

## COMMENTARY

## OPEN

# Help for Future Research: Lessons Learned in Trial Design, Recruitment, and Delivery From the “hELP” Study

Rosalind C. Simpson, PhD,<sup>1</sup> Ruth Murphy, PhD,<sup>2</sup> Daniel J. Bratton, PhD,<sup>3</sup> Matthew R. Sydes, PhD,<sup>3</sup> Sally Wilkes, PhD,<sup>1</sup> Helen Nankervis, PhD,<sup>1</sup> Shelley Dowey, BSc,<sup>1</sup> Hazel Bell, FRCP,<sup>4</sup> Margaret Cruickshank, PhD,<sup>5</sup> Karen Gibbon, FRCP,<sup>6</sup> Cathy M. Green, FRCP,<sup>7</sup> Christina Wong, FRCP,<sup>8</sup> Caroline M. Owen, FRCP,<sup>9</sup> Kate London, MBChB,<sup>10</sup> Shaheen Haque, MRCP,<sup>11</sup> and Kim S. Thomas, PhD<sup>1</sup>

**Key Words:** vulvar, erosive lichen planus, systemic treatment, vulvovaginal, randomized controlled trial

(*J Low Genit Tract Dis* 2018;00: 00–00)

The aim of this commentary is to document our experience and lessons learned of running a randomized controlled trial (RCT) in vulvar erosive lichen planus (ELPV), an uncommon and underresearched condition. Vulvar erosive lichen planus causes painful vulvovaginal erosions, which affect daily function and quality of life.<sup>1</sup> Response to standard first-line therapy (superpotent topical corticosteroids) is often inadequate, and there are no RCTs to guide second-line treatment.<sup>2</sup> The “hELP” (Systemic Therapy for Vulvar Erosive Lichen Planus) trial was a pilot study to assess feasibility of a definitive trial comparing systemic treatments for ELPV. Ethical approval (14/YH/0046), prospective trial registration (ISRCTN: 81883379), and protocol publication<sup>3</sup> occurred.

“hELP” was a multicenter, four-arm, assessor-blind, pilot RCT recruiting from 12 UK sites for 14 months. Eligible participants were randomized to a 6-month course of hydroxychloroquine, methotrexate, or mycophenolate mofetil or a 4-week reducing regimen of prednisolone (comparator group); all received superpotent topical corticosteroids.

Inclusion criteria were the following: women older than 18 with a clinical diagnosis of moderate to severe ELPV, despite 3-month treatment with clobetasol propionate 0.05%, plus documented vulvar biopsy that excluded malignant/premalignant disease. Participants must have agreed to clinical photographs.

Exclusion criteria were the following: (1) lichen sclerosus/lichen planus overlap; (2) received any of the systemic trial drugs within the last month; (3) a previous or current diagnosis of malignant

disease; (4) premalignant cervical or vulvar disease; (5) live vaccine administration in the last 2 weeks; (6) pregnancy or breastfeeding; (7) allergy to any of the trial medications; (8) history of clinically significant renal/liver impairment or concurrent medications that would interact with the trial drugs; and (9) any other reason that the trial medications would not be given in usual clinical practice.

Feasibility outcomes were the proportion of eligible participants randomized; the proportion of patients adhering to treatment, quality and suitability of clinical images, suitability of trial design, and suitability of clinical outcomes. The primary clinical outcome was treatment “success” at 6 months. Because of the absence of validated outcome measures for ELPV, the definition of “success” was agreed after qualitative work with expert clinicians.<sup>4</sup> Treatment was classed as successful if both the following outcomes were met:

1. Patient global assessment of disease severity of “none” or “mild” (on a 4-point scale of none, mild, moderate, or severe disease).
2. Any improvement from baseline judged by blinded assessment of clinical photographs.

The trial was pragmatically designed; interventions were tested in an environment that was as close to real-life as possible in terms of setting, study population, intervention, comparator, and outcomes.<sup>5</sup>

Of 180 patients screened, only 44 (24%) were eligible. Ineligibility reasons are in Figure 1. Of those eligible, 22 (50%) of 44 were randomized; 20 did not consent to take a tablet treatment. The study was closed without reaching its recruitment target of 40. For those 22 patients who entered the trial, study medications were not started by four participants, four stopped trial treatment early and two were lost to follow-up (Figure 1).

Only 14 of 22 participants had complete before and after images, and overall quality was poor despite being taken by medical photography. Treatment “success” only occurred in the hydroxychloroquine (2/6, 33%) and mycophenolate mofetil (2/5, 40%) groups.

hELP was an ambitious trial because it was looking to recruit patients with an uncommon skin condition for second-line treatment. However, preliminary data had suggested that the recruitment target was achievable. The lessons learned are summarized in Table 1, and specific lessons learned for future ELPV trials are expanded upon hereinafter.

Despite 180 patients being identified, many were not eligible. The main ineligibility reason was mild disease. In counseling potential participants for hELP, some were found to not be using topical steroids effectively; re-education on topical treatment, for some, led to better disease control and negated the need for systemic therapy. This suggests that over time, patients' technique of applying and understanding of the importance of topical treatments was lessening and not being regularly assessed by clinical care teams.

Of those eligible, the main reason for nonparticipation was that people did not want to take a tablet treatment, despite clinically moderate/severe disease. People with ELPV are often of an

<sup>1</sup>Centre of Evidence Based Dermatology, King's Meadow Campus, Lenton Lane, University of Nottingham, Nottingham, UK; <sup>2</sup>Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK; <sup>3</sup>MRC Clinical Trials Unit at UCL, Institute of Clinical Trials & Methodology, London, UK; <sup>4</sup>Broadgreen Hospital, Royal Liverpool and Broadgreen University Hospitals NHS Trust, Liverpool, UK; <sup>5</sup>Aberdeen Royal Infirmary, NHS Grampian, Aberdeenshire, UK; <sup>6</sup>Whipps Cross University Hospital, Barts Health NHS Trust, London, UK; <sup>7</sup>Ninewells Hospital & Medical School, NHS Tayside, Dundee, UK; <sup>8</sup>Salford Royal Hospital, Salford Royal NHS Foundation Trust, Salford, UK; <sup>9</sup>Royal Blackburn Hospital, East Lancashire Hospitals NHS Trust, East Lancashire, UK; <sup>10</sup>St Luke's Hospital, Bradford Hospitals Foundation Trust, West Yorkshire, UK; and <sup>11</sup>Addenbrookes Hospital, Cambridge Hospitals NHS Foundation Trust, Cambridge, UK. Reprint requests to: Rosalind C Simpson, PhD, Centre of Evidence Based Dermatology, King's Meadow Campus, Lenton Lane, University of Nottingham, NG7 2NR. E-mail: Rosalind.simpson@nottingham.ac.uk. M.S. holds grants from Astellas, Clovis Oncology, Janssen, Novartis, Pfizer, and Sanofi Aventis to support research in prostate cancer. D.J.B. has been an employee of GlaxoSmithKline since January 2016.

Research ethics committee approval was prospectively obtained from the Sheffield NRES Committee – York and The Humber (reference 14/YH/0046).

Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the ASCCP. This is an open access article distributed under the Creative Commons Attribution License 4.0 (CCBY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

DOI: 10.1097/LGT.0000000000000407

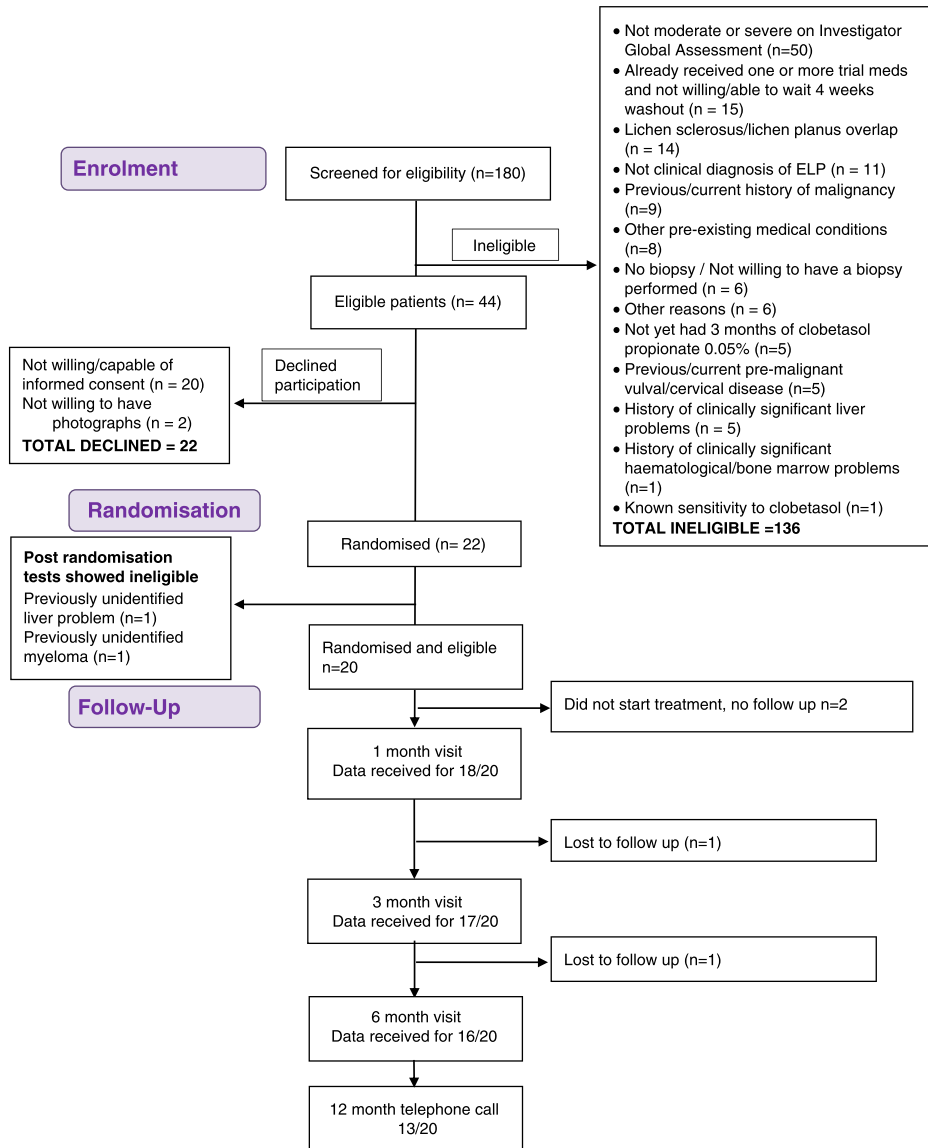


FIGURE 1. CONSORT diagram of participant flow in the hELP pilot trial.

older age group, likely to have comorbidities and be more anxious about combining medications or adverse effects. This should be borne in mind for future trials as reluctance for systemic therapy may always present a barrier to recruitment.

Patient-reported symptoms are a guide for therapeutic decision-making<sup>4</sup> and are arguably the most important outcome to measure. However, because this was an open-label trial, we wanted to ensure a blinded component to the clinical end point through using objective assessment of clinical photographs. Only four participants achieved our definition of “treatment success.” However, 10 of 16 showed improvement in patient global assessment and 6 of 16 continued treatment after 6 months. This suggests that the composite primary outcome was too stringent and a set of “core outcome measures”<sup>6</sup> is essential to success of future ELPV trials.

Despite clinical photography being usual practice in the management of vulval disease, the concept of taking images deterred 2 (4%) of 44 of eligible patients from consenting to the study. In addition, 6 (46%) of 13 contacted at 12 months stated that they found the photographs embarrassing or that they were not keen on having them taken.

Photographs received were of varying quality, despite the provision of a standardized photographic protocol. Medical imaging provision varied widely between centers. Some had photographers present in the clinic who could take the images immediately. Others only operated at specific times, often in a different location within the hospital. The latter led to practical difficulty, especially if images needed to be retaken because of inadequate initial images.

Important lessons applicable to developing and delivering future trials have been learned by conducting the hELP study. Running a pilot trial was an important step to assess feasibility and in this case stopped a full-scale RCT from proceeding. Valuable resources have therefore been saved, and we hope that the lessons learned will prevent future research waste in other areas.

#### ACKNOWLEDGMENTS

This study was funded by the National Institute of Health Research as part of a Doctoral Research Fellowship (DRF-2012-05-166). This report is independent research arising from a Doctoral Research Fellowship supported by the National Institute for Health Research (NIHR). The views expressed in this publication

**TABLE 1.** Lessons Learned From the hELP Study: The Lessons Learned Have Been Categorized and Potential Solutions Suggested to Inform Other Researchers' Trial Designs

	Problem identified	Potential solution
Trials of rare conditions	Small patient numbers	Screen all patients as every patient counts and may potentially be eligible, if not now, at a later stage
	Identified patients ineligible for trial	Trial design should allow flexibility to re-approach patients on the screening log if initially they were not eligible but subsequently meet eligibility criteria (especially important for relapsing-remitting conditions)
	Study profile loses prominence as each site only recruits a few patients	Teams need to feel a sense of ownership and responsibility for the study. Regular communication and feedback with recruiting sites maintains momentum and keeps study profile prominent.
	Rare conditions are often only managed in specialist setting	Engaging with wider clinical networks is essential in terms of identifying and referring potential participants to recruiting sites
Multiarmed studies	PIL lengthy and may be confusing to patients	Consider an initial summary leaflet in advance of the full patient information leaflet
	Eligibility criteria may be particularly restrictive especially in certain patient populations, e.g., older people.	Patient involvement in trial design will be key in establishing whether people will be willing to enter the study
Trials for ELPV and vulval skin conditions	Better use of topical treatment improved disease control for some participants	Ensure regular assessment of patient's technique and understanding of importance of topical treatment application
	No validated outcome measures	A set of internationally agreed core outcome measures would ensure the most appropriate outcome measure tools would be used in future studies
	Significant variation between sites in quality of clinical photographs	Clinical services could be enhanced by the standardization of use of photographs to monitor patients
	Not all patients consent to photographs being taken even when anonymous	Photographs should be part of usual clinical care for monitoring purposes. Standardization of vulval services to include regular clinical imaging would make patients feel more comfortable about having photographs taken
	Specialty clinics run infrequently	Ensure that funding for research visits is available, even for pragmatic studies, to allow flexibility for patients when clinic appointments are far apart

are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health.

This research was developed with the help and support of the University of Nottingham and the UK Dermatology Clinical Trials Network (UK DCTN). The UK DCTN is grateful to the British Association of Dermatologists and the University of Nottingham for financial support of the Network. Additional trial administrative support was provided by the University of Nottingham. Thank you to Natasha Rogers for assistance with data cleaning. Research nurse support was provided through the NIHR Clinical Research Networks.

The development and running of this trial would not have been possible without statistical and scientific support from the Medical Research Council's Clinical Trials Unit, the enthusiasm and commitment of the recruiting clinicians and nurses and the voluntary involvement of the Trial Steering Committee and Data Monitoring Committee members.

**Trial Development Group:** R.S., K.T., R.M., M.S., D.B., Sandra Lawton (Dermatology Nurse Consultant, Nottingham University Hospitals), M.K. (patient representative, preferred not to be named), Joanne Chalmers (Senior Research Fellow, University of Nottingham).

**Trial Management Group:** R.S., K.T., R.M., H.N., S.D., S.W.

**Trial Steering Committee:** Independent Chair: Dr. John Ingram (University Hospital Wales, Cardiff), Dr. Gudula Kirtschig (University of Tübingen, Germany), Dr. Maulina Sharma (Royal Derby Hospitals, Derby), Nicola Greenlaw (Statistician, University

of Glasgow), Diana Malone (Patient representative), Angela Shone (Sponsor representative, University of Nottingham).

**Data Monitoring Committee:** Independent chair: Dr. Julia Schofield (University of Hertfordshire), Dr. Claire Fuller (Chelsea and Westminster Hospital, London), Heather Murray (Statistician, University of Glasgow).

**Independent assessors of clinical images:** Dr. Jan McLelland, Dr. Susan Cooper, Dr. Anne Howard.

**Recruiting centers:** **Queen's Medical Centre, Nottingham University Hospitals NHS Trust:** Dr. Ruth Murphy (PI), Jo McWilliams (RN); **Aberdeen Royal Infirmary, NHS Grampian:** Dr. Maggie Cruickshank (PI), Judith Wilson (RN); **Royal Blackburn Hospital, East Lancashire Hospitals NHS Trust:** Dr. Caroline Owen (PI), Sarah Keith (RN), Wendy Goddard (RN), Alisa Watt (RN); **St Luke's Hospital, Bradford Hospitals Foundation Trust:** Dr. Kate London (PI), Jennifer Ott (RN); **Addenbrookes Hospital Cambridge Hospitals NHS Foundation Trust:** Dr. Shaheen Haque (PI), Dr. Ravinder Aktar (CoI); **University Hospital of Wales, Cardiff and Vale University Health Board:** Dr. Ru Katugampola (PI); **Ninewells Hospital & Medical School, NHS Tayside:** Dr. Cathy M Green (PI), Janice Rowland (RN), Hilary Nicholson (RN); **Chapel Allerton Hospital, Leeds Teaching Hospitals NHS Trust:** Dr. Caroline Wilson (PI), Sue Williamson (RN), Dr. Robert Sheehan-Dare (CoI); **Broadgreen Hospital, Royal Liverpool and Broadgreen University Hospitals NHS Trust:** Dr. Hazel Bell (PI), Ashima Lowe (Co-I) Tracey O'Rourke (RN); **Whipps Cross University Hospital, Barts Health NHS Trust:** Dr. Karen Gibbon (PI),

Jennifer Ross (RN), Bibi Badal (RN), Adebanke Aboaba (RN) Dr. Ekeowa-Anderson (CoI), Dr. Clare Marshall (CoI), Dr. Anthony Hollingworth (CoI), Satwinderjit Shinhmar (Co-I); **St Mary's Hospital, Central Manchester University Hospitals NHS Foundation Trust**: Dr. Ursula Winters (PI), Dr. Christina Wong (CoI), Rebecca Leech (RN); **Salford Royal Hospital, Salford Royal NHS Foundation Trust**: Dr. Christina Wong (PI), Dr. Vikram Rajkomar (CoI).

## REFERENCES

1. Lundqvist EN, Wahlin YB, Bergdahl M, et al. Psychological health in patients with genital and oral erosive lichen planus. *J Eur Acad Dermatol Venereol* 2006;20:661–6.
2. Cheng S, Kirtschig G, Cooper S, et al. Interventions for erosive lichen planus affecting mucosal sites. *Cochrane Database Syst Rev* 2012;CD008092.
3. Simpson RC, Murphy R, Bratton DJ, et al. Systemic therapy for vulval Erosive Lichen Planus (the 'hELP' trial): study protocol for a randomised controlled trial. *Trials* 2016;17:2.
4. Simpson RC, Thomas KS, Murphy R. Vulval Erosive Lichen Planus: A qualitative investigation of U.K. clinician views and principles of management. *Br J Dermatol* 2013;169:226–7.
5. Thorpe KE, Zwarenstein M, Oxman AD, et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *J Clin Epidemiol* 2009;62:464–75.
6. Foster DC, Stockdale CK, Simpson R, et al. Core Outcome Sets for Clinical Trials and Observational Studies in Vulvovaginal Disease. *J Low Genit Tract Dis* 2017;21:163–5.