Core Outcome Set for Genital Lichen Sclerosus: Development of Core Domains

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Short title:	Core Outcomes for ReseArch in Lichen Sclerosus
Acronym:	CORALS
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Study Sponsor:	University of Nottingham
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STUDY PERSONNEL AND CONTACT DETAILS

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Mr David Foster (Gynaecologist)
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Mr Martin Promm (Paediatric Urologist)
Mr Stefano Lauretti (Urologist)
Mr Angelo Augenti (Urologist)
Ms HB (UK patient)
Ms. Suzanne von Seitzberg (Lead of Danish patient support group)
Mr RP (Male patient representative)

Study Statistician: N/A

Study Coordinating Centre: Centre of Evidence Based Dermatology

SYNOPSIS

Title	Core Outcomes for ReseArch in Lichen Sclerosus
Acronym	CORALS
Short title	CORALS
Chief Investigator	Dr Rosalind Simpson
Objectives	To obtain international agreement on what aspects of disease ('domains') should be measured as a minimum requirement in interventional trials of genital LS.
Study Configuration	International electronic Delphi consensus exercise
Setting	Online survey
Sample size estimate	N/A
Number of participants	Optimum 6 - 12 participants from each stakeholder group
Eligibility criteria	Stakeholder in the field of lichen sclerosus (patients, representatives of patients, health professionals, researchers, journal representatives, industry representatives)
Description of interventions	Online electronic-Delphi consensus survey to be carried out over 3 rounds, each survey will take approximately 10 minutes to complete. Each survey will be open for 2 weeks for participants to complete
Duration of study	Start September 2019, finish survey December 2019
Methods of analysis	Consensus methodology using Delphi method. Definition of consensus to be defined a priori

ABBREVIATIONS

Add to / amend accordingly (please ensure ALL abbreviations used in the protocol are listed here)

CI	Chief Investigator overall
COS	Core Outcome Set
CRF	Case Report Form
GCP	Good Clinical Practice
LS	Lichen sclerosus
NHS	National Health Service
PI	Principal Investigator at a local centre
PIS	Participant Information Sheet
REC	Research Ethics Committee
R&D	Research and Development department
UoN	University of Nottingham

TABLE OF CONTENTS

The table of contents will need updating (this can be done once all changes have been made and before documents are submitted to the Sponsor for review) to do this right click anywhere on the table of contents and click update fields

STUDY BACKGROUND INFORMATION AND RATIONALE

Genital skin conditions are common, particularly vulval conditions. A study of UK General Practitioners demonstrated that over half saw more than 3 patients with vulval disease per month[1]. A US community survey of 303 adult females reported one fifth with lower genital tract discomfort lasting longer than 3 months[2].

Lichen sclerosus (LS) is a commonly encountered non-infectious inflammatory genital skin condition in clinical practice[2]. It probably affects at least 1% of women, although estimates of incidence and prevalence are not well defined and remain controversial [3-5]. Anecdotal evidence suggests it is just as common in men and boys. An estimated 3-5% of cases go on to develop malignancy [6-8]. It has a significant impact on quality of life and affects psychosocial and sexual well-being. This negative impact has been shown to contribute towards self-harm or suicidal thoughts [9, 10].

In women and pre pubertal girls, LS primarily affects the vulva. A variety of symptoms, for example, intense itch, pain and splitting occur. The physical appearance of the vulva is affected. These symptoms of lichen sclerosus impact upon daily function. Delay or poor response to treatment leads to ongoing inflammation. Subsequent scarring can cause labial fusion, narrowing of the vaginal opening and burying of the clitoris. In girls, lichen sclerosus can result in an itchy vulva and often pain with defecation; medical treatment helps but cure is not expected in most and the disease will continue in adult life.

In men and boys, lichen sclerosus tends to develop on the glans penis and sometimes on the foreskin. Symptoms in men may be difficulty urinating due to narrowing of the urethra, difficulty in retracting the foreskin due to scarring, and painful sexual intercourse. In boys, lichen sclerosus will usually lead to a tight foreskin (phimosis). Circumcision is often required, especially when symptoms are poorly controlled with topical treatment. It is not known if this procedure is curative or not.

The anatomical changes that occur in lichen sclerosus are usually irreversible and can have a detrimental effect upon day to day function and psychological health of those affected. Men are at risk of serious urethral disease. People with lichen sclerosus also appear to have an increased risk of genital cancer.

Despite this, genital disease in general is a neglected area of health: it has received little attention from the research community and there is paucity of existing high-quality evidence to guide clinical practice in vulval skin conditions. In the case of LS, this is in part, due to a lack of validated outcome measures as published randomised controlled trials are heterogeneous, of poor methodological quality and difficult to combine in meta-analyses [11].

In addition, there is lack of knowledge about clinical features and management of LS and genital skin conditions within the wider medical community. Patients describe delays in diagnosis, poor pathways of care and varying advice on how to treat their condition. Genital LS in males and in children is both less prevalent and less recognized in the medical community. Children may be misdiagnosed with diaper rash or with questions of sexual abuse when signs of genital disease are seen.

This project has been prioritised following the ‘Lichen Sclerosus Priority Setting Partnership’, which agreed internationally to the ‘Top 10’ future research priorities for genital LS [12] , of which one of the Top 10 future research questions was:

'Which aspects of lichen sclerosus should be measured to assess response to treatment?'

In addition, previous calls to action for Core Outcome Set (COS) development in vulvovaginal conditions have been published[13].

A group of multidisciplinary clinicians, led by Rosalind Simpson (Dermatologist), David Foster (Gynaecologist) and Gudula Kirtschig (Dermatologist), have formed a team who wish to develop core outcome sets for the different types of vulval skin disorders [14]. This is the 'Core Outcome Set for Vulvovaginal Conditions' (vulvovaginal COS) initiative. Dr Simpson and Dr Kirtschig plan to lead the work for LS (CORALS), which at this initial stage will be inclusive for men and children, although women will be the main focus.

The vulvovaginal COS initiative is registered with the COMET initiative (Core Outcome measures for Effectiveness Trials) [15] and CROWN initiative (Core Outcomes for Women's and Neonatal health) [16]. We have engaged with CS-COUSIN (Cochrane Skin – Core Outcome Set Initiative) team [17] who will support the methodological aspects of this work.

This research is timely given the current research landscape: the importance of 'Core Outcome Sets', which represent **minimum outcomes to be measured and reported in all clinical trials of a specific condition**, are well recognised in general [15] and in particular in dermatology [18, 19]. Furthermore, the themes of this work; prioritising women's health matters, reducing the burden of chronic conditions and addressing disease in older people, are outlined as priorities by the World Health Organisation[20] the NHS Five Year Forward View [21]. It is important to note that a COS does not stop researchers from measuring other outcomes relevant to their research question. The purpose of the COS is to ensure that future trials measure at least the key same outcomes so that they are comparable and results can be combined/compared during metaanalysis.

This work is clinically relevant as improving care for patients with LS is vital to minimise the negative impact of the LS on physical, psychological and psychosexual wellbeing [10, 22]. Particular priorities are reducing patients' symptoms, the risk of scarring, which might affect sexual relationships, leisure activities, and work, and risk of malignant transformation. There is some evidence that the risk of scarring and malignant transformation may be reduced by continuous long-term treatment [23].

Including domains pertinent to males and children will expand the utility of this project.
As there is currently no agreement on which outcomes should be used to gauge response to treatment, this project will ultimately inform future randomised controlled trials and systematic reviews, which will lead to improved evidence-based care and reduce the long-term complications cause by LS.

STUDY OBJECTIVES AND PURPOSE

PURPOSE

PRIMARY OBJECTIVE

The objective of this project is to answer the following research question:

In genital lichen sclerosus, what types of outcomes (outcome domains) should be measured as a minimum requirement in interventional randomised controlled trials?

Scope

The Steering Group have considered the scope of this project at length. The main focus of this initiative is adult females with LS with applicability to males and children. This is a unique opportunity to collect data from men and children with LS and so responses from these groups will be welcomed during the development of core domains. If there is considerable difference between the groups it will be considered whether the groups should be separated for subsequent stages of the COS development.

CORALS is intended to be an international project to agree core outcome measures for interventional clinical trials in patients with genital LS.

STUDY DESIGN

STUDY CONFIGURATION

International electronic Delphi (e-Delphi) consensus survey (3 rounds).

STUDY MANAGEMENT

The central coordinating centre is the Centre of Evidence Based Dermatology, from which the study will be managed and led. The project will have an international multidisciplinary Steering Group including patient representation.

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

The data custodian will be the Chief Investigator.

DURATION OF THE STUDY AND PARTICIPANT INVOLVEMENT

Study Duration: Enrolment will begin one month prior to launching the e-Delphi survey. Three rounds of the survey will be run over a three month time period. Total duration of study will be 4 months.

Participant Duration: 1 month prior to start of survey potential participants will be invited to participate in the study (invitation via professional networks/social media/internet groups). Participants will be asked to complete three rounds of an online e-Delphi survey over a period of 3 months. The duration of participants in the initial e-Delphi process will be 4 months.

Following the e-Delphi process, participants will be asked if they wish to take part in a second stage which is a one off day consensus meeting (separate ethical approval to be sought). Following this all involvement will be ceased. Participation in the first and second stages will be completely voluntary.

End of the Study

End of the study will be the end of the e-Delphi survey.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

Participants will be recruited via professional networks, social media and internet groups. Therefore, the initial approach will be through remote contact. Information about the study will be available through the study's webpage.

The investigator or members of the steering group will be available to answer any questions pertaining to participation in the study. Potential participants will be able to contact the team via a central email address if there are any queries.

We will aim to translate the information page of the survey into different languages where possible to aid people whose first language is not English. This will be limited to the languages spoken by our Steering Group and our networks. The main survey will not be available in other languages.

It will be explained to the potential participant that entry into the study is entirely voluntary. 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.

Eligibility criteria

Informed consent will be assumed if a participant responds to the surveys.and ticks the 'check box' on the survey for consent.

Inclusion criteria

Anyone who is a stakeholder in the field of lichen sclerosus.
Ability to complete the online survey
Ability to give informed consent

Stakeholders for this COS project include a number of groups who are involved in the management of patients with LS, who have LS themselves, who plan/publish/research studies for interventions in LS or who develop treatments for LS. The following groups are considered stakeholders to be involved as participants in the study to agree core domains:

- Dermatologists
- Gynaecologists
- Histopathologists
- Specialist Nurses
- Urologists
- Oncologists
- Sexual Health Medicine practitioners
- Patients
- Journal Editors
- Regulatory bodies
- Industry Representatives
- Clinical trialists
- Systematic reviewers

Exclusion criteria

Anyone who is not a stakeholder in the area of lichen sclerosus

Expected duration of participant participation

Study participants will be participating in the study for 3 months.

Participant Withdrawal

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

Informed consent

Completion of the online survey will be taken as informed consent and separate written informed consent will not be sought. At the beginning of the survey, participants will be asked to 'check a box to give their consent to participate in the survey. Details of the study will be available through the Participant Information Sheet. The Investigator or a member of the Steering Group will answer any questions that the participant has concerning study participation.

STUDY REGIMEN

Potential participants will be invited via professional groups and social media. They will be provided a link to an online information sheet and project webpage. They will be asked to send an expression of interest to participate in the study via email. Those who wish to participate will then be electronically sent a link to the online survey once the study becomes live.

A consensus study using e-Delphi methodology involving international stakeholders will be used to select the most important/relevant of the identified outcome domains from a long list developed by the Steering Group. The COMET Initiative's 'Delphi Manager' web-based system will be used for survey management [24]. The e-Delphi process is one in which a panel of participants answer a series of questionnaires over two or more rounds in an attempt to achieve consensus.

The Steering Group have chosen web-based software to administrate the survey rather than paper based forms. Although they would increase the accessibility of the survey, paper based forms are impractical and require a large amount of resource and coordination. The LS Priority Setting Partnership, was an internet based survey with 653 and 954 respondents over round 1 and 2 respectively. There was participation from a wide age range of patients including 48% aged 51-70 and 4% > age 70. We therefore believe that a good spread of representation is possible from this COS project. We will aim to translate the information page of the survey into different languages where possible to aid people whose first language is not English. There will be a named contact for each of the different languages to provide support for completing the survey.
The steering group patient representatives will help to ensure that instructions for completing the Delphi surveys are clear and understandable. In addition, the COMET PoPPIE (Patient Participation, Involvement and Engagement) group will be asked to review the wording. The

language used to describe each potential outcome for the core set must be unambiguous and will be piloted with a group of patients prior to release of the main e-Delphi survey.

In round 1 participants are asked to score the importance of including a particular outcome in a core outcome set on a scale of 1-9 (1-3=not important, 4-6=important but not critical, 7-9=Critical). An option for 'unable to score' is also available. Participants will be able to provide feedback on individual items and suggest additional outcome domains if they feel any are missing. Feedback will be collated and if necessary, rewording of the items will take place following discussion with the Steering Group. Additional items will be assessed against the long list of domains (and items included within those domains) to check whether they are truly missing. Following agreement with the Steering Group, the outcome domains that have been missed will be added to the list of domains in the second round of the Delphi survey.

Definition of consensus will be determined a priori.

Compliance

During the e-Delphi survey, emails will automatically be sent to participants at key stages of the process to ensure maximum return of the Delphi survey questionnaire.

Criteria for terminating the study

It is not anticipated that this study will need to be terminated early. If recruitment from certain stakeholder groups is poor, this will be addressed by targeting specific networks/social media groups to boost numbers of those who are underrepresented.

ANALYSES

Methods

The DelphiManager software will automatically analyse the responses entered by participants. Definition of consensus for the e-Delphi will be determined a priori. The survey asks for participants to rate items on a scale of 1-9 (1-3=not important, 4-6=important but not critical, 7-9=Critical). An option for 'unable to score' is also available.

Criteria for an outcome to be considered as part of the COS are:

- at least 70% of participants score an outcome as 7, 8, or 9

And

- 15% or less of participants score it as 1, 2, or 3.

If too many outcomes are still on the list (after a max. of three rounds) organising by rank order may be necessary.

The survey instrument will be amended following round one and additional outcome domain items suggested by participants will be included in the subsequent round.

In subsequent rounds participants will receive feedback; they will be shown the distribution of scores from other participants, grouped by stakeholder, along with the score that they

attributed to the individual outcomes. They will be asked to reflect, and rescore if they want to, having been shown the views of the other participants.

The e-Delphi will be concluded after a maximum of 3 rounds. Rounds will be held approximately 1 month apart. Participants will be given 2 weeks to complete each individual round.

Sample size and justification

For each of the stakeholder groups an optimum number of 6 - 12 participants are required.

There will be 12 stakeholder groups including:

- Dermatologists
- Gynaecologists
- Histopathologists
- Specialist Nurses
- Urologists
- Oncologists
- Sexual Health Medicine practitioners
- Male patients
- Female patients
- Representatives of paediatric patients
- Journal Editors/Clinical trialists/Systematic reviewers
- Regulatory bodies/Industry Representatives

ADVERSE EVENTS

The occurrence of an adverse event as a result of participation within this study is not expected and no adverse event data will be collected.

ETHICAL AND REGULATORY ASPECTS

ETHICS COMMITTEE AND REGULATORY APPROVALS

The study will not be initiated before the protocol and participant information sheets have received approval / favourable opinion from the University of Nottingham Ethics committee.

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice and the UK Department of Health Policy Framework for Health and Social Care, 2017.

INFORMED CONSENT AND PARTICIPANT INFORMATION

Completion and subsequent return of questionnaires will be taken as informed consent and separate written informed consent will not be sought

RECORDS

Case Report Forms

The e-Delphi survey will be filled in electronically using online software. There will not be any paper based forms to complete. In order for the e-Delphi to be sent out in a series of rounds,

participants need to register their email address with the system. Therefore, true confidentiality cannot be maintained. However, the survey collects opinion, not medical information or any sensitive data.

Source documents

Source documents shall be filed electronically at the investigator's site and may include but are not limited to, consent forms, study records, field notes, interview transcriptions and audio records. A CRF may also completely serve as its own source data. Only study staff shall have access to study documentation other than the regulatory requirements listed below.

Direct access to source data / documents

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

DATA PROTECTION

All study staff and investigators will endeavour to protect the rights of the study's participants to privacy and informed consent, and will adhere to the Data Protection Act, 2018. The survey will only collect the minimum required information for the purposes of the study. Computer held data including the study database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method).

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

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

The University of Nottingham as research Sponsor indemnifies its staff, research participants and research protocols with both public liability insurance and clinical trials insurance. These policies include provision for indemnity in the event of a successful litigious claim for proven non-negligent harm.

STUDY CONDUCT

Study conduct may be subject to systems audit for inclusion of essential documents; permissions to conduct the study; CVs of study staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, timeliness of visits); accountability of study materials and equipment calibration logs.

STUDY DATA

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

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Code of Research Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The study documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all anonymised audio recordings, study databases and associated meta-data encryption codes.

DISCONTINUATION OF THE STUDY BY THE SPONSOR

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

STATEMENT OF CONFIDENTIALITY

Individual participant medical or personal information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above.

If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

Data generated as a result of this study will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

Dissemination to healthcare professionals will be through presentations at clinical conferences and via publication in a peer reviewed journal. Participants will not be identifiable in any published material.

All participants involved in the research will be informed of the study outcomes via a newsletter and through study updates on the Centre of Evidence Based Dermatology website.

USER AND PUBLIC INVOLVEMENT

This project was developed following the Lichen Sclerosus Priority Setting Partnership, a project which involved patients and health professionals to identify future important research topics for lichen sclerosus.

This CORALS project has patient representation on its Steering Group with two female and one male patient represntatives. The concept of COS development is that patients are involved in the process of agreeing important outcomes and therefore patients will be actively involved in the COS process, as Steering Group members, by using patient networks to raise awareness of the project and by engaging patients to participate in the project.

STUDY FINANCES

Funding source and conflict of interest

This study has been funded by the UK Dermatology Clinical Trials Network (UK DCTN) through the 2018 Themed call Research Award. The funders do not have a role in the design. Development or implementation of the project. The only exception to this is that they may be asked to disseminate information regarding the survey and its results to UKDCTN network members.

Dr Rosalind Simpson has no conflicts of interest to declare
Dr Gudula Kirtschig has no conflicts of interest to declare
Dr Amanda Selk has no conflicts of interest to declare
Mr David Foster
Dr Martin Promm
Dr Jan Kottner has no conflicts of interest to declare
Professor Kim Thomas has no conflicts of interest to declare
Ms Ione Bissonnette has no conflicts of interest to declare
Ms Gitte Vittrup has no conflicts of interest to declare
Ms HB has no conflicts of interest to declare
Mr RP has no conflicts of interest to declare
Ms. Suzanne von Seitzberg has no conflicts of interest to declare

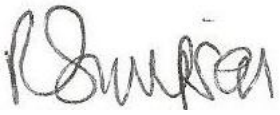
Participant stipends and payments

Participants will not be paid to participate in the study. Travel expenses will be offered for any out of pocket costs related to participating in the study.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: (name)_____Dr Rosalind Simpson_____

Signature: 

Date: 23/10/19

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