Future research priorities for lichen sclerosus – results of a James Lind Alliance Priority Setting Partnership

Running head: Lichen Sclerosus Priority Setting Partnership

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Conflicts of interest:

None

Lichen sclerosus (LS) is a chronic, inflammatory genital skin condition affecting men, women and children. Long-term complications include loss of normal anatomy from scarring, and malignant transformation. Uncertainties exist about the cause, diagnosis and management of LS. For example, the aetiology is contested; evidence suggests that chronic irritation by occluded urine is important in males,[1] however, autoimmune mechanisms are proposed in females.[2] Genetic associations are suggested in both sexes.[2] Existing evidence on which to make recommendations about management and the prevention of malignancy, is generally poor quality.[2-4]

We conducted a Priority Setting Partnership (PSP) from June 2017-July 2018 using James Lind Alliance (JLA) methodology[5]. The aim was to identify future research priorities about the causes, diagnosis, management and prevention of LS in men, women and children. This ~~report~~ letter details the key findings, a full detailed report will be available in the public domain[6].

The protocol was prospectively written and made publicly available[6]. The steering group, chaired by a JLA independent adviser, included 7 patient representatives (5 patients, 1 parent of child with LS, 1 patient support organisation representative), 7 health professionals (5 dermatologists, 1 gynaecologist and 1 nurse) and 3 researchers/administrators. From September-October 2017 we conducted the first of two online surveys using SurveyMonkey™. These surveys, available in English, were promoted by partner organisations and social media to reach patient and health professional stakeholders internationally (see acknowledgements), as well as posters in outpatient clinics.

The first survey gathered patients' and health professionals' views. Participants submitted up to five questions that they had about LS. This survey was supplemented by evidence gaps identified from three key systematic reviews and guidelines in the literature.[2-4]

There were 653 respondents from 28 countries. Of these 64% were patients (92% females, 5% parents) and 35% were health professionals (29% gynaecologists, 26% dermatologists, 16% sexual health physicians, 10% general practitioners, 9% urologists). Of 2580 submitted questions 660 were removed as they were out of scope, illegible/unintelligible, or too ill-defined. The remainder were grouped and refined, to produce 38 'unique uncertainties' which reflected the overarching themes of the individual submissions and had not already been answered by previous research. Input from all members of the Steering Group ensured that questions were worded to be understood by the general public.

An 'interim prioritisation' online survey (March-April 2018) was completed by 954 participants, with the same patient/health professional ratios as in survey 1 (except for proportionally higher gynaecology respondents) from 35 countries. Participants were asked to select their 10 most important questions from the 38 uncertainties identified during stage one. Uncertainties were presented to individuals in a random order to minimise selection bias.

~~Following the second survey, the Steering Group agreed on additional merging/re-wording resulting in revised list of 31 uncertainties.~~ The top-rated uncertainties overall, plus the most important uncertainties from each of the stakeholder groups (health professionals, females, males and children) were selected to form a shortlist of 23 questions.

These 23 questions were discussed at a face-to-face workshop (London, June 2018) involving 3 independent JLA facilitators, 14 patients (10 female, 2 male, 2 parents) and 15 health professionals. Using nominal group technique, after two rounds of small group discussions and a final whole group discussion, consensus on the 'Top 10' priorities was agreed by all workshop participants (Table 1). There was agreement for further merging and rewording of some of the questions which reduced

the shortlist of questions from 23 to 20~~(Table 1).~~ Increasing knowledge and awareness of LS was felt to be a key overarching theme for any future research in this field.

The strength of this project is the global reach, large number of respondents and transparent methodology.

The main challenge was in ensuring adequate representation of male patients. Possible reasons are twofold; First, males are less willing than women to engage with health-related surveys;[7] second, LS treatment in males differs to women as circumcision potentially offers a cure. Therefore the proportion of males with 'unanswered questions' about LS may be far fewer than women. Similarly, representation of children with LS was low; possibly because LS is less common in children and may go undiagnosed. As a result, the Steering Group took care to ensure that the uncertainties were worded to be applicable to all patient groups (where possible), and workshop participants representing men and children were specifically asked to confirm that the final Top 10 reflected priorities relevant to them.

Results of this PSP will now be widely publicised. Due to the high level of stakeholder engagement, these Top 10 questions will be attractive to both researchers and funders, leading to future studies which will inform clinical practice and minimise research waste.[8]

Acknowledgements:

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In addition to those listed as authors, the Steering Group consisted of an additional four patients (Mrs MD, Mrs HB, Mrs SS, Miss LH) whose identities have been kept anonymous for confidentiality reasons. Without their input we would not have been able to conduct this high quality work. We would like to thank all those who took part in the on-line surveys, and those who attended the final workshop. Thanks also to the Australian and New Zealand Vulval Society (ANZVS), UK Dermatology Clinical Trials Network (UK DCTN), British Association of Dermatologists (BAD), British Dermatological Nursing Group (BDNG), British Association for Sexual Health and HIV (BASHH), British Association for Urological Surgeons (BAUS), British Society for Paediatric Dermatology (BSPD), Danish Lichen Sclerosus Support Group, Dutch Lichen Sclerosus Support Group, German speaking Lichen sclerosus group based in Switzerland, Dermnet.nz, International Society for the Study of Vulval Disease (ISSVD), Manchester Vulval Support Network (MVSN), Primary Care Dermatology Society (PCDS), Society for Academic Primary Care (SAPC), Vulval Pain Society, social media networks and those groups without social media presence, for assistance in distributing information and encouraging participation of different stakeholder groups.

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Following the final workshop one member of the Steering Group chose not to be an author on this publication due to disagreement over the final top 10 priorities agreed by consensus.

Table 1: Results of the Lichen Sclerosus Priority Setting Partnership final workshop: The Top 10 uncertainties to be addressed by future research

1	What is the best way to prevent and manage anatomical changes caused by lichen sclerosus? • *Anatomical changes* includes fusion, altered shape of the genitals and scarring.
2	What is the best way to diagnose lichen sclerosus (diagnostic criteria)? • *Diagnostic criteria* may include assessing clinical features (visible signs), taking a biopsy (skin sample) or doing tests (e.g. blood tests). The criteria may also include indicators of disease severity. Necessity of biopsy and adverse effects from biopsy may also be investigated.
3	What surgical treatments should be offered for lichen sclerosus? • *Surgical treatments* include (but are not limited to) laser, platelet-rich plasma or lipofilling (fat transfer) • These treatments can be used in the management of scarring, anatomical changes or symptoms associated with lichen sclerosus. • When should surgical treatments be offered and what are the long-term outcomes?
4	Are there effective topical treatments other than topical steroids in the treatment of lichen sclerosus? • This includes what should be done when topical steroids fail. • 'Other topical treatments' may include (but are not limited to) topical calcineurin inhibitors such as tacrolimus and pimecrolimus.
5	What is the risk of developing cancer in patients with lichen sclerosus? • This includes being able to identify those at greatest risk and whether certain treatments increase or lower/reduce the risk of cancer
6	Which aspects of lichen sclerosus should be measured to assess response to treatment?
7	Can lichen sclerosus be prevented from occurring and what are the trigger factors? • *Trigger factors* include both factors responsible for development of lichen sclerosus and for its flare ups. These may include (but are not limited to) irritation from clothing/chemicals/urine, trauma, environmental factors, drugs and medications
8	Is it necessary to continue treatment for patients with lichen sclerosus who do not have any symptoms and/or signs of disease activity? • *Patients without symptoms* includes those who are in remission after treatment, as well as those who have asymptomatic disease. • This includes follow-up arrangements such as includes frequency (how often), duration (how long) and by whom (which health professionals)?
9	What is the impact on quality of life? • *Quality of life* includes effect on day to day living, psychological health and sexual relationships • This includes how can psychological or social support be best used to help people with lichen sclerosus?
10	Does the disease course of lichen sclerosus differ in boys and girls, adult males and females? • This includes whether lichen sclerosus can remit completely
~~11~~	~~Are tablets or injection medications that dampen the immune system effective in treating lichen sclerosus?~~ • ~~This may include (but not limited to) medications such as methotrexate, biologic treatments, low dose naltrexone~~

~~12~~	~~What is the best topical steroid regimen for treating a flare and maintaining remission in lichen sclerosus?~~ • ~~This includes steroid strength, site of application, duration and frequency~~ ~~What is the long-term safety of applying steroids to the skin in lichen sclerosus~~
~~13~~	~~Is there a role for complementary therapies in the management of lichen sclerosus?~~ • ~~Complementary therapies may include (but are not limited to) homeopathic remedies, acupuncture, vitamin supplements or natural products~~ ~~Which are the best to use in addition to standard topical treatment?~~
~~14~~	~~How best can knowledge and awareness of lichen sclerosus be increased?~~ ~~This includes healthcare professionals, patients, public and professional bodies~~
~~15~~	~~What role do hormones have in causing or influencing the severity of lichen sclerosus?~~ • ~~'Hormones' can be during menopause, throughout the menstrual cycle, during pregnancy~~ ~~This includes whether hormone treatments have a role in the management of lichen sclerosus~~
~~16~~	~~Are there any lifestyle changes that can help in the management of lichen sclerosus?~~ ~~This includes genital hygiene, sex life and day to day activities~~
~~17~~	~~Is lichen sclerosus in women and children an autoimmune condition?~~ ~~Should patients be screened for other autoimmune conditions?~~
~~18~~	~~Is lichen sclerosus in women and children caused or linked to medical conditions other than autoimmune conditions?~~
~~19~~	~~What is the genetic link for the development of lichen sclerosus?~~
~~20~~	~~What role does diet have in causing or influencing the severity of lichen sclerosus?~~ • ~~This includes whether there is a role for dietary changes in the management of the condition~~ • ~~*'Diet'* may include (but not limited to) eating sugar, being deficient or intolerant of certain nutrients~~

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