participants under long-term care who were already been considered for systemic therapy) or those randomised to the control group, who do not need any safety screening investigations.

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

Procedures to be carried out at baseline:

- Informed consent
- Confirmation of eligibility criteria.
- Pregnancy test for women of child bearing potential
- Assessment of patient and clinician reported outcome measures
- Pain/soreness using a visual analogue scale.
- Patient Global Assessment at baseline
- Investigator Global Assessment by treating clinician at baseline
- Investigator Global assessment by physician of other oral and vaginal sites

- Hospital Anxiety and Depression Scale
- Assessment of sexual function
- Vulval 'Skindex-29' (Ponte 2009) and 'Short Form 36'(Brazier 1992)
- Digital images to be taken.
- Randomise patient
- Perform safety screening investigations

Once eligibility is confirmed at this visit, participants will be randomised. Only once treatment allocation is known will the relevant safety screening investigations be performed. These will be standard care safety baseline investigations specific to the treatment allocation as recommended through national guidance. As this is a pragmatic trial, it is only appropriate to perform the safety baseline investigations post randomisation as each treatment requires a different set of tests. To perform all of these tests on all of the patients pre-randomisation would be costly and in some aspects, unethical, particularly as a chest x-ray would be required to cover the methotrexate group (but is not required in any of the other groups). In usual practice the investigations would only be performed once a decision has been made about treatment for the patient, and so this is what will happen in the trial.

7.4.3 Safety Screening Visit (Visit 2)

At this visit the results of the safety baseline investigations will be reviewed and if satisfactory, treatment will be commenced.

Participants will be randomised to one of four treatment groups as outlined in Table 36, page 271. The treatment regimens are those that were agreed during structured interviews with clinicians (Chapter 3) and subsequent discussion with collaborators on the trial.

Table 36: Table of treatment groups for hELP trial

Trial treatment arm	Dose summary
Control group: Clobetasol propionate 0.05% ointment alone plus initial reducing course of oral prednisolone	Clobetasol propionate 0.05% once daily for one month followed by alternate day application for one month then twice weekly application. Increase to daily during times of flare and then gradually reduce as before. A course of oral prednisolone starting at 20mg OD for 1 week then reduce by 5mg/week until stop. Oral prednisolone should be used as per usual practice following national guidelines; use of bone protection and gastro protection is not prohibited by this study.
Group A: Hydroxychloroquine plus clobetasol propionate 0.05% ointment	Hydroxychloroquine 400mg p.o. daily. May be reduced to 200mg daily depending upon clinical response. Maximum dose 6.5mg/kg/d. Oral hydroxychloroquine should be used as per usual practice following national guidelines including and appropriate safety monitoring. Clobetasol propionate 0.05% ointment to be used as in control group.
Group B: Methotrexate plus clobetasol propionate 0.05% ointment	Methotrexate starting dose 5-10mg p.o. weekly, increase by 2.5-5mg every 2 weeks until disease stabilised. Maximum dose 25mg weekly. Oral methotrexate should be used as per usual practice following national guidelines including and appropriate safety monitoring; use of folic acid is not prohibited by this study. Clobetasol propionate 0.05% ointment to be used as in control group.
Group C: Mycophenolate mofetil plus clobetasol propionate 0.05% ointment	Mycophenolate mofetil starting dose 500mg p.o. daily for the first week, 500mg twice daily for the second week then increase by 500mg each week until maximum dose reached. Maximum dose 3g daily (in divided doses). Oral Mycophenolate mofetil should be used as per usual practice following national guidelines including and appropriate safety monitoring. Clobetasol propionate 0.05% ointment to be used as in control group.

7.4.4 1 month clinic visit (Study visit 3)

Outcomes will not be formally assessed at this stage.

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

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

7.4.5 3 month clinic visit (Study visit 4)

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

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

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

7.4.6 6 month clinic visit (Study visit 5)

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

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

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

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

7.4.7 12 month follow-up

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

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

- Assess patient and clinician reported outcome measures
- Assess current medication usage

Table 37: Summary table of assessments for hELP trial

Assessment	0 months (baseline and safety screening)	1 month	3 months	6 months	12 months (by telephone, letter or email)
Informed consent	√				
Eligibility checks	√				
Medical history	√				√
Demographics	√				
Randomisation	√				
Standard safety monitoring	√	√	√	√	
Pregnancy test [#]	√	√	√	√	
Prescription given	√	√	√	√	
Digital images[$]	√			√[£]	
Pain/Soreness VAS [*]	√		√	√	
Patient Global Assessment (PGA) [*]	√		√	√	√
Investigator Global assessment of vulva	√		√	√	
Investigator Global assessment of other sites	√		√	√	
Anxiety and depression scale score[*]	√			√	√
Assessment of sexual function[*]	√			√	√
Vulval Skindex 29[*]	√			√	√
SF36[*]	√			√	√
Patient diary[*]	√	√	√	√	
Adverse Events		√	√	√	

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

[$] Images do not need to be taken by medical photography. Images are to assess general improvement and detail is not required.

[£] Analysis by blinded assessor

[*] Assessment completed by the participants

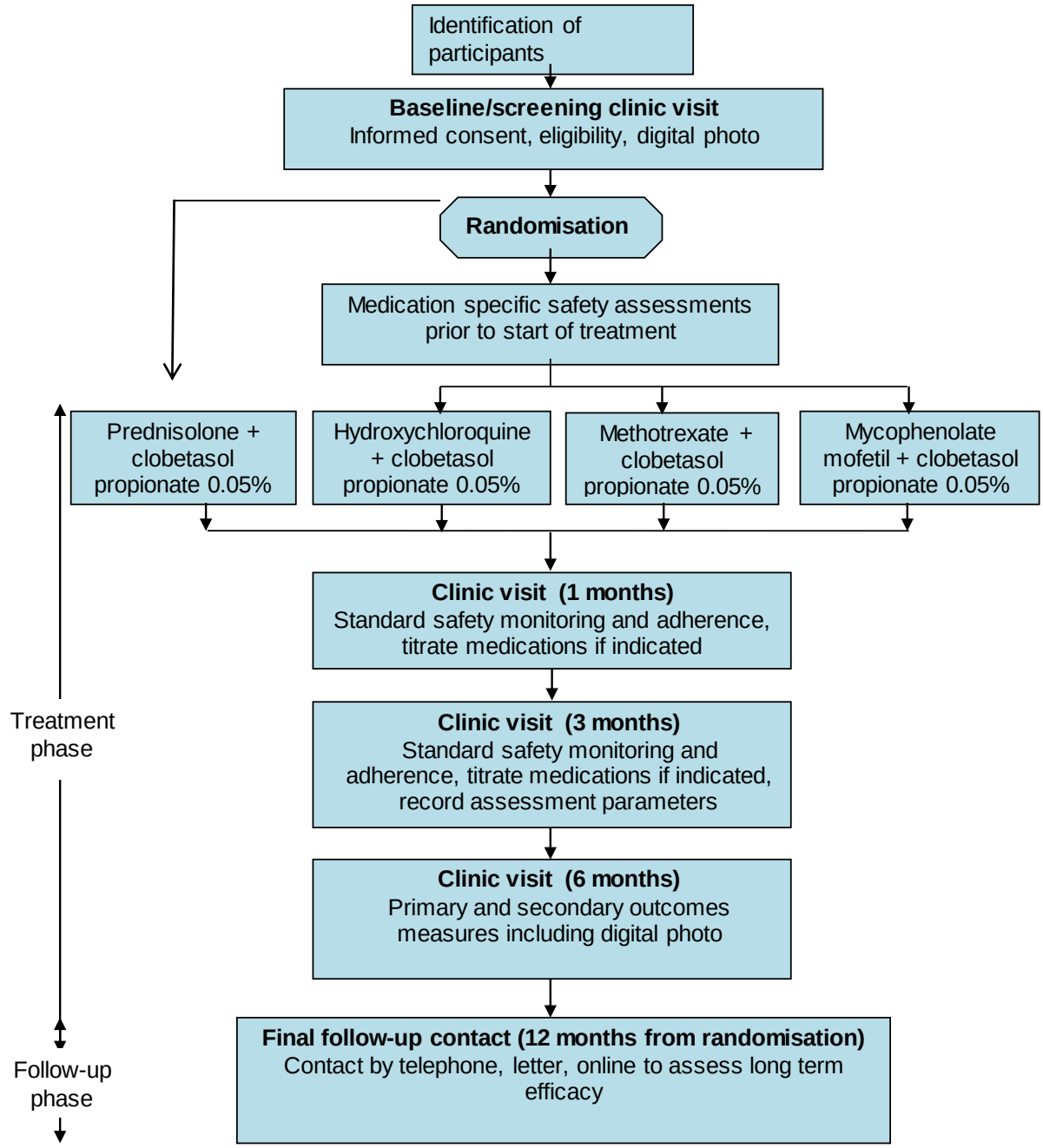

Figure 28: hELP Trial flow chart

7.4.8 Ongoing monitoring investigations

7.4.8.1 All participants

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

7.4.8.2 Control group:

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

7.4.8.3 Active interventions:

As part of usual practice participants receiving hydroxychloroquine, methotrexate or mycophenolate mofetil require monitoring investigations. Monitoring of these should follow national recommendations from the BSR/BHPR guideline for disease-modifying anti-rheumatic drug therapy in consultation with the British Association of Dermatologists (Chakravarty 2008) and the individual medication SmPCs . Communication with clinicians (Chapter 3) indicated that these are the guidelines followed in normal daily practice

7.5 Concomitant and Rescue Medications and Treatments

All medications being continued by a participant on entry to the study and all medication given in addition to the study treatment during the study will be documented on the CRF and also in the participant's medical records. Any changes to these treatments and dosage will be documented.

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

7.5.1 Non-permitted concomitant treatment and medications:

Participants will **not be entered** into the intervention phase if randomisation could potentially result in the combinations documented in Table 38, page 279.

Table 38: Contraindicated medications for hELP Trial

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

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

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

7.5.3 Rescue therapy

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

withdrawn from the treatment (although they will continue to be followed up where possible).

7.5.4 Compliance

As this is a pragmatic study, it will seek to reflect current practice as far as possible (regardless of whether or not the drugs have been taken appropriately). Adherence will be assessed by the managing physician and through self-assessment as reported by the participants at outpatient visits. Acceptable adherence is defined as a participant taking their medication as instructed and partaking in the necessary monitoring investigations.

7.6 Trial management

The trial will have a Chief Investigator who will have overall responsibility for the study and will oversee all study management. The trial will be coordinated centrally from the Centre of Evidence Based Dermatology by the Trial Manager.

There will be a Trial Management Group, a Trial Steering Committee and a Data Monitoring Committee in place to ensure the safe and transparent running of the trial.

7.7 Interventions

The chosen investigational products have been shown through the work in chapters 2 and 3, plus the literature review in chapter 1, to be part of normal practice when treating ELPV and anecdotally have the greatest success rates. However, as there is currently no RCT evidence for any of the trial interventions it was impossible to pick one alone to test in a traditional two-armed, RCT. As patient numbers are scarce and resources limited in this population it was decided to design a four-armed study which will efficiently assess the medications in this group of patients and will give an indication of which one of these interventions is the most effective.

The treatment regimens to be used are as per usual practice following national guidelines for the individual medications. In addition, the regimens have been agreed with collaborators who will be recruiters for the trial.

As this is an open-label trial all of the investigational medical products will be prescribed as normal by the treating clinician and will be dispensed from the participant's usual pharmacy with labelling in accordance with the dispensed medicines regulations.

7.7.1 Treatment groups

Participants will be randomised to one of four treatment groups:

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

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

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

Research arm 3: Oral mycophenolate mofetil (starting at 500mg OD titrated upwards over 3-4 months to a ceiling dose of 3g/day)

PLUS topical clobetasol propionate 0.05% in the same regimen as in the control group. Oral mycophenolate mofetil should be used as per usual practice following national guidelines including appropriate safety monitoring.

All participants will receive an emollient to be used as soap substitute and moisturiser. This was demonstrated as standard care in Chapter 3. The choice of emollient will be usual medical practice for that recruiting site.

7.7.2 Detailed information about the investigational products

7.7.2.1 Clobetasol propionate 0.05%

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

Standard practice for ELPV has been shown to be the use of clobetasol propionate 0.05% on a reducing regimen over three months. It is typically used once daily for one month (to try and induce remission of ELPV) and then weaned to alternate days for

one month then twice weekly for maintenance therapy. If this regimen is ineffective then a patient is likely to be asked to use clobetasol propionate 0.05% at the minimum frequency that maintains symptoms at a tolerable level. If a patient commences systemic therapy they will use clobetasol propionate 0.05% concurrently as systemic therapies can take weeks to months to produce optimum effect and although clobetasol propionate 0.05% is not effective by itself, it is likely to have at least some suppressive disease activity if stopped ELPV may flare severely. As the systemic therapies take effect, disease control will improve and patients will find that they can reduce the frequency of application of clobetasol propionate 0.05% without experiencing flares. If the condition is not controlled by the systemic agent they will continue to use clobetasol propionate 0.05% on a more frequent basis. Therefore the frequency of application of clobetasol propionate 0.05% will act as a surrogate marker of disease control achieved by the systemic agents.

7.7.2.2 Prednisolone

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

Prednisolone will be taken by the control group only (standard care) as a short course for the first four weeks of treatment. Participants

will be treated with 20mg reducing by 5mg per week over a 4 week period. It will be used as per usual practice following national guidelines which will include the use of bone and gastro-protection where necessary.

Prednisolone is included in the control group on the basis that clobetasol propionate 0.05% has failed to control the patient's ELPV thus far and that it would be unethical to continue this completely by itself. Therefore standard care comprising a short course of oral prednisolone for the first month was decided following discussion with collaborators.

7.7.2.3 Hydroxychloroquine sulfate (HCQ)

Hydroxychloroquine will be used up to a dose of up to 200mg twice daily.

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

7.7.2.4 Methotrexate (MTX)

Methotrexate will be prescribed by the oral route for this study. It is available as 2.5mg and 10mg tablets, the 2.5mg strength will be used (which is standard practice within dermatology). Methotrexate is taken on a once weekly basis.

Oral methotrexate should be used as per usual practice following national guidelines in conjunction with folic acid to reduce the incidence of side effects.

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

7.7.2.5 Mycophenolate mofetil (MMF)

Mycophenolate mofetil in both 250mg and 500mg strengths will be required for this study as the dose is gradually titrated to the maximum tolerated amount that is therapeutic for the participant. If a participant is intolerant to the tablet form of mycophenolate mofetil the prescriber may consider prescribing an oral suspension which anecdotally causes fewer gastrointestinal symptoms.

Oral mycophenolate mofetil will be used as per usual practice following national guidelines including appropriate safety monitoring.

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

7.8 Sample size and justification

For the sample size calculation, assumptions for the success rate in the control and intervention arms, and potential loss to follow up rate, had to be made. As there are limited data in the literature to draw conclusions from, these assumptions were based upon expert opinion and clinical experience.

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

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

A staged approach to recruitment will be taken for the trial. After six months, or the recruitment of 40 participants (whichever comes first) it will be assessed whether with the time and resources remaining the target of 76 or 96 patients (as per the sample size calculation for a definitive trial) can be achieved. On the basis that ELPV is a rare condition and the pool of eligible patients limited, two sample sizes have been given. The power of the trial will ultimately be determined by the number of patients that can be recruited with the resources available.

7.9 Randomisation and blinding

Randomisation will be based on minimisation criteria on recruiting centre and disease severity (moderate or severe on the Investigator Global assessment scale, Figure 27, page 263). The randomisation sequence will be concealed until interventions are all assigned and recruitment, data collection, and data cleaning are complete.

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

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

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

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

7.10 Adverse events

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

- Patient-reported side effects at the time of their clinic consultation;
- The managing clinician detecting abnormalities in monitoring blood tests;
- The participant contacting the managing clinician in between clinic appointments to state any problems.

Adverse events will be collected if they are considered secondary to the study drug. All *serious* events will be collected.

7.10.1 Reporting of adverse events

Participants will be asked to contact the study site immediately in the event of any serious adverse event. All adverse events will be recorded and closely monitored until resolution, stabilisation, or until it has been shown that the study medication or treatment is not the cause.

In the event of a pregnancy occurring in a trial participant monitoring shall occur during the pregnancy and after delivery to ascertain any trial related adverse events in the mother or the offspring.

7.11 Stopping of the trial/discontinuation of medications

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

- they have poor ongoing control of disease despite good adherence to the treatment regimen and optimising topical clobetasol propionate 0.05% use and the clinician feels it is unethical to continue; or
- side effects indicate that the participant should not carry on with the designated treatment regimen.

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

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

Participants who are randomised but are subsequently found to be ineligible will be replaced and will not be included in the intention to

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

7.12 Duration of the trial

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

The recruitment period is anticipated to last for 12 months. If the number of participants entering the trial is low, then recruitment may be extended.

Each participant will participate in the trial for 12 months (treatment period: 6 months, follow-up phone call 12 months after randomisation). Her participation will commence upon signing the consent form.

7.13 Ethics Committee and regulatory Approvals

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

The trial will not be initiated before the protocol, informed consent forms and participant and GP information sheets have received approval from the Medicines and Healthcare products Regulatory Agency (MHRA), Research Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) department.

7.14 Publication and Dissemination

Following the analysis of the trial, it is of paramount importance that the findings are disseminated appropriately. The specialties that manage ELPV include dermatologists, gynaecologists, genitourinary physicians and specialist nurses. The optimal way to reach these groups, in addition to publications in peer reviewed journals, will be through the British and International Societies for the Study of Vulval Disease (BSSVD and ISSVD, section 1.7, page 46). These multidisciplinary groups each hold a biennial conference at which the findings will be presented. It would also be planned to present at the British Association of Dermatologists (BAD) Annual meeting.

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

Further collaboration with the BAD will be sought to update their PIS on Lichen Planus as the current version does not cover the erosive subtype. Other groups that have collaborated with, or have links with the trial team include:

- The UK Dermatology Clinical Trials Network
- The UK Lichen Planus Society (UKLP)
- NHS Choices
- Nottinghamshire Collaboration for Leadership in Applied Health Research and Care (CLAHRC)

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

7.15 Chapter 7 Summary

This chapter describes the protocol for a future randomised controlled trial to assess four of the most commonly used treatment regimens for ELPV that is resistant to standard first-line therapy.

The trial has been developed with input from patients, clinicians and members of expert specialist societies in the field of vulval skin disease. Work described in the earlier chapters of this thesis has informed many aspects of the protocol and has ensured that the end result is pragmatic, answers a question of clinical relevance and measures outcomes that are important to patients and clinicians.

The trial has received the relevant regulatory approvals and is planned to commence in 2014.

8 Impact of this research and next steps

8.1 Introduction

Vulval skin disorders have long been underfunded and under-researched. This thesis began by demonstrating that vulval erosive lichen planus, as a rare disease has very little evidence base to support current treatment regimens (Chapter 1), resulting in considerable variation in practice. In addition, this research identified that diagnostic criteria for the disease were not standardised, that there were no accepted outcome measures for the condition and that there was little known about the patient experience of living with the disease.

In identifying these issues, this thesis has evolved. A pragmatic trial needs to follow usual clinical practice, ensure that the included patients are correctly diagnosed with the disease and measure outcomes that are clinically relevant to patients and clinicians. It was therefore important that these areas which were uncertain previously were addressed in order to develop the randomised controlled trial.

Each of the individual studies that comprise this thesis have added to the existing evidence base for vulval erosive lichen planus and work has been well received the clinical community. The following is a reflection on the impact of this project.

8.2 Case-based review and UK multi-centre case note audit.

This study was published in the British Journal of Dermatology in June 2012. It highlighted to the clinical community that:

- Management and assessment of ELPV in the UK is variable and needed be standardised.

- Both objective and subjective assessments of disease severity and impact should be considered when treating vulval disorders such as ELPV.

- A number of systemic treatments may be used for patients with ELPV resistant to first-line therapy but formal assessment of their efficacy needed to be determined through well designed randomised controlled trials.

In the absence of evidence-based guidance for the management of ELPV, the audit standards used in this study, which had been agreed by the members of the British Society for the Study of Vulval Disease, were suggested be used as an interim guide to patient care and as predetermined standards for clinical audit purposes in other centres to assess their practice. In 2013 an abstract was published by an Australian group who have adopted these audit standards (Maor 2013).

8.3 Qualitative investigation into UK clinician views and principles of management of erosive lichen planus affecting the vulva

This study, which consisted of structured interviews with clinicians, was published in the British Journal of Dermatology in July 2013.

It demonstrated a need to consolidate diagnostic criteria and develop outcome measures relevant to both patients and clinicians. It also backed up the results of the case note audit by hearing from clinicians that evidence towards treatment strategies, especially for patients not responding to first-line therapy, was needed.

8.4 International electronic-Delphi Consensus Exercise

This study was published by the British Journal of Dermatology in August 2013. It was also presented to the British Association of Dermatologists in the Plenary session at their annual meeting in July 2013, and to the University of Nottingham School of Medicine Postgraduate Research Forum in June 2013. The work was well received by the scientific and clinical community and the presentations were awarded first prize at both meetings.

Using the e-Delphi technique a set of diagnostic criteria were internationally agreed by physicians with expertise in the diagnosis and management of vulval disease including ELPV. The diagnostic dataset is intended to guide the clinical diagnosis of ELPV and to help standardise the inclusion of patients into clinical trials. Other research groups have already begun to validate these criteria, the work of which is currently in progress.

The e-Delphi methodology used is not restricted to diagnostic criteria or to skin disorders, and can be translated to other fields of medicine where expert opinion is required to answer a question which cannot be answered using the existing evidence base. The audiences to which the work was presented were very interested in the wider applications of the e-Delphi method resulting and have asked for advice on how to utilize the process in their own fields of medicine.

8.5 Systematic review for outcome measures in vulval skin disorders

This systematic review was published by the British Journal of Dermatology in September 2013. It was also presented as a poster at the 'COMET' (Core Outcome Measures in Effectiveness Trials) meeting in June 2013.

The study highlighted that interventional trials of vulval skin conditions have used multiple different scales to measure the same outcome. Furthermore, despite being a major cause of morbidity, functional impairment was rarely assessed by trials of vulval skin conditions. It was recommended that in line with the COMET Initiative a move to standardise outcomes for vulval skin conditions was made.

8.6 Patients' views

This exploratory study investigated the effects of ELPV on peoples' lives and ascertained specific problems encountered from the patients' perspective. The four main themes identified from the focus groups were i) symptoms experienced by patients and subsequent consequences from these symptoms such as effect on quality of life, impact on daily functioning, and psychological distress; ii) negative experiences of management in primary and secondary care due to lack of understanding, poor continuity of care and inadequate communication between specialties; iii) lack of support networks and information available to patients; iv) positive experiences including coping mechanisms and faith in expert clinicians.

The findings have provided a framework on which to base future qualitative investigations in this field and also guide areas for improvement in the clinical care.

Furthermore, patients were consulted upon the proposed randomised controlled trial design. The resulting protocol has therefore been developed with active patient involvement to ensure it is relevant and acceptable to them as service users.

8.7 Randomised controlled trial

This will be the first therapeutic trial of systemic therapy in ELPV and as such will contribute to the existing therapeutic evidence base. The study will investigate whether any of the three investigational agents are better than topical treatment in the management of ELPV resistant to first-line therapy. This four-armed study will guide future research in this field, particularly in identifying which, if any, of the systemic agents should be further investigated in a two-armed randomised controlled trial.

Furthermore, it is hoped that the methodology employed will be translated to randomised controlled trials of other rare conditions. In disease areas where evidence for treatments is lacking and there are a number of possible interventions to test in a controlled trial setting, this multi-armed methodology has the potential to reduce research waste by comparing multiple therapies in one trial. It therefore will provide an answer more quickly and require fewer

patient numbers than performing multiple randomised controlled trials.

8.8 Future research direction

This thesis has made steps to improve care for patients with vulval erosive lichen planus. The randomised controlled trial, which is planned to start recruitment in spring 2014, will provide much needed information on systemic treatments for the condition and the results will guide researchers for future therapeutic trials.

The agreed diagnostic criteria should be formally validated to assess their sensitivity and specificity in diagnosing cases of ELPV. As previously discussed, other research groups have already begun to action this.

As suggested by the systematic review, outcome measures for vulval skin disorders urgently need to be standardised. The outcomes decided for use in the randomised controlled trial are the 'best-fit' of existing current measures. However, time should be dedicated to devising a vulval-specific outcome measure tool. Furthermore, in line with the COMET Initiative, core-outcomes for vulval skin conditions should be agreed on an international level. The electronic-Delphi process would be ideal for use in this setting. Agreed outcomes should then be used in all trials of vulval skin conditions going forward.

Themes identified from the focus group should be further explored on a larger scale. The findings represent a small group of patients from one geographical location. Although they were in keeping with results from the UK Lichen Planus survey, the focus group only provided preliminary in-depth data on patients' experiences and the impact of the disease on their lives. Through involving a greater number of patients from more diverse settings, richer data will be obtained and will provide more substantial evidence on which to base changes in care structure that will ultimately enrich the patient experience.

Our understanding of vulval erosive lichen planus could be improved by future research addressing the following questions:

- What is the true incidence and prevalence of vulval erosive lichen planus?
- Which regimen of super-potent topical corticosteroids is optimum to use as first-line therapy?
- Which regimen of super-potent topical corticosteroids is optimum to maintain remission in those who have responded to first-line therapy? In particular, whether proactive treatment with super-potent topical corticosteroids once or twice weekly is more efficacious than reactive treatment on an as and when basis
- Whether early aggressive therapy reduces progression to scarring and malignant change

8.9 Concluding remarks

Research invariably produces further questions that need to be answered, as demonstrated by this thesis. The cycle of identifying and prioritising research agendas, carrying out research to answer a question and subsequently identifying further areas for exploration is paramount to moving practice forward, regardless of disease area. For patients who suffer the distressing condition of vulval erosive lichen planus this is only the beginning and it is with great hope that this project will stimulate others to take an interest in this condition and help to make a difference through continuing the research cycle.

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10 Appendices

Appendix 1:

ISSVD Patient Information Leaflet on Vulval Erosive Lichen Planus

VULVAR LICHEN PLANUS

What is it?

Lichen planus (LP) is a disease of the skin caused by inflammation. It occurs most commonly in women 50-60 years old. It can affect the genital area, including both the vulva and the vagina. The most common symptoms are burning and soreness. Some women describe itching as well. Lichen planus causes a rash of small purplish bumps, often on the arms, legs or back. It can affect the mouth (oral disease) with a whitish eruption or ulcers. In some cases, the nails and the scalp are also involved. It is possible to have the disease in one area without ever having a problem elsewhere. Many patients with vulvar LP have LP in the mouth as well and sometimes on the skin.

How common is it?

It is estimated that 1 in 4000 women will have vulvar or vaginal LP compared to 1 in 100 who may have oral LP. About 50% of women who have oral lichen planus may have vulvar or vaginal LP but the diagnosis may be missed as dentists do not generally enquire about genital symptoms and the mouth may not be routinely examined in those presenting with genital disease.

What causes LP?

The cause of LP is unknown. There may be a problem with the immune system, the system that protects a person from diseases. In LP the system is overactive and can act against itself (this is called an auto-immune reaction). In some cases, it is possible that an infection or medication can start this reaction. We do not know why the lesions develop in some places and not others. LP may be associated with other auto-immune conditions such as vitiligo (white patches on the skin), thyroid disease and alopecia areata (patches of hair loss).

Lichen planus is NOT contagious and cannot be passed to a sexual partner or to another part of your body.

What are the symptoms and what do I see?

- Soreness, burning and rawness are very common symptoms. Less commonly there may be itching. If the outer layers of the skin break down (erosions), these areas appear moist and red.
- There may be a white lacy pattern on the vulva. This pattern can also be seen around the edges of the erosions
- The vulva may appear pale white or pink/red. Scarring with loss of the inner lips (labia minora) may be seen. The clitoris may be buried under scar tissue. There may be shiny, red, raw areas.
- Intercourse can be painful if the vagina is involved or there is scar tissue narrowing the entrance of the vagina.
- Erosions can occur inside the vagina in a patchy or generalized pattern. Some women have a sticky, yellow or yellow-green discharge, which can be bloodstained, especially after intercourse. The vaginal entrance may become smaller if the inner walls of the vagina or the skin around the entrance sticks together when it heals. This is one reason why intercourse can be painful or even impossible. Sometimes it is difficult for a doctor to perform an internal examination.
- On rare occasions, the skin may have thickened areas. These may have a warty appearance.

If the skin is affected in other parts of the body, the rash is usually on the inside of the wrist, the forearms and the ankles. The spots are a purple color and you may see some fine white streaks on the top of the spots. A similar white, lacy streaking may be seen inside the mouth, but there may not be any symptoms. There may be sore, red, ulcerated areas around the gum margins, tongue and inside of cheeks. Occasionally LP can affect the tear ducts and oesophagus (the tube that carries food from the mouth to the stomach). If you experience excessive watering of the eyes, difficulty in swallowing or it feels as if food gets stuck, you should tell your doctor about this.

How is LP diagnosed?

Doctors familiar with the condition may diagnose it by looking at the skin and seeing the characteristic appearance. The diagnosis is usually confirmed by taking a small piece of skin to be sent to the laboratory and then looked at under a microscope. This is called a biopsy. This is a simple procedure that can be done in the doctor's office after numbing with an anesthetic given on the skin or injected under the skin to be biopsied.

How is LP treated?

There are many treatments used to treat lichen planus. Treatment needs to be selected to fit your problem. Different people respond to different things. The medications will control but often will not cure the LP. Treatment is a long process and close follow up with you and your care-giver is important.

Lichen planus is often managed with medication as there is no absolute cure for LP. However, in some cases, LP seems to come and go of its own accord and it is possible that it will disappear completely. All irritating products must be stopped. Avoid using soap or perfumed products in the area.

As the activity of the immune system is increased in LP, the treatments aim to slow it down. The usual treatment for LP is a strong topical steroid also known as cortisone. The ointment form (petrolatum like) is generally used rather than the cream (white, like thick plain yogurt). This strong cortisone is very safe to use in this condition, and it is safe to use 30 grams in 3 months. This is used once a day for about a month and then on alternate days and eventually as needed. Occasionally, ointments containing calcineurin inhibitors are used (tacrolimus, pimecrolimus). These are treatments that are used to treat other types of inflammation on the skin such as eczema. These will help some people but may sting when they are first applied.

If the vagina is involved, then a vaginal preparation containing cortisone can be inserted into the vagina. For scarring and narrowing of the vagina and/or the entrance into the vagina, physiotherapy of the pelvic floor or dilators are advised. Only rarely is surgery needed.

If the ointments do not control the inflammation, then cortisone tablets taken orally or some types of cortisone injection can be helpful. Medication to lower the overactive immune system may be needed. Examples of these are methotrexate or ciclosporin (Cyclosporine). These are medications that require blood tests to monitor their side-effects and this will all be discussed with you if you require them. Women on cortisone can have a safe pregnancy. However, it is very important that you do not become pregnant if you are taking any of the other drugs discussed above, as they can be harmful to the baby.

What should I watch for?

As LP is a long lasting inflammatory skin condition, there is a very slight increased risk of developing local types of skin cancer in the area compared to women without LP. The risk is about 3%. Any new raised, bleeding or non-healing areas in your genital area should be reported to your healthcare provider. It is important that your LP is monitored and that you attend for follow-up visits with your healthcare provider at least once per year.

Appendix 2

Data Abstraction Form for Case Note audit and Review

Section 1 - General details and disease history

Please complete for all patients with erosive lichen planus seen in your department in the past 12 months.

GENERAL DETAILS	
Centre ID	
Patient ID	
Age	
Co morbidities (possible exclusion criteria for RCT)	□ History of alcohol excess □ Renal impairment □ Pregnant/lactating □ Liver impairment □ Previous or current malignancy (cutaneous or internal)
Concurrent medications? Please indicate if the patient is taking any of the following: (possible exclusion criteria for RCT)	□ Acitretin □ Aciclovir □ Digoxin □ Doxycycline □ Hydroxychloroquine □ Leflunomide □ Omeprazole □ Phenytoin

GENERAL DETAILS			
DISEASE HISTORY			
Duration of disease (years)			
How was disease severity recorded?	□ Schematic diagram □ Description of symptoms □ Ability for sexual activity □ Visual analogue score □ DLQI □ Other skin sites recorded? □ Oral cavity examined?		
Which specialties are involved in management	□ GP □ General dermatology □ Dermatologist with a special interest □ Oral medicine □ Gynaecology		
Was biopsy taken?	□ Yes □ No	Biopsy result?	□ Consistent with ELP □ No features of ELP but ruled out other pathology □ Inconclusive Zoon's Vulvitis

CENTRE ID: PATIENT REVIEW ID:

GENERAL DETAILS	
Sites affected -	☐ Skin ☐ Mouth ☐ Vulva ☐ Vagina ☐ Scalp ☐ Anus ☐ Oesophagus ☐ Not recorded

Section 2 - Treatment history

For each patient please use this section to summarise their treatment regimens to date:

TREATMENT HISTORY			
Treatment regimens to date:	□ Topical only (□ Dermovate, □ Protopic) □ Systemic only □ Combination systemic/topical		
CURRENT TREATMENT REGIMEN			
Name treatment(s)		Treatment code(s)	
Treatment regimen/dose		Regimen code (s)	
Duration of treatment (months)			
Side effects (if any)		Side effect code (s)	

PAST TREATMENT REGIMEN 1			
Name treatment(s)		Treatment code (s)	
Treatment regimen/dose		Regimen code (s)	
Duration of treatment (months)			
Side effects (if any)		Side effect code(s)	
Reason treatment stopped	□ Treatment successful □ Treatment failed □ Side effects □ Patient's choice □ Other (please state)		

PAST TREATMENT REGIMEN 2			
Name treatment (s)		Treatment code (s)	
Treatment regimen/dose		Regimen code (s)	
Duration of treatment (months)			
Side effects (if any)		Side effect code(s)	
Reason treatment stopped:	□ Treatment successful □ Treatment failed □ Side effects □ Patient's choice □ Other (please state)		

PAST TREATMENT REGIMEN 3			
Name treatment (s)		Treatment code (s)	
Treatment regimen/dose		Regimen code (s)	
Duration of treatment (months)			
Side effects (if any)		Side effect code(s)	
Reason treatment stopped:	□ Treatment successful □ Treatment failed □ Side effects □ Patient's choice □ Other (please state)		

PAST TREATMENT REGIMEN 4			
Name treatment (s)		Treatment code (s)	
Treatment regimen/dose		Regimen code (s)	
Duration of treatment (months)			
Side effects (if any)		Side effect code(s)	
Reason treatment stopped:	□ Treatment successful □ Treatment failed □ Side effects □ Patient's choice □ Other (please state)		

PAST TREATMENT REGIMEN 5			
Name treatment (s)		Treatment code (s)	
Treatment regimen/dose		Regimen code (s)	
Duration of treatment (months)			
Side effects (if any)		Side effect code(s)	
Reason treatment stopped:	□ Treatment successful □ Treatment failed □ Side effects □ Patient's choice □ Other (please state)		

Section 1 - General details and disease history

Please complete for all patients with erosive lichen planus seen in your department in the past 12 months.

GENERAL DETAILS	
Centre ID	
Patient ID	
Age	
Co morbidities (possible exclusion criteria for RCT)	□ History of alcohol excess □ Renal impairment □ Pregnant/lactating □ Liver impairment □ Previous or current malignancy (cutaneous or internal)
Concurrent medications? Please indicate if the patient is taking any of the following: (possible exclusion criteria for RCT)	□ Acitretin □ Aciclovir □ Digoxin □ Doxycycline □ Hydroxychloroquine □ Leflunomide □ Omeprazole □ Phenytoin

GENERAL DETAILS			
DISEASE HISTORY			
Duration of disease (years)			
How was disease severity recorded?	□ Schematic diagram □ Description of symptoms □ Ability for sexual activity □ Visual analogue score □ DLQI □ Other skin sites recorded? □ Oral cavity examined?		
Which specialties are involved in management	□ GP □ General dermatology □ Dermatologist with a special interest □ Oral medicine □ Gynaecology		
Was biopsy taken?	□ Yes □ No	Biopsy result?	□ Consistent with ELP □ No features of ELP but ruled out other pathology □ Inconclusive Zoon's Vulvitis

CENTRE ID: PATIENT REVIEW ID:

GENERAL DETAILS	
Sites affected -	□ Skin □ Mouth □ Vulva □ Vagina □ Scalp □ Anus □ Oesophagus □ Not recorded

CENTRE ID: PATIENT REVIEW ID:

Section 2 - Treatment history

For each patient please use this section to summarise their treatment regimens to date:

TREATMENT HISTORY			
Treatment regimens to date:	□ Topical only (□ Dermovate, □ Protopic) □ Systemic only □ Combination systemic/topical		
CURRENT TREATMENT REGIMEN			
Name treatment(s)		Treatment code(s)	
Treatment regimen/dose		Regimen code (s)	
Duration of treatment (months)			
Side effects (if any)		Side effect code (s)	

PAST TREATMENT REGIMEN 1			
Name treatment(s)		Treatment code (s)	
Treatment regimen/dose		Regimen code (s)	
Duration of treatment (months)			
Side effects (if any)		Side effect code(s)	
Reason treatment stopped	□ Treatment successful □ Treatment failed □ Side effects □ Patient's choice □ Other (please state)		

PAST TREATMENT REGIMEN 2			
Name treatment (s)		Treatment code (s)	
Treatment regimen/dose		Regimen code (s)	
Duration of treatment (months)			
Side effects (if any)		Side effect code(s)	
Reason treatment stopped:	□ Treatment successful □ Treatment failed □ Side effects □ Patient's choice □ Other (please state)		

PAST TREATMENT REGIMEN 3			
Name treatment (s)		Treatment code (s)	
Treatment regimen/dose		Regimen code (s)	
Duration of treatment (months)			
Side effects (if any)		Side effect code(s)	
Reason treatment stopped:	□ Treatment successful □ Treatment failed □ Side effects □ Patient's choice □ Other (please state)		

PAST TREATMENT REGIMEN 4			
Name treatment (s)		Treatment code (s)	
Treatment regimen/dose		Regimen code (s)	
Duration of treatment (months)			
Side effects (if any)		Side effect code(s)	
Reason treatment stopped:	□ Treatment successful □ Treatment failed □ Side effects □ Patient's choice □ Other (please state)		

PAST TREATMENT REGIMEN 5			
Name treatment (s)		Treatment code (s)	
Treatment regimen/dose		Regimen code (s)	
Duration of treatment (months)			
Side effects (if any)		Side effect code(s)	
Reason treatment stopped:	□ Treatment successful □ Treatment failed □ Side effects □ Patient's choice □ Other (please state)		

Appendix 3:

Structured Interview Questionnaire

Vulval Erosive Lichen Planus
Structured Interviews

Interview Number: Date:

1. What are your current feelings on treating patients with vulval erosive lichen planus?
   (Assessing behaviour/experience)

2. Do you often follow patients up long term?
   a. What is the reason for this?
   (Assessing opinion/belief/experience)

3. How do you diagnose vulval erosive lichen planus (ELPV)?
   a. Clinical features: please specify

      (Assessing knowledge/experience)

   b. Pathological features

      (Assessing knowledge/experience)

4. Do you routinely biopsy patients with a clinical diagnosis of ELPV?
   a. If no, in which circumstances would you perform a biopsy?

   (Assessing experience)

5. Do you record clinical severity of ELPV? *(Assessing experience)*
   a. How do you assess it?

   b. Do you use any particular tools?

6. Do you assess impact of disease on the patient? *(Assessing experience)*

   a. How do you assess it?

   b. Do you use any particular tools?

7. Are there any specific outcomes you feel should be used for clinical trial purposes? Opinion/belief

8. What is your treatment approach for patients with ELPV? *(Assessing knowledge/experience)*

a. First line?

b. Second line?

c. How soon after commencing treatment do you follow up a patient to assess whether treatment is working? How do you make that assessment?

d. What makes you move up the therapeutic ladder?

9. Which of the following drugs are you happy using within your *general* dermatological practice? *(Assessing experience)*

a. Acitretin

b. Hydroxychloroquine

c. Methotrexate

d. Mycophenolate mofetil

e. Minocycline

f. Minocycline + nicotinamide

10. Are there any that you have never prescribed or do not prescribe? *(Assessing experience and opinion)*

a. Are there specific reasons for this?

11. Would you prescribe these for patients with ELPV? *(Assessing opinion)*

12. Do you leave a specific washout period for these agents before commencing an alternative systemic treatment?
(Assessing experience)

13. What do you think a wash out period should be for clinical trial purposes when transitioning between therapies? *(Assessing knowledge and opinion)*

a. 1 month

b. 3 months

c. Other

14. i)Have any patients under your care experienced any *significant* adverse effects (such as acute liver/renal/bone marrow failure, hypersensitivity, severe rash etc.) when receiving the following treatments: *(Assessing experience)*

    a. Acitretin

    b. Hydroxychloroquine

    c. Methotrexate

    d. Mycophenolate mofetil

    e. Minocycline

    f. Minocycline + nicotinamide

    ii) Have any of these adverse events *stopped* you from further prescribing the agent(s)?

15. i. What is your standard dosing regimen for the following agents (i.e. as per BAD/BNF guidelines, or do you have your own preferred dose escalation regimen/max dose?) *(Assessing experience and knowledge)*
    a. Acitretin

    b. Hydroxychloroquine

    c. Methotrexate

    d. Mycophenolate mofetil

    e. Minocycline

    f. Minocycline + nicotinamide

    ii. Is this different if you use these agents in the treatment of ELPV? *(Assessing opinion)*

16. Are there any restrictions within your centre for prescribing the following treatments? If so, please state what these restrictions are: *(Assessing knowledge)*

    a. Acitretin

b. Hydroxychloroquine

c. Methotrexate

d. Mycophenolate mofetil

e. Minocycline

f. Minocycline + nicotinamide

17. If any of the aforementioned treatments were agents in a randomized controlled trial for patients with ELPV, would this prevent your participation in the trial? *(Assessing opinion)*

    a. Which ones and why?

18. Do you routinely recommend soap substitution and regular use of an emollient for patients with ELPV? *(Assessing opinion/experience)*

    a. Which is your preferred agent?

    b. Do you think the agent should be specified for patients included in an RCT or should advice only be given about vulval skin care?

19. Do you think a therapeutic trial for ELP should include patients with genital OR oral disease, or restrict to the genital population only? *(Assessing opinion)*

20. Do you have any further comments regarding systemic treatments for ELPV? *(Assessing opinion)*

21. Would you be willing to be consulted about the design of a trial protocol for an RCT in this area? *(Assessing opinion)*
22. Would you be willing to recruit patients to an RCT? *(Assessing opinion)*
23. Would you be put off recruiting into an RCT if one of the treatment arms was a placebo? *(Assessing opinion)*

24. What sort of hospital do you work in? *(Assessing background)*

25. Do you have a dedicated vulval clinic/clinician with a subspecialist interest in vulval disease? *(Assessing background)*

26. How many patients with vulval disease do you typically see each month? *(Assessing background)*
    a. How many have vulval ELP?

27. What specialty do you fall under? *(Assessing background)*

    a. Dermatology

    b. Gynaecology

    c. Genitourinary medicine

    d. Other

28. Are you a member of the ISSVD, BSSVD or any other specialist societies that have an interest in vulval disease? *(Assessing background)*

Appendix 4

Electronic Delphi Consensus Exercise Round 1 Questionnaire

Diagnostic Criteria for Vulval Erosive Lichen Planus

Round 1 - Introduction

Thank you for participating in this Delphi Consensus exercise to reach an agreement on diagnostic criteria for erosive lichen planus affecting the vulva (ELPV). It is hoped that the outcome of this project will help physicians in the early recognition of ELPV and lead to prompt treatment and alleviation of symptoms. A defined set of diagnostic criteria will also assist recruitment into clinical trials that advance knowledge of this difficult condition.

In preparation for this project, we have performed a review of the literature to summarise diagnostic criteria that have been used in previous studies of ELPV. We have also spoken to physicians through interviews to establish their current practice. This questionnaire is therefore based upon published literature and current clinical opinion.

The ‘Delphi’ method which we are using for this consensus work will be run in 3 rounds.

- Round 1 (the current round): you will be asked to assess a list of potential diagnostic criteria for ELPV. You will have the opportunity to add any items that you perceive are missing.

- Round 2: you will receive feedback detailing the entire group’s responses. You will have the opportunity to reflect upon and modify your answers if you wish.

- Round 3: you will be asked to rank the items that have reached consensus in the first two rounds so that a 'core set' of major and minor diagnostic criteria for ELPV can be determined.

We appreciate that due to the skill mix of participants some questions may appear more relevant to your daily practice than others. It is important that you answer all questions even if you need to respond 'not sure'. It is also important that you make every effort to complete all three rounds as non-response may have consequences for the end results. Each round will only take a few minutes to complete.

You will be asked for your name at the end of the survey. This is purely for administrative purposes as only responders can participate in subsequent rounds. Only the study administrator will see your name and it will be deleted once the analysis of each round is complete.

Once again, thank you for participating.

Rosalind Simpson
Ruth Murphy

Diagnostic Criteria for Vulval Erosive Lichen Planus

Round 1 - Clinical criteria

The following questions are regarding CLINICAL criteria for diagnosing erosive lichen planus of the vulva.

***1. In your opinion, how important are the following CLINICAL criteria to make the diagnosis of erosive lichen planus of the vulva:**

	Very important	Important	Less important	Not important	Not sure
1. Well demarcated erosions at the vaginal introitus	◯	◯	◯	◯	◯
2. Well demarcated glazed erythematous areas at the vaginal introitus	◯	◯	◯	◯	◯
2. Symmetrical distribution of lesions	◯	◯	◯	◯	◯
3. Hyperkeratotic white border to erythematous areas/erosions	◯	◯	◯	◯	◯
4. Wickham's striae present in areas of surrounding skin	◯	◯	◯	◯	◯
5. Scarring/loss of normal architecture e.g. labial adhesions, loss of labia minora, narrowing of introitus, clitoral burying	◯	◯	◯	◯	◯
6. Presence of an erosive vaginitis	◯	◯	◯	◯	◯
7. Presence of vaginal discharge	◯	◯	◯	◯	◯
8. Pain on Q-tip pressure	◯	◯	◯	◯	◯
9. Involvement of other mucocutaneous sites, e.g. mouth, skin/scalp/nails, eyes, oesophagus	◯	◯	◯	◯	◯

2. Are there any additional CLINICAL items that you perceive to be important in diagnosing erosive lichen planus of the vulva? (Please list)

1.
2.
3.

Diagnostic Criteria for Vulval Erosive Lichen Planus

Round 1 - Pathological criteria

The following questions are regarding HISTOPATHOLOGICAL criteria for diagnosing erosive lichen planus of the vulva.

***3. In your opinion, how important are the following HISTOPATHOLOGICAL criteria to make the diagnosis of erosive lichen planus of the vulva:**

	Very important	Important	Less important	Not important	Not sure
1. Presence of a well-defined inflammatory band in the superficial connective tissue that involves the dermo-epidermal junction	◯	◯	◯	◯	◯
2. Presence of an inflammatory infiltrate that consists predominantly of lymphocytes	◯	◯	◯	◯	◯
3. Signs of basal cell layer degeneration	◯	◯	◯	◯	◯

4. Are there any additional HISTOPATHOLOGICAL items that you perceive to be important in diagnosing erosive lichen planus of the vulva? (Please list)

1.
2.
3.

Diagnostic Criteria for Vulval Erosive Lichen Planus

Round 1 - Other information

5. Do you have any further comments about diagnostic criteria for erosive lichen planus affecting the vulva?

Diagnostic Criteria for Vulval Erosive Lichen Planus

Round 1 - Demographic information

***6. Please indicate your specialty of practice:**

- ◯ Dermatology
- ◯ Gynecology
- ◯ Histopathology
- ◯ Genitourinary medicine/Venerology/Sexual medicine
- ◯ Other (please specify)

***7. Please indicate your clinical grade:**

- ◯ Consultant
- ◯ Resident/Specialist registrar
- ◯ Nurse specialist
- ◯ Other (Please specify)

***8. How long have you held a specialist interest in vulval skin disorders?**

- ◯ Less than 5 years
- ◯ 6-10 years
- ◯ 11-15 years
- ◯ 16-20 years
- ◯ More than 20 years

***9. Please indicate your country of practice:**

***10. Please indicate your name (this is for administrative purposes and will be deleted once analysis is complete).**

Diagnostic Criteria for Vulval Erosive Lichen Planus

Thank you

Thank you for taking the time to submit your answers. We will be in contact with the results of Round 1 shortly. This research is being run from the Centre of Evidence Based Dermatology at the University of Nottingham.

If you have any queries please contact:

rosalind.simpson@nottingham.ac.uk

Appendix 5

Electronic Delphi Consensus Exercise Round 2 Questionnaire

Diagnostic Criteria for Vulval Erosive Lichen Planus

Round 2 - Introduction

Dear Participant,

Welcome to Round 2 of the Consensus Exercise to agree diagnostic criteria for erosive lichen planus affecting the vulva (ELPV). Your continuing input is crucial to helping the International Community better standardize management of ELPV.

It is important that you answer ALL ROUNDS as any dropout of participants will THREATEN THE SCIENTIFIC CREDIBILITY of the exercise.

In light of the responses to Round 1 the questionnaire has been modified. Some wording has been amended and some questions have been removed. We now ask for your brief responses to Round 2, this should less than 10 minutes.

Responses to Round 1 have been analyzed and are displayed as a percentage along the response bar. When answering these questions again, please consider the changes we have made and the group's overall previous response. We hope that in this round a move towards consensus will occur for the diagnostic criteria that participants believe are important.

We have taken into account additional comments from Round 1 as much as possible; remember that we are trying to agree a DIAGNOSTIC dataset based upon CLINICAL and/or HISTOPATHOLOGICAL findings. Therefore secondary features of the disease e.g. dyspareunia, poor response to treatment etc. are intentionally NOT included in the questionnaire.

When answering the questions it may be helpful to consider the terms 'very important' and 'important' synonymous with 'major (essential)' and 'minor'. We appreciate that it is difficult to quantify the importance of a particular feature but we hope to come up with a list of criteria that are 'essential' for diagnosing ELPV and a list of 'optional' others that are helpful, but not essential.

Thank you for your continued input,

Rosalind Simpson
Ruth Murphy

Diagnostic Criteria for Vulval Erosive Lichen Planus

The questions on the following pages are regarding CLINICAL criteria for diagnosing erosive lichen planus of the vulva. It is stated whether the questions are the same or have been amended from Round 1.

Some questions have been removed from Round 2. This is because in Round 1 they reached a critical threshold of opinion and were rated as either 'less important' or 'not important' by participants. The questions that have been removed are:

- In your opinion how important is it that lesions are symmetrical to make the diagnosis of erosive lichen planus of the vulva?

- In your opinion how important is the presence of vaginal discharge to make the diagnosis of erosive lichen planus of the vulva?

- In your opinion how important is the presence of pain on Q-tip pressure to make the diagnosis of erosive lichen planus of the vulva?

1. If you disagree with the exclusion of any these statements then please comment below:

Diagnostic Criteria for Vulval Erosive Lichen Planus

Round 2 - Clinical criteria

The wording for this question has been amended and we have combined the clinical features of well demarcated erosions OR glazed erythematous areas into one diagnostic criteria. These were asked as two separate questions in Round 1.

Scores from Round 1 for each of these features have been combined and are displayed in brackets.

*2. In your opinion how important is the following CLINICAL feature to make the diagnosis of erosive lichen planus of the vulva:

	Very important (39.1%)	Important (43.9%)	Less important (11.0%)	Not important (2.8%)	Not sure (3.4%)
Well demarcated erosions or glazed erythematous areas at the vaginal introitus	◯	◯	◯	◯	◯

Diagnostic Criteria for Vulval Erosive Lichen Planus

Round 2 - Clinical criteria

The wording for this question has been amended and we have combined the clinical features of a hyperkeratotic white border AND/OR Wickham's striae in surrounding skin into one diagnostic criteria. These were asked as two separate questions in Round 1.

Scores from Round 1 for each of these features have been combined and are displayed in brackets.

*3. In your opinion how important is the following CLINICAL feature to make the diagnosis of erosive lichen planus of the vulva:

	Very important (12.4%)	Important (35.0%)	Less important (34.3%)	Not important (13.7%)	Not sure (4.8%)
Presence of a hyperkeratotic white border to erythematous areas/erosions +/- Wickham's striae present in surrounding skin	◯	◯	◯	◯	◯

Diagnostic Criteria for Vulval Erosive Lichen Planus

Round 2 - Clinical criteria

The wording for this question remains the same as in Round 1. Scores from Round 1 are displayed in brackets.

***4. In your opinion how important is the following CLINICAL feature to make the diagnosis of erosive lichen planus of the vulva:**

	Very important (26%)	Important (46.6%)	Less important (20.5%)	Not important (5.5%)	Not sure (1.4%)
Scarring/loss of normal architecture e.g. labial adhesions, loss of labia minora, narrowing of introitus, clitoral burying	◯	◯	◯	◯	◯

Diagnostic Criteria for Vulval Erosive Lichen Planus

Round 2 - Clinical criteria

This question has been amended to be more specific. In Round 1 it read:

'Presence of an erosive vaginitis'

Scores from the original Round 1 question are dislpayed in brackets.

***5. In your opinion how important is the following CLINICAL feature to make the diagnosis of erosive lichen planus of the vulva:**

	Very important (13.7%)	Important (38.4%)	Less important (38.4%)	Not important (6.8%)	Not sure (2.7%)
Presence of vaginal inflammation +/- vaginal scarring	◯	◯	◯	◯	◯

Diagnostic Criteria for Vulval Erosive Lichen Planus

Round 2 - Clinical criteria

The wording for this question remains the same as in Round 1. Scores from Round 1 are displayed in brackets.

***6. In your opinion how important is the following CLINICAL feature to make the diagnosis of erosive lichen planus of the vulva:**

	Very important (31.5%)	Important (35.6%)	Less important (19.2%)	Not important (13.7%)	Not sure (0 %)
Involvement of other mucocutaneous sites e.g mouth, skin/scalp/nails, oesophagus	◯	◯	◯	◯	◯

Diagnostic Criteria for Vulval Erosive Lichen Planus

Round 2 - Additional clinical criteria

The following questions are additional to Round 1 based upon participants' previous comments.

***7. In your opinion how important are the following CLINICAL criteria for diagnosing erosive lichen planus of the vulva?**

	Very important	Important	Less important	Not important	Not sure
Findings on wet mount preparation	◯	◯	◯	◯	◯
Symptoms of pain/burning	◯	◯	◯	◯	◯

Diagnostic Criteria for Vulval Erosive Lichen Planus

The questions on the following pages are regarding HISTOPATHOLOGICAL criteria for diagnosing erosive lichen planus of the vulva. No questions from Round 1 have been removed from this section.

Diagnostic Criteria for Vulval Erosive Lichen Planus

Round 2 - Histopathological criteria

The wording for this question remains the same as in Round 1. Scores from Round 1 are displayed in brackets.

N.B. It is assumed that biopsy specimen has been taken from the EDGE OF A LESION for the described histological findings to be present.

***8. In your opinion how important is the following HISTOPATHOLOGICAL feature to make the diagnosis of erosive lichen planus of the vulva:**

	Very important (39.7%)	Important (47.9%)	Less important (5.5%)	Not important (0%)	Not sure (6.8%)
Presence of a well-defined inflammatory band in the superficial connective tissue that involves the dermo-epidermo junction	◯	◯	◯	◯	◯

Diagnostic Criteria for Vulval Erosive Lichen Planus

Round 2 - Histopathological criteria

This question remains the same as in Round 1. Scores from Round 1 are displayed in brackets.

N.B. It is assumed that biopsy specimen has been taken from the EDGE OF A LESION for the described histological findings to be present.

***9. In your opinion how important is the following HISTOPATHOLOGICAL feature to make the diagnosis of erosive lichen planus of the vulva:**

	Very important (12.3%)	Important (64.4%)	Less important (13.7%)	Not important (2.7%)	Not sure (6.8%)
Presence of an inflammatory infiltrate that consists PREDOMINANTLY of lymphocytes	◯	◯	◯	◯	◯

Diagnostic Criteria for Vulval Erosive Lichen Planus

Round 2 - Histopathological criteria

The wording for this question has been amended. Specific features describing keratinocyte destruction have been added into the description.

In Round 1 the question read:

'signs of basal cell degeneration.'

Scores from the original Round 1 question are displayed in brackets.

N.B. It is assumed that biopsy specimen has been taken from the EDGE OF A LESION for the described histological findings to be present.

***10. In your opinion how important is the following HISTOPATHOLOGICAL feature to make the diagnosis of erosive lichen planus of the vulva:**

	Very important (17.8%)	Important (56.2%)	Less important (13.7%)	Not important (0%)	Not sure (12.3%)
Signs of basal cell layer degeneration e.g the presence of Civatte bodies,abnormal keratinocytes or basal apoptosis	◯	◯	◯	◯	◯

Diagnostic Criteria for Vulval Erosive Lichen Planus

Round 2 - Additional histopathological criteria

The following questions are additional to Round 1 based upon participants' previous comments. N.B. It is assumed that biopsy specimen has been taken from the edge of a lesion for the described histological findings to be present.

*11. In your opinion how important are the following HISTOPATHOLOGICAL criteria for diagnosing erosive lichen planus of the vulva?

	Very important	Important	Less important	Not important	Not sure
Epidermal changes e.g. wedge shaped hypergranulosis, saw toothed acanthosis	◯	◯	◯	◯	◯
Absence of dermal hyalinasation	◯	◯	◯	◯	◯

*12. In your opinion:

	Very important	Important	Less important	Not important	Not sure
How important are DIRECT IMMUNOFLUORESCENCE findings in diagnosing erosive lichen planus of the vulva?	◯	◯	◯	◯	◯

Diagnostic Criteria for Vulval Erosive Lichen Planus

Round 2 - Terminology

This is an additional question based upon comments from Round 1.

***13. What is the best nomenclature for the finding of painful erosions/glazed erythematous lesions at the vaginal introitus (+/- vaginal involvement):**

- ◯ Vulval erosive lichen planus
- ◯ Vulvovaginal erosive lichen planus
- ◯ Vulvovaginal lichen planus

Round 2 - Demographic information

***14. Please indicate your specialty of practice:**

- ◯ Dermatology
- ◯ Histopathology/Dermatopathology
- ◯ Genitourinary medicine/Venerology/Sexual medicine
- ◯ Gynecology/O+G

***15. Please indicate your clinical grade:**

- ◯ Associate Specialist
- ◯ Consultant
- ◯ Nurse specialist
- ◯ Professor/Associate Professor
- ◯ Resident/Specialist registrar
- ◯ Other (Please specify)

***16. How long have you held a specialist interest in vulval skin disorders?**

- ◯ Less than 5 years
- ◯ 6-10 years
- ◯ 11-15 years
- ◯ 16-20 years
- ◯ More than 20 years

***17. Please indicate your country of practice:**

***18. Please indicate your name (this is for administrative purposes and will be deleted once analysis is complete).**

Diagnostic Criteria for Vulval Erosive Lichen Planus

Thank you

Thank you for taking the time to submit your answers. We will be in contact with the results of Round 2 shortly. This research is being run from the Centre of Evidence Based Dermatology at the University of Nottingham.

If you have any queries please contact:

rosalind.simpson@nottingham.ac.uk

19. Please leave any additional comments here:

Appendix 6

Electronic Delphi Consensus Exercise Round 3 Questionnaire

ELPV - Round 3

Round 3 - Introduction

Dear Participant,

Thank you for returning to this survey for Round 3.

In this stage we would like to narrow down the items that reached agreement in the previous rounds into ‘essential’ and ‘supportive' diagnostic criteria. We also want to establish HOW MANY 'supportive' criteria should accompany 'essential' criteria in a final diagnostic dataset.

'Essential' means that a diagnostic feature MUST be present to make the diagnosis.

'Supportive' means that the feature does not have to be present, but adds weight to other diagnostic features that are present.

A small number of statements have been revised. Where this has happened we have indicated the previous wording and highlighted any changes.

To try and reach consensus in this round, the response options have been set at ‘essential/supportive/neither' or 'agree/disagree'. You will have the option to comment after each item.

Items that did not reach consensus in Round 2, have been excluded from Round 3. You will have the opportunity to view and comment upon excluded items if you wish.

We hope that your answers from this round will form a definitive diagnostic dataset that can be utilised in clinical practice.

Thank you for your continued input into this project.

Rosalind Simpson
Ruth Murphy

ELPV - Round 3

Round 3 - Terminology

In Round 2 we asked whether participants to comment upon the nomenclature that should be used for the condition. The options that were given were:

Vulval erosive lichen planus;

Vulvovaginal erosive lichen planus;

Vulvovaginal lichen planus.

Consensus was not reached and many commented that the nomenclature depends upon the individual clinical context.

For the purposes of this exercise we will continue to use the term 'EROSIVE LICHEN PLANUS OF THE VULVA' (ELPV), although we appreciate that not all patients will have true erosions and some may have involvement more extensive than just the vulva.

In practice, it seems that physicians will use the diagnostic term 'erosive lichen planus of the [....]' suffixed by the site(s) affected e.g. Erosive lichen planus of the vulva and vagina, Erosive lichen planus of the vulva and gingiva etc.

The diagnostic criteria agreed in this exercise will identify patients with vulvo-vaginal involvement but subsets involving other mucosal surfaces will rely on further clinical evaluation of signs and symptoms e.g. oral, oesophageal, cervical and conjunctival involvement.

1. Please add any comments regarding nomenclature of the condition

ELPV - Round 3

Round 3 -Clinical criteria

The questions on the following pages are regarding CLINICAL diagnostic criteria. Please state whether you believe the diagnostic items are 'essential' or 'supportive' to make the diagnosis.

Remember:

'ESSENTIAL' means that a diagnostic feature MUST be present to make the diagnosis;

'SUPPORTIVE' means that the feature does not have to be present, but adds weight to other diagnostic features that are present.

The wording of these questions have not changed from Round 2.

*2. How do you rate the following feature in making the diagnosis of ELPV?

	Essential	Supportive	Neither
Well demarcated erosions or glazed erythematous areas at the vaginal introitus	◯	◯	◯

Comments

*3. How do you rate the following feature in making the diagnosis of ELPV?

	Essential	Supportive	Neither
Presence of a hyperkeratotic white border to erythematous areas/erosions +/- Wickham's striae in surrounding skin	◯	◯	◯

Comments

ELPV - Round 3

***4. How do you rate the following feature in making the diagnosis of ELPV?**

	Essential	Supportive	Neither
Symptoms of pain/burning	◯	◯	◯

Comments

ELPV - Round 3

Round 3 - Amended clinical criteria

This question has been rephrased from Round 2.

In Round 2 the statement read:

'Scarring/loss of normal architecture e.g. labial adhesions, loss of labia minora, narrowing of introitus, clitoral burying'

Vaginal scarring has been added to this statement.

Please state whether you believe the diagnostic items are 'essential' or 'supportive' to make the diagnosis.

*5. How do you rate the following feature in making the diagnosis of ELPV?

	Essential	Supportive	Neither
Scarring/loss of normal architecture e.g. labial adhesions, loss of labia minora, narrowing of introitus, clitoral burying, vaginal scarring	◯	◯	◯

Comments

ELPV - Round 3

Round 3 - Amended clinical criteria

This question has been rephrased from Round 2 for clarity.

In Round 2 the statement read:

'Presence of vaginal inflammation +/- vaginal scarring'

Vaginal scarring has been included in Question 5, where scarring of other anatomical sites is also considered. This question now relates to inflammatory processes affecting the vagina as scarring is considered elsewhere.

Please state whether you believe the diagnostic items are 'essential' or 'supportive' to make the diagnosis.

*6. How do you rate the following feature in making the diagnosis of ELPV?

	Essential	Supportive	Neither
Presence of vaginal inflammation including desquamitive inflammatory vaginitis (DIV)	◯	◯	◯

Comments

ELPV - Round 3

Round 3 - Amended clinical criteria

This question has been rephrased from Round 2 for clarity.

In Round 2 the statement read:

'Involvement of other mucocutaneous sites e.g. Skin/scalp,nails, mouth, oesophagus'

As the skin may be affected by lichen sclerosus, it is not a discriminating factor for lichen planus. Therefore, this has been removed from this question.

Please state whether you believe the diagnostic items are 'essential' or 'supportive' to make the diagnosis.

*7. How do you rate the following feature in making the diagnosis of ELPV?

	Essential	Supportive	Neither
Involvement of other mucosal surfaces e.g. Mouth, oesophagus, conjunctiva, cervix, anus, larynx	◯	◯	◯

Comments

Round 3 - Histopathological criteria

The questions on the following pages are regarding HISTOPATHOLOGICAL criteria for diagnosing erosive lichen planus of the vulva.

Please state whether you believe the following HISTOPATHOLOGICAL items are 'essential' or 'supportive' to make the diagnosis.

Remember:

'ESSENTIAL' means that a diagnostic feature MUST be present to make the diagnosis;

'SUPPORTIVE' means that the feature does not have to be present, but adds weight to other diagnostic features that are present.

The wording of these questions have not changed from Round 2.

N.B. It is assumed that biopsy specimen has been taken from the EDGE OF A LESION for the described histological findings to be present.

*8. How do you rate the following feature in making the diagnosis of ELPV?

	Essential	Supportive	Neither
Presence of a well-defined inflammatory band in the superficial connective tissue that involves the dermo-epidermo junction	◯	◯	◯

Comments

*9. How do you rate the following HISTOPATHOLOGICAL feature in making the diagnosis of ELPV?

	Essential	Supportive	Neither
Presence of an inflammatory band that consists PREDOMINANTLY of lymphocytes	◯	◯	◯

Comments

***10. How do you rate the following HISTOPATHOLOGICAL feature in making the diagnosis of ELPV?**

	Essential	Supportive	Neither
Signs of basal cell layer degeneration e.g. the presence of Civatte bodies, abnormal keratinocytes or basal apoptosis	◯	◯	◯

Comments

11. How do you rate the following HISTOPATHOLOGICAL feature in making the diagnosis of ELPV?

	Essential	Supportive	Neither
Absence of dermal hyalinasation	◯	◯	◯

Comments

ELPV - Round 3

Round 3 - Clinico-pathological correlation

The following questions aim to establish opinion of whether biopsy is mandatory to make a diagnosis of ELPV. These questions have been added since Round 2.

*12. This question has been added since Round 2:

	Agree	Disagree	Neither
A diagnosis of erosive lichen planus affecting the vulva should satisfy BOTH clinical AND histopathological criteria	◯	◯	◯
A biopsy of suspected ELPV is ALWAYS required when there is diagnostic uncertainty or concern of neoplastic change	◯	◯	◯
A biopsy should ALWAYS be taken before starting systemic therapy	◯	◯	◯

Please comment on any of the above statements if you wish

ELPV - Round 3

Round 3 - Excluded items

Several items from Round 2 did NOT reach consensus. These items have been excluded from scoring in Round 3. You have the option to review and comment on these items if you wish.

*13. Options

- ◯ I would like to continue to see the statements that have been excluded
- ◯ I would like to skip these statements

Round 3 - Excluded items

The following items have been excluded as they did not reach consensus in Round 2:

1. Findings on wet mount preparation.

2. Epidermal changes e.g. wedge shaped hypergranulosis, saw toothed acanthosis.

3. Findings on direct immunofluorescence.

14. Please add any comments on the exclusion of these items

ELPV - Round 3

Round 3 - Final diagnostic dataset

Throughout this survey you have been asked to rate clinical and histopathological features as 'ESSENTIAL' or 'SUPPORTIVE'.

'Essential' features MUST be present to make the diagnosis, whereas 'supportive' features add weight to a diagnosis, but do not necessarily have to be present.

We want you to think about HOW MANY of the essential and supportive features you have selected need to be present to make a diagnosis of ELPV. The combination of features can include BOTH clinical and histological domains. Participants' answers from this section will be used towards a definitive diagnostic dataset.

For example, to make a diagnosis of systemic lupus erythematosus the American Rheumatology Association require at least 4 out of 11 supportive criteria to be present, each of which are equally weighted.

We will ask you to comment upon how many 'supportive' features must be present in addition to the 'essential' features that you identified to make the diagnosis of ELPV. If you have not identified any 'essential' criteria, we will ask how many 'supportive' need to be present.

N.B You can access your previous answers by selecting 'previous' at the bottom of the page. No data will be lost by doing this.

*15. To make the diagnosis of ELPV:

	Agree	Disagree
ALL of your identified ESSENTIAL criteria should be met	◯	◯

If you DISAGREE please leave a comment

*16. To make the diagnosis of ELPV

	No additional supportive features required	One supportive feature	Two supportive features	Three supportive features	Four supportive features	Five supportive features	Six supportive features
In addition to the ESSENTIAL criteria, what is the MINIMUM number of SUPPORTIVE criteria that should be present? (NB The criteria can include clinical and/or histological domains)	◯	◯	◯	◯	◯	◯	◯

Other (please specify)

*17. If no 'essential' features are present, or you have not identified any 'essential' criteria from your previous answers

	Not applicable, my selected essential criteria must be present	One supportive feature	Two supportive features	Three supportive features	Four supportive features	Five supportive features	Six supportive features
What is the MINIMUM number of SUPPORTIVE criteria that should be present to disgnose ELPV? (NB The criteria can include clinical and/or histological domains. All supportive criteria are equally weighted)	◯	◯	◯	◯	◯	◯	◯

Other (please specify)

Round 3 - opinion on further rounds

Once Round 3 has been analysed we will know exactly which diagnostic criteria have reached consensus for 'essential' and 'supportive' criteria. We will also know what combination of 'essential' and 'supportive' criteria participants feel are necessary to diagnose ELPV.

Would you like to see and have the opportunity to comment upon the final diagnostic dataset? If you answer 'yes' then we will email you with the results in due course.

*18. Would you like to see and comment upon the final diagnostic dataset?

- ◯ Yes
- ◯ No

Round 3 - Demographic information

***19. Please indicate your specialty of practice:**

- ◯ Dermatology
- ◯ Histopathology/Dermatopathology
- ◯ Genitourinary medicine/Venerology/Sexual medicine
- ◯ Gynecology/O+G

***20. Please indicate your clinical grade:**

- ◯ Associate Specialist
- ◯ Consultant
- ◯ Nurse specialist
- ◯ Professor/Associate Professor
- ◯ Resident/Specialist registrar
- ◯ Other (Please specify)

***21. How long have you held a specialist interest in vulval skin disorders?**

- ◯ Less than 5 years
- ◯ 6-10 years
- ◯ 11-15 years
- ◯ 16-20 years
- ◯ More than 20 years

***22. Please indicate your country of practice:**

***23. Please indicate your name (this is for administrative purposes).**

Future acknowledgements

We would like to acknowledge all participants completing Round 3 in any subsequent publication or presentation. We will only do this with your consent and will NOT link your name to any specific comments or answers.

*24. Acknowledgement

- ◯ I consent to acknowledgement in any future presentation or publication
- ◯ I wish to remain anonymous and do NOT consent to acknowledgement in any future publication or presentation

ELPV - Round 3

Thank you

Thnk you for taking the time to submit your answers.

This study has been co-ordinated from the Centre of Evidence Based Dermatology at the University of Nottingham as part of a Doctorate Research Fellowship.

If you have any queries please contact:

rosalind.simpson@nottingham.ac.uk

Appendix 7

Electronic Delphi Consensus Exercise Feedback Questionnaire

ELPV - Feedback survey

Feedback survey - Introduction

Dear Participant,

The purpose of this short survey is for you to review and have your say into the final diagnostic dataset for erosive lichen planus affecting the vulva (ELPV). The nine items that make up the dataset have been selected following consensus from 69 participants over three rounds.

This survey has been sent to you as you expressed an interest to see the final results. Your comments are really important in the final interpretation of the findings.

We are particularly interested to know how many of the nine items you think should be present to diagnose ELPV.

Many thanks for your opinion,

Rosalind Simpson
Ruth Murphy

ELPV - Feedback survey

Feedback survey -Final diagnostic dataset

The following list of nine items have been agreed by consensus as 'supportive' features to diagnose erosive lichen planus affecting the vulva. Items i-vi represent clinical criteria and vii-ix represent histopathological criteria:

i) Presence of well-demarcated erosions/erythematous areas at the vaginal introitus

ii) Presence of scarring/loss of normal architecture

iii) Presence of a hyperkeratotic border to erythematous areas/erosions +/- Wickham’s striae in surrounding skin

iv) Involvement of other mucosal surfaces

v) Symptoms of pain/burning

vi) Presence of vaginal inflammation including desquamative inflammatory vaginitis-like changes

vii) Presence of a well-defined inflammatory band involving the dermo-epidermo junction

viii) Inflammatory infiltrate consists predominantly of lymphocytes

ix) Signs of basal layer degeneration.

1. Do you agree with this final diagnostic dataset?

◯ Yes

◯ No

Please leave any comments here:

2. How many of the supportive features listed above should be present to diagnose erosive lichen planus affecting the vulva? When you answer this question please bear in mind other conditions that may cause diagnostic difficulty -the number of criteria you chose should be sufficient to exclude these alternative diagnoses.

- ◯ One or more
- ◯ Two or more
- ◯ Three or more
- ◯ Four or more
- ◯ Five or more
- ◯ Six or more
- ◯ Seven or more
- ◯ Eight or more
- ◯ Nine

Please leave any additional comments:

3. Which other conditions may fulfil some of these criteria and therefore cause diagnostic difficulty?

ELPV - Feedback survey

Thank you

Thank you for taking the time to submit your answers.

This study has been co-ordinated from the Centre of Evidence Based Dermatology at the University of Nottingham as part of a Doctorate Research Fellowship.

If you have any queries please contact:

rosalind.simpson@nottingham.ac.uk

Appendix 8

Medline Search Strategy for Systematic Review of Outcome Measures for Vulval Skin Conditions

Medline RCT vulval disease search 18/7/12

1. (vulval or vulvar or vulvo$).ti,ab.
2. exp *Vulvitis/
3. exp Paget Disease, Extramammary/ or exp *Vulvar Neoplasms/
4. exp Vulvodynia/
5. exp Vulvar Vestibulitis/
6. or/1-5
7. randomized controlled trial.pt.
8. controlled clinical trial.pt.
9. randomized.ab.
10. placebo.ab.
11. clinical trials as topic.sh.
12. randomly.ab.
13. trial.ti.
14. 7 or 8 or 9 or 10 or 11 or 12 or 13
15. (animals not (humans and animals)).sh.
16. 14 not 15
17. 6 and 16
18. remove duplicates from 17

Appendix 9

Focus Group Session 1 Prompt Sheet

To be printed on local headed notepaper

Erosive Lichen Planus Focus Groups: Proposed Dialogue and Prompts

The following dialogue and prompts are planned for use in the focus groups sessions. These have been kept relatively broad to begin with, to encourage free discussion, then will become more focussed upon specific topics where we require patient input.

Focus Group Session 1

Living with ELPV (Carron)

- For the first 10-15 minutes I want you to talk openly about what it's like to live with erosive lichen planus. In particular, I would like to know how the condition impacts upon your life. At the end of the discussion I will attempt to draw up a list of aspects which bother you the most and impact the greatest on your life. RS may interject with methods of measuring these outcomes

  If needed:

  - Which symptoms of ELPV bother you the most? Looking for pain/discomfort/soreness, appearance, scarring. May mention mouth symptoms, difficulty in daily activities (see below)
  - How does it affect your day to day life e.g. walking, sitting, going to the toilet, work, social life, sport and intimate relationships? Does it stop people doing these or does do they carry on despite being uncomfortable?
  - Does it affect you psychologically i.e. feeling low or depressed?
  - How do you find using the treatments e.g. easy or difficult to apply, time consuming, comfortable/uncomfortable? Some will be on tablets, others using creams. May want a show of hands and get people to talk about their different experiences
  - What one thing would you improve about living with erosive lichen planus or its treatment? i.e. what should we be asking you about in clinic to judge how well you are?
  - In your opinion what constitutes adequate control? V Important

Outcome measures (Roz – will combine with Carron's section above)

- There are a number of different ways in which a doctor can assess whether treatment has been successful or not. For example by looking at the vulval skin and making a clinical assessment of whether it has improved or not, or by asking the patient to complete questionnaires. It is becoming more frequent to base treatment decisions on *patient* assessment of disease severity, using the results of these questionnaires. There are a number of different questionnaires or 'tools' that may be used in the outpatient clinic, but none have been devised specifically for ELP or vulval skin conditions. Therefore, we want to hear your opinion on these commonly used tools and whether they cover relevant issues to your condition, or not.

  - Firstly in your own time, could you fill in these forms? Afterwards we will discuss the pros and cons of each one.

- We will also ask you to rank the tools in order of which are best and most user-friendly to use
- What do you think about the ways we should see if the medication has worked? Are there any things specifically that you think should be included?

Focus Group Session 2

Additional points to clarify following FG session 1:

- Talking about symptoms and main worries form ELP, you mentioned the term 'FUSION'. Is this something you have picked up from doctors in clinic, or is it from the information sheets you have/internet – the reason we ask is that it is quite a specific term and we refer to it as a form of scarring. We aren't sure whether patients elsewhere in the country would use the same term and it's therefore important to know in what setting you have heard the term.
- You talked about psychological aspect being one of the worst – is this because you are having to deal with a long-term condition that may not go away, in a similar way to diabetes or heart disease, or is it **more than that** given the location and nature of the condition?
- We talked about adequate control and you seemed to say that you wanted comfort most of the time and to be able to do the things you want to do in comfort. Putting that into real terms, **what would you consider a worthwhile improvement in your symptoms** – for example, if you are sore ever day, would soreness every other day be considered a worthwhile improvement? Or would you want to reduce symptoms to once or twice a week to consider it better?
    - How about taking a tablet medication – how much better would you want your symptoms to get to consider taking a tablet worthwhile?
- We also talked quite a bit about questionnaires that can be used to monitor your symptoms and progress and you were keen on the following:
    - Visual Analogue Scale for Soreness (0-10)
    - 0-10 scale for other symptoms individually – itch and burn. Not so keen on a 3 point scale, but how about a compromise of 0-5 for overall disease control in your opinion? E.g 0-no disease, 1 – very mild, 2 – mild, 3-moderate, 4 – severe, 5-very severe
    - BUT how about a method of assessing overall control of your ELP – which wording seems most appropriate
        - *How would you rate your symptoms in the last week?*
        - *How much bother has your ELP caused in the last week?*
        - *How has your overall disease control been in the last week?*
    - How would you like to rate the overall control (wording will depend upon which question is decided)
        - *None/ a little/ moderate/ severe/ very severe*
        - *10 point scale – 0=no bother, 10=most bother you can imagine*
    - OR…do you consider scoring soreness as the most important way to measure control?
    - We talked quite a lot about day to day function, including sexual function – one of the simpler scales seemed preferable to you, do you think we should ask patients about this in clinic – how helpful to you is it to be asked, or **would you rather we focused on quality of life and other day to day activities**?
    - If you were in a study would you prefer to complete information, at the outpatient clinic (less frequent) or at home (e.g. mobile phone or computer or paper based?) which would be more frequent(but you would need to remember to do it), or by telephone call from the coordinator?

A brief powerpoint presentation will be given to give an overview of the proposed randomised controlled trial. Participants will then be asked to voice their thoughts on the overall design. If needed the following prompts will be used:

Study design

- What are your first, honest impressions?
- What further information would you like to know if you were told about this in clinic?
- Are any aspects of the study you particularly like?
- Are there any parts of the study which concern you? (prompts: ask about timing and number of visits including telephone calls, questionnaires, disease state, medications, blood tests etc).
- What things could be changed to make the study more attractive to potential participants?
- What are your thoughts on the planned medications? Is there anything that should be put in the information leaflet that would allay your fears?
- How would you feel about photographs being taken? (If they are not happy with this ask 'how would you feel about having an independent assessor examine them for severity during their follow up appointment?') ro would you rather your own Doctor?
- Overall is the proposed study acceptable to you as a patient and would you be willing to take part in a study like this? If not, what sort of study would you be willing to take part in?
- **Need to ascertain if any participants would be interested in helping with further work – re discussing trial protocol, PIL lay review for trial, patient member of TSC and TMG, be interested in recruiting into trial?**
    - Consent form already states they are happy to be contacted further

Appendix 10

Outcome measure tools preferred by patients in focus groups

Hospital Anxiety and Depression Scale (HADS)

GL assessment
the measure of potential

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

FOLD HERE

FOLD HERE

A	D		A	D
		I feel tense or 'wound up'		
3		Most of the time		
2		A lot of the time		
1		From time to time, occasionally		
0		Not at all		
		I still enjoy the things I used to enjoy		
	0	Definitely as much		
	1	Not quite so much		
	2	Only a little		
	3	Hardly at all		
		I get a sort of frightened feeling as if something awful is about to happen		
3		Very definitely and quite badly		
2		Yes, but not too badly		
1		A little, but it doesn't worry me		
0		Not at all		
		I can laugh and see the funny side of things		
	0	As much as I always could		
	1	Not quite so much now		
	2	Definitely not so much now		
	3	Not at all		
		Worrying thoughts go through my mind		
3		A great deal of the time		
2		A lot of the time		
1		Not too often		
0		Very little		
		I feel cheerful		
	3	Never		
	2	Not often		
	1	Sometimes		
	0	Most of the time		
		I can sit at ease and feel relaxed		
0		Definitely		
1		Usually		
2		Not often		
3		Not at all		
		I feel as if I am slowed down		
		Nearly all the time		3
		Very often		2
		Sometimes		1
		Not at all		0
		I get a sort of frightened feeling like 'butterflies' in the stomach		
		Not at all	0	
		Occasionally	1	
		Quite often	2	
		Very often	3	
		I have lost interest in my appearance		
		Definitely		3
		I don't take as much care as I should		2
		I may not take quite as much care		1
		I take just as much care as ever		0
		I feel restless as if I have to be on the move		
		Very much indeed	3	
		Quite a lot	2	
		Not very much	1	
		Not at all	0	
		I look forward with enjoyment to things		
		As much as I ever did		0
		Rather less than I used to		1
		Definitely less than I used to		2
		Hardly at all		3
		I get sudden feelings of panic		
		Very often indeed	3	
		Quite often	2	
		Not very often	1	
		Not at all	0	
		I can enjoy a good book or radio or television programme		
		Often		0
		Sometimes		1
		Not often		2
		Very seldom		3

Now check that you have answered all the questions

	A	D
TOTAL		

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GL Assessment is part of the Granada Group

Vulval-specific Skindex-29

These questions concern your feelings over the past 4 weeks about your vulvar condition.
Check the answer that comes closest to the way you have been feeling.

	HOW OFTEN DURING THE PAST 4 WEEKS DO THESE STATEMENTS DESCRIBE YOU?	NEVER 1	RARELY 2	SOMETIMES 3	OFTEN 4	ALL THE TIME 5
1	My vulva hurts	☐1	☐2	☐3	☐4	☐5
2	My vulvar condition affects how well I sleep	☐1	☐2	☐3	☐4	☐5
3	I worry that my vulvar condition may be serious	☐1	☐2	☐3	☐4	☐5
4	My vulvar condition makes it hard to do work or hobbies	☐1	☐2	☐3	☐4	☐5
5	My vulvar condition affects my social life	☐1	☐2	☐3	☐4	☐5
6	My vulvar condition makes me feel depressed	☐1	☐2	☐3	☐4	☐5
7	My vulva burns or stings	☐1	☐2	☐3	☐4	☐5
8	I tend to stay at home because of my vulvar condition	☐1	☐2	☐3	☐4	☐5
9	I worry about getting scars from my vulvar condition	☐1	☐2	☐3	☐4	☐5
10	My vulva itches	☐1	☐2	☐3	☐4	☐5
11	My vulvar condition affects how close I can be with those I love	☐1	☐2	☐3	☐4	☐5
12	I am ashamed of my vulvar condition	☐1	☐2	☐3	☐4	☐5
13	I worry that my vulvar condition may get worse	☐1	☐2	☐3	☐4	☐5
14	I tend to do things by myself because of my vulvar condition	☐1	☐2	☐3	☐4	☐5
	HOW OFTEN DURING THE PAST 4 WEEKS DO THESE STATEMENTS	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE

	DESCRIBE YOU?	1	2	3	4	TIME 5
15	I am angry about my vulvar condition	☐1	☐2	☐3	☐4	☐5
16	Water bothers my vulvar condition (i.e. bathing)	☐1	☐2	☐3	☐4	☐5
17	My vulvar condition makes showing affection difficult	☐1	☐2	☐3	☐4	☐5
18	I worry about side effects from vulvar medications/treatments	☐1	☐2	☐3	☐4	☐5
19	My vulva is irritated	☐1	☐2	☐3	☐4	☐5
20	My vulvar condition affects my interactions with others	☐1	☐2	☐3	☐4	☐5
21	I am embarrassed by my vulvar condition	☐1	☐2	☐3	☐4	☐5
22	My vulvar condition is a problem for the people I love	☐1	☐2	☐3	☐4	☐5
23	I am frustrated by my vulvar condition	☐1	☐2	☐3	☐4	☐5
24	My vulva is sensitive	☐1	☐2	☐3	☐4	☐5
25	My vulvar condition affects my desire to be with people	☐1	☐2	☐3	☐4	☐5
26	I am humiliated by my vulvar condition	☐1	☐2	☐3	☐4	☐5
27	My vulva bleeds	☐1	☐2	☐3	☐4	☐5
28	I am annoyed by my vulvar condition	☐1	☐2	☐3	☐4	☐5
29	My vulvar condition interferes with my sex life	☐1	☐2	☐3	☐4	☐5

Participant ID: ☐☐☐☐☐ Participant initials: ☐☐☐

Date of completion | D | D | M | M | M | Y | Y |

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please tick the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
▼	▼	▼	▼	▼
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
▼	▼	▼	▼	▼
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a	<u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c	Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d	Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e	Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f	Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g	Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h	Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i	Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j	Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and low?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a	I seem to get ill more easily than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Derogatis sexual functioning index

Ask the patient:

'Are you able to have sexual intercourse?'

- 1= yes, no pain
- 2 = yes, painful
- 3 = no, in too much pain to try
- 4 = no, no opportunity
- 5 = not sexually active

NB – patient will be asked this question but it will be on the CRF and so they will not see this sheet per se

Appendix 11

Categories from Thematic Analysis of Focus Groups

Level I	Level II	Level III	Level IV
Management experiences			
	Experiences of Clinical examination		
		Fear of physical examination	
	Lack of faith in non-specialists		
	Wanting to be managed by female doctors		
	Negative experiences		
	Treatments		
		Negative experiences	
		Difficulty in managing as asked by Dr	
	Adequate control		
	Co-existing diagnoses and subsequent problems		
Misunderstandings			
	General public misunderstanding		
	Healthcare workers misunderstanding		
	Patient misunderstanding about disease	Wanting to be managed by female doctors (i.e. feeling that male doctors misunderstand them)	
		(Leading to) Fear - Anxiety	
	Patient misunderstanding about management		
		Inquisitive (wanting to know more)	
			Inquisitive about the disease
			Inquisitive about treatments
Route/pathway to diagnosis			
	Diagnostic tests		
		Fear of procedures	
	Improvements in diagnosis		
	Inconsistency in care received		

Level I	Level II	Level III	Level IV
	Incorrect diagnosis made		
	Time taken for diagnosis to be made		
Effects of disease on the patient	Symptoms		
		Dryness	Effect on daily activities
		Itching	
		Pain v soreness	
		Triggers_pattens of disease	
			Fear of deterioration
			Seasonal variation
	Duration of disease		
	Sites affected		
Problems caused by the condition	Anxiety		
	Effect on daily activities		
		Clothing	
		Eating	
		Mobility_physical activity	
		Sitting	
		Sleep	
		Urination	
	Effect on intimite relationships		
		Emotional side of intimacy	
		Guilt	
		Physical side of intimacy	
		Takes pressure off partner	
	Quality of life		

Level I	Level II	Level III	Level IV
Psychological effects			
	Distress		
	Feeling guilty		
	Low mood		
	Stoicism		
		Acceptance of disease over time	
	Fear		
		Fear - Anxiety	
		Fear of physical examination	
		Fear of deterioration	
	Embarrasment		
		Ashamed by what is happening to them	
		Embarassed in public by symptoms	
		Embarassed to talk to doctors	
	Coping mechanisms		
		Coping by humorising the situation	
		Physical coping techniques	
Support available for patients			
	Concerned about impacting on other people		
	Wanting reassurance		
	Information available		
		Internet	
		Healthcare professionals	
			Lack of understanding and poor informationavailable leads to patients being inquisitive but also leads to lack of faith and psychological effects
Terminology			
	Anatomy		

Level I	Level II	Level III	Level IV
	Fusion_scarring		

Appendix 12

Thematic Map from Focus Group Results


Incorrect Δ mode
Δ ic tests
Route to Δ
Improvements in how Δ can be made
Inconsistency in care received
fear of procedures
Difficult to manage as req by pt
Negative experiences
Treatments
Clinical examn
Fear of physical examn
Management Experiences
Adequate control
Co-existing Δ / subsequent problems
Lack faith non-specialists
Waiting to be seen by ♀ doctors
Patient misunderstanding about disease
Healthcare workers misunderstanding
MISUNDERSTANDING
Healthcare professionals
Information Available
Internet
Support for Patients
Wanting reassurance
Concerned about impacting on other people
General public misunderstanding
Problems caused by condition
Effects of disease on patient
Anxiety
Effect on daily activities
Symptoms
Fear of deterioration
Dryness / Itching / Soreness / Triggers
Pt misunderstanding re: mx
Effects daily activities
Seasonal variation
Inquisitive
Inquisitive about mx
Inquisitive about disease
Anxiety
Fear
Distress
Fear of deterioration
Stoicism (Acceptance over time)
Psychological effects
Low mood
Feeling guilty
Embarrassed
Embarrassed in public by symptoms
Embarrassed to talk to Dr
Ashamed by what is happening to them