mitochondrial abnormalities observed (Figure 1a). Preliminary evidence suggests that HF s may attempt to compensate by upregulating MT-CO1 and VDAC1, but this requires further investigation (unpublished work by R.P.).

Next, to probe how the controlled induction of EMT and IP collapse affected bulge mitochondrial function, we utilized a ‘cocktail’ to promote EMT and IP collapse in the bulge of healthy human scalp HFs, thereby imitating LPP pathogenesis ex vivo. Vimentin and E-cadherin expression was used to verify EMT induction in treated HFs (not shown).

A significant decrease in the expression of TFAM in the bulge of healthy anagen scalp HFs was observed following 3 days of cocktail treatment (Figure 1c). Moreover, the respiratory rate of cocktail-treated HFs was drastically reduced compared with vehicle-treated control HFs, as assessed by O2 consumption assay (Figure 1d). These data suggest that a proinflammatory signalling milieu sufficient to induce bulge IP collapse and EMT also promotes mitochondrial dysfunction in human eHFSCs.

Together, our gene and protein expression, ultrastructural and energy metabolism data highlight a functionally important role of eHFSC mitochondrial dysfunction in LPP development. This not only introduces an important new principle into LPP pathobiology, but further encourages systematic exploration of novel mitochondrial stimulatory agents that target eHFSCs in LPP management.2

Going forward, future research following up this pilot study firstly needs to elucidate whether mitochondrial defects are secondary to LPP-associated HF inflammation or represent a constitutive abnormality that predisposes to eHFSC damage and LPP development; this could in part be investigated by ultrastructural analysis of mitochondria after EMT induction. Secondly it should be examined how bulge mitochondrial dysfunction is acquired, how it progresses and whether it is reversible therapeutically. On this basis, it would be interesting to investigate PPAR-γ coactivator α, whose expression is increased upon mitochondrial dysfunction.7 Thirdly, it would be useful to investigate whether and how mitochondrial dysfunction contributes to bulge IP collapse and/or pathological EMT. Finally, we need to understand whether this dysfunction is linked to LPP-associated abnormalities in PPAR-γ-mediated signalling and whether PPAR-γ-specific agonists may be therapeutic in stimulating HF epithelial mitochondrial function, given the recognized impact of the latter on mitochondrial HF 3

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Outcome domains in lichen sclerosus

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Dear Editor, Lichen sclerosus (LS) is a chronic inflammatory dermatosis predominantly affecting the genitals. It can affect men, women and children. LS affecting female genitalia typically presents with itchy patches that impact on physical and psychosocial-sexual functioning.1,2 Symptoms in men include difficulty urinating due to urethral narrowing, difficulty in foreskin retraction due to scarring, and dyspareunia. Complications include loss of anatomy and malignant transformation.

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Clinical trials are vital for evidence-based practice by providing current supportive evidence to inform clinical decision-making. When results of multiple clinical studies are pooled, a stronger evidence base is obtained than with a single study. However, there is inconsistency in outcomes measured in trials of vulval skin conditions; one systematic review found 28 vulval randomized controlled trials, measuring 25 outcomes using 49 different scales. The heterogeneity of these outcomes/scales means they cannot be effectively compared or combined in meta-analyses, which is a source of research wastage.

Minimizing differences in outcomes collected during trials by developing and using core outcome sets can reduce this research ‘waste’. A ‘core outcome set’ is an agreed standardized minimum collection of outcomes that should be measured and reported across all clinical trials of a specific condition.

The aim of this study was to inform the development of a core outcome set for genital LS by establishing outcome domains of importance to patients and healthcare professionals.

An online survey was disseminated to international stakeholders from September to October 2017 during a James Lind Alliance LS Priority Setting Partnership. As this was patient and public involvement into research, ethical approval was not required.

Anonymized free-text responses about ‘important symptoms or aspects of LS’ were collected. Data were analysed using NVivo12 software through an iterative sequence of qualitative analyses. Firstly, keywords were identified using word frequency counts. They were subsequently analysed in the wider context of the data in a ‘keyword-in-context’ analysis. This informed a thematic analysis, where each response was summarized/characterized using a ‘code’ (a simple label of content). Similar ‘codes’ were grouped within broader ‘themes’, with review of themes (and data captured therein) informing the generation of outcome domains.

The survey was completed by 653 respondents submitting 1953 responses in total. There were 404 patients/carers (92% female, 5% male) of whom 5% were children/representatives of children, 222 healthcare professionals (64 gynaecologists, 58 dermatologists, 35 sexual health physicians, 23 primary care physicians, 19 urologists and 23 ‘other health professional’) and 27 ‘other’.

Word counts identified that itch was the most commonly used ‘keyword’ (used 395 times); a contextual review identified variation in how ‘keywords’ were used (e.g. ‘presence of itch’ or ‘itch ceasing’). Consistent use of keywords informed the creation of 37 distinct ‘codes’, each code capturing a commonly reported experience/opinion. Codes were organized within six broader ‘themes’, which drew together closely related or connected codes (Table 1).

Each theme points to an outcome domain of importance for LS, the thematic analysis therein provides insight about how to potentially operationalize that domain.

Symptoms of LS, such as itching and pain, and their persistent nature cause significant discomfort and psychological distress (Symptoms). As such LS impacts on daily activities and

| Theme/Domains                      | Codes                          | Examples of raw data                                                                 |
|------------------------------------|--------------------------------|--------------------------------------------------------------------------------------|
| Symptoms                           | Itching                        | ‘Flare ups of agonizing unceasing itching’                                           |
|                                    | Pain                           | ‘Cracking of the skin in the vulva area, which is rather painful’                    |
| Quality of life                     | Impact on daily activities/normal function | ‘It takes a lot of everyday life … when you have to pee, you want to have sex, go swimming, go cycling, etc … I miss being spontaneous’ |
|                                    | Psychological distress         | ‘The psychological impact it has on your relationship to your partner’               |
| Sexual dysfunction                  | Physically unable to have sex  | ‘Being able to have a normal sex life with vaginal intercourse (without risk of damage or pain from scratches, skin growing together, thin skin and other anatomical changes)’ |
|                                    | Dyspareunia                    | ‘Able to have intercourse without the pain during and after’                         |
|                                    | Emotional impact on relationships | ‘Fusing, anything to stop the fusing, my partner asked why I had been circumcised, I’m white British female, I haven’t been circumcised’ |
| Appearance                          | Anatomical change              | ‘Architecture, I no longer have external labia, neither a noticeable clitoris and my vulva looks like a pair of white bicycle inner tubes … I very much feel missing like a complete woman’ |
| Progression of the condition        | Cosmetic appearance            | ‘Scarring/ugly red patches on the genitals’                                         |
|                                    | Cancer risk                    | ‘Anxiety about the possible development of cancer’                                  |
| Management of the condition         | Better awareness               | ‘The tendency for GPs and other practitioners to wrongly diagnose LS … and dismiss women presenting with repeated problems’ |
|                                    | Earlier diagnosis               | ‘Develop an easier way to diagnose the disease so more women will be able to be tested early enough’ |
|                                    | Better treatment               | ‘Clearer and consistent guidance on treatment … what works best, when, how and how much/frequently’ |

GP, general practitioner; LS, lichen sclerosus.
normal functioning (Quality of life). People with LS reported problems with dyspareunia, physical inability to engage in intercourse due to narrowing of the vaginal opening, and lack of sexual drive from loss of sensation. They referred to the emotional impact on relationships as well as their own psychosocial-sexual wellbeing (Sexual dysfunction). Responses placed greater significance on the changes related to anatomical structure (229 responses) than on variations in cosmetic appearance (70 responses) (Appearance).

Many participants described fear of potential progression to malignancy and irreversible stenosis (Progression of the condition). The importance of better awareness of LS among the general public and doctors was highlighted to aid earlier diagnosis and prevention of scarring. Many patients called for treatment that quickly resolves symptoms, reduces flare-ups and is easier to use than the standard first-line therapy of topical steroids (Management of the condition).

The six key themes/domains identified above will inform the first stage of development for a LS core outcome set through the CORALS (Core Outcomes for ReseArch in Lichen Sclerosus) initiative.5 The first stage will obtain international consensus on core outcome domains via an electronic-Delphi exercise. Subsequent work to identify appropriate outcome measurement instruments will then be needed to use in the final core outcome set.

Although CORALS is intended for use in randomized trials, we believe that understanding these outcomes of importance is valuable for managing LS in the outpatient clinic. Ensuring that these issues are addressed during the consultation will benefit patient experience and overall quality of care.

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Are all Buruli ulcers caused by Mycobacterium ulcerans?

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Dear Editor, Buruli ulcer (BU) is the third most common mycobacterial disease worldwide and affects mainly poor human populations living in tropical and subtropical areas.1,2 In 2018, Africa and Australia reported the most cases (2335 and 358 cases, respectively), followed by French Guiana (FG, five cases) and Japan (three cases).3 Clinical signs of the disease include painless nodules, plaques and oedema followed by the development of skin ulcers.1 In Africa the disease mainly affects children while in Australia and FG most BU cases are reported in adults.1,2 In Africa, osteomyelitis is frequent (up to 14% of cases) when compared with Australia and FG (< 1%).2

The transmission of Mycobacterium ulcerans (MU), the causative agent of BU, remains elusive.1 It has long been thought that the transmission of MU from a freshwater environment to ‘dead-end’ human hosts most likely occurs from contact with traumatized skin.1,2 The variability in BU incidence and severity between countries have driven the scientific community to focus on the diversity of MU strains and mycolactone types.1 Here, we looked at BU cases for the potential presence of co-infections from several mycobacteria or infections from mycobacteria species other than MU, which could explain the observed BU variability.

Using DNA metabarcoding, we tested the presence of 40 mycobacterial metagenomic operational taxonomic units (MOTUs; from 7753 complete mycobacterium genomes) in patients with suspected BU admitted to Cayenne Hospital in 2016 and 2017. Table 1 shows the results of the six (of eight) skin lesions diagnosed by P.C. that were subjected to: (i) Zielh–Neelsen staining (swabs) for bacillus acido-alcohol resistance (BAAR); (ii) quantitative polymerase chain reactions (qPCRs) targeting IS2404 and KR (ketoreductase B domain of the mycolactone polyketide synthase gene);1,2 (iii) MU