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Core outcome domains for lichen sclerosus: a CORALS initiative consensus statement

Running Head: CORALS Core Domains

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Abstract

Background: Lichen sclerosus (LS) is a chronic inflammatory condition mainly affecting genital skin. It causes distressing symptoms that impact daily quality of life (QoL). It causes progressive anatomical changes and a potential risk of cancer. Published randomised controlled trials are of varying methodological quality and difficult to combine in meta-analyses. This is partly due to lack of agreed outcome measures to assess treatment response. Identification of core outcome sets (COSs), which standardise key outcomes to be measured in all future trials, is a solution to this problem.

Objectives: To obtain international agreement on which outcome domains should be measured in interventional trials of genital LS.

Methods: Recommended best practice for COS domain development was followed: 1) Identification of potential outcome domains: a long-list was generated through up-to-date LSliterature search, including information collected during the LS Priority Setting Partnership. 2) Provisional agreement of outcome domains: A 3-stage multi-stakeholder international electronic-Delphi consensus study; 3) Final agreement of outcome domains: Online consensus meeting with international stakeholders including anonymised voting.

Results: In total, 123 participants (77 patients, 44 health professionals, 2 researchers) from 20 countries completed 3 rounds of the electronic-Delphi study. 11 outcome domains were rated as 'critical' and were discussed at the online consensus meetings. The first set of consensus meetings involved 42 participants from 13 countries. Consensus was met for '*symptoms'* (100% agreed) and '*quality of lif –LS specific'* (92% agreed). After set two of meetings, involving 29 participants from 12 countries, '*Clinical (visible) signs'* also met consensus (97% agreed).

Conclusions: The international community have agreed upon 3 key outcome domains to measure in all future LS clinical trials. We recommend that trialists and systematic reviewers incorporate these domains into study protocols with immediate effect. CORALS will now work with stakeholders to select an outcome measurement instrument per prioritised core domain.

Introduction

Core outcome sets (COS) aim to reduce research waste by ensuring that outcomes measured in randomised controlled trials (RCTs) of a specific condition can be compared and combined in meta-analyses to provide a stronger treatment evidence base.[1] COSs ensure that all trials of a particular condition measure the same key outcomes so that they are comparable. However, it does not prevent researchers from measuring other additional outcomes relevant to their specific study.[2] There is an international movement to promote COS, supported by initiatives such as COMET (Core Outcome Measures for Effectiveness Trials)[3], CROWN (Core Outcomes for Women's and Neonatal Health*)*[4] and C3 (The CHORD COUSIN Collaboration).[5] Leading peer reviewed journals support implementation of COS by ensuring that if one exists, the core outcomes are reported in published research.[6]

There is considerable variation in outcome measurement for vulval disease.[7] Lichen sclerosus (LS) is an important, albeit under recognised condition which affects at least 1% of women of all ages [8-10] but also affects children and men, and usually runs a chronic course. An estimated 3-5% of cases develop malignancy.[11,12] LS has a significant impact on quality of life (QoL) and affects psychosocial and sexual wellbeing [13-15] Lack of validated outcome measures and heterogeneity in published RCTs limits high quality evidence to guide clinical practice.[16] Agreement regarding outcomes has been identified as a need in an international priority setting partnership.[17] Due to an increase of trials testing new treatments for LS, such as laser, platelet rich plasma and alternative topical treatments, which may be costly and/or have potential serious side effects, the need to standardise outcome measurement in LS is paramount.

CORALS (Core Outcomes for Research in Lichen Sclerosus) is an initiative led by a multi-stakeholder steering group which aims to create, via international consensus, a COS for future genital LS trials. COS development takes place in two stages: 1. Agreement of core outcome domains and 2. Agreement of core outcome measurement instruments.

The aim of this stage of CORALS was to obtain international agreement on which *domains* should be measured as a minimum requirement in interventional trials of genital LS.

Methods

A multidisciplinary steering group with representation from dermatology, gynaecology, nursing, urology, patients (male and female) and methodologists, with independent oversight from a C3 representative, was formed to drive this initiative forward. Ethical approval was obtained from the Faculty of Medicine

and Health Sciences Research Ethics Committee of the University of Nottingham (Ref: 376-1908). Online consent was obtained for participation in the electronic-Delphi (e-Delphi) survey.

The protocol was developed in line with CS-COUSIN (Cochrane Skin Core Outcomes Initiative, now known as C3) guidance and followed Core Outcome Set-STAndards for Development (COS-STAD) recommendations[18] and accepted methodology.[19] It was prospectively made publicly available. [20] The intention to develop a COS in LS was also registered on the COMET, CROWN and C3 websites. The scope of this COS was all patients with LS, all treatments, and all settings.

Development of domains took a three-stage process:

1. Identification of possible domains using key documents in the literature
2. Provisional agreement of the most important domains via a 3-stage e-Delphi consensus study
3. Final agreement of domains: international virtual consensus meetings

Identification of potential domains

A long list of possible outcome domains was identified through randomised controlled trials included in key guideline and systematic review documents [10,16,21] as well as qualitative published studies. [22-24]

Domains were extracted from these documents independently by three steering group members (RS, GK, AS). These were then reviewed by the whole Steering Group and any domains perceived to be missing were added. Similar domains were grouped together and summarized to create a list of meaningful concepts and definitions, based upon agreed taxonomy.[25] Patient representatives advised on wording of domains to be understandable by members of the public.

Provisional agreement of the most important domains

The long list of domains was entered into a three-stage e-Delphi consensus study using 'Delphi Manager' software from the COMET group.[26] Although the main e-Delphi survey was in English, to increase accessibility, participant information sheets and the survey welcome page were available into nine different languages. Support for participants with translation of the survey was offered although this was not taken up.

Stakeholders included health care professionals, patients, patient representatives/carers, researchers and systematic reviewers in the field of LS, industry representatives and journal editors. Stakeholders were identified through the International Society for the Study of Vulvovaginal Disease (ISSVD), the British Society for the Study of Vulval Disease (BSSVD), the Australian and New Zealand Vulvovaginal Society (ANZVS), European College for the Study of Vulvar Disease (ECSVD), the Indian Chapter of the ISSVD and the North American Chapter of the ISSVD. Editors of journals signed up to the CROWN and COMET initiatives were invited. Patients were identified through international LS patient support groups. Invitations were sent via a range of methods including advertisements on social media, mailshots to members of the relevant societies and direct email invitations to people recognised as key figures in the field of LS. Those stakeholders who expressed interest via an online form were subsequently provided with the survey links once available.

Delphi round 1 asked participants to score the importance of each outcome domain on a 9-point Likert scale (1-3=not important, 4-6=important but not critical, 7-9=critical) and an 'unable to score' option. Each domain had a plain English description of its definition available by 'hovering' over the domain. Participants were allowed to provide feedback on individual domains and suggest additional domains if they felt any were missing. Feedback was collated and discussed with the Steering Group with plans to reword domains if necessary. Additional items were categorised and assessed against the long list of domains to check whether any were missing. Outcome domains that were missed were added for voting upon in the second round of the e-Delphi survey.

Definition of consensus was determined *a priori*. Criteria for a domain to be considered as part of the COS was if at least 70% of participants scored an outcome as 'critical' with 15% or less of participants voting as not important'. Analysis was undertaken by downloading Delphi-manager scores to a Microsoft Excel spreadsheet and calculating for each of the domains the percentage of respondents who voted 1-3 (not important), 4-6 (important but not critical), 7-9 (critical).

Domains that did not meet consensus as 'critical' after two rounds were removed. Subsequently, round 3 used 'Survey-monkey'[27] to present the outcome domains that had reached consensus as being 'critical' and asked participants to rank them in terms of their importance (1= most important, 11=least important). Items were presented to participants in a randomised order to minimise bias when ranking. Survey-monkey automated analysis was used to calculate the average ranking for each answer choice to determine which answer choice was most preferred overall i.e., the answer choice with the largest average ranking represents the most preferred choice. We calculated ranking for each stakeholder group, as well as overall rankings.

Reminder emails were sent to participants at key stages of the process to ensure maximum return of the e-Delphi survey questionnaire.

International consensus meetings

The aim of the consensus meeting was to agree on core domains for the future LS COS. As a result of the COVID-19 pandemic, it was not felt appropriate to hold 'in-person' consensus meetings as described from previous published COSs. Therefore, using 'Microsoft Teams', we held two sets of virtual consensus meetings. Each meeting set had two dates at different times where the content and processes were repeated. This provided the opportunity for stakeholders from different time zones to participate. To encourage as wide international engagement as possible, the meetings were opened to CORALS' wider contact network as well as those who participated in the e-Delphi surveys. Pre-meeting information was circulated detailing the process to date and results from the e-Delphi surveys. Tasks were set to encourage participants to consider in advance which domains meant most to them.

The sessions comprised a mixture of presentations, whole group discussion and smaller moderated breakout groups. Moderators were instructed to remain impartial and facilitate discussion but not voice their opinion. There was a moderator guide (Appendix S1) to support standardisation of the breakout groups.

In the whole group session, outcome domains were presented in detail. Then to prioritise domains down to the core minimum, the smaller groups were asked to determine their 'top 3' domains. Breakout group results were presented to the main group and after further discussion participants were asked to vote anonymously, using Microsoft Forms, for each of the domains by asking the question *'should the domain be in the final core outcome set? Yes/no/not sure'*. A backup questionnaire was prepared to

send immediately after the meeting had ended to participants who identified as unable to vote during the live sessions. To avoid bias, results from the consensus meetings were not shown to participants until both meetings were complete and those who couldn't vote live had been given the opportunity to complete the questionnaire.

Definition of consensus was if 70% or more agreed, then the domain would be in the COS. If more than 30% disagreed, the domain was not added into the COS. In the situation where <70% agreed, but less than 30% disagreed, the domain was considered as "provisionally in the COS", pending further discussion and voting. Any dissenting views were discussed with the whole group to allow others to consider and gather wider opinion.

Results

Apart from the decision to conduct two online consensus meetings instead of face-to-face meetings, there were no deviations from the protocol.

Initial literature review identified a list of 11 broad outcome domains (Table 1). Demographics of participants in the e-Delphi consensus process and the virtual consensus meetings are in table 2.

Delphi consensus survey

During round 1 (April 26th 2021 – June 4th 2021), 64 additional items were suggested by participants to include. Of these 46 were not outcomes (treatments n=14, LS causes n=8, disease course n=7, LS clinical follow-up n=4, LS education n=4, LS treatment regimen n=2, other n=7). The 18 suggested outcomes were categorised into 3 overarching domains (adverse events, emotional/psychological impact, treatment acceptability). Therefore, in Round 2 (8th-31st August 2021), participants voted on 14 outcomes. Of these 11 were voted as 'critical' by at least one stakeholder group (table 3) and went through to round 3 for ranking. The three outcome domains removed were impact on important relationships, histological changes and societal/resource use.

Following the ranking round, the top three domains for health care professionals'/researchers' (n=45) were: 1. Symptoms; 2. Control of disease; 3. Development of cancer. The top three domains for patients/patient representatives' (n=77) were: 1. Control of disease; 2. Symptoms; 3. Sexual functioning. Combined ranking results for all stakeholder groups are shown in Figure 1.

Virtual consensus meetings

Meetings held on January 26th and 28th 2022 had 42 participants (21 health professionals, 15 patients/patient representatives, 6 researchers) from 12 different countries. Representation from all stakeholder groups, including minority groups (men and representatives of children), was present. Due to technical difficulties, not all participants voted despite the opportunity to do so during the meeting. A follow-up questionnaire was available for those who couldn't vote in real-time. Overall, each of the outcome domains received votes from at least 90% (38/42) of participants.

Of those who voted, 100% voted 'yes' for the '**symptoms'** domain to be in the COS. Overall, 92% (36/39) voted for '**quality of life – LS specific'** to be in the final COS. '**Control of disease'** and '**clinical (visible) signs'** were close to consensus (65% and 64% voted 'yes', respectively). A further meeting was arranged for further discussion and voting of these latter two domains. The remaining seven outcome domains were not voted into the final COS.

The second set of consensus meetings (May 25th and June 9th 2022) focused on '**control of disease**' and '**clinical (visible) signs**' only. There were 29 participants overall (14 health care professionals, 9 patients/patient representatives, 6 researchers) from 12 countries. Discussion centred around the definition of 'control of disease' and whether it represented a standalone outcome or incorporated repeated measures of other markers of control (e.g., signs, symptoms, quality of life) over time. There was also discussion about 'clinical signs' as being an objective measure as it is measured by the clinician rather than being patient reported.

The domain 'Clinical (visible) signs' was voted to be included in the final COS (28/29, 97% votes), whereas 'control of disease' did not receive sufficient votes to be included in the final COS (5/29, 17% votes).

During the consensus meetings, the 'development of cancer' and 'sexual function' domains were also discussed at length. It is acknowledged that whilst these are significantly important outcomes, they are not relevant to all trials of genital LS in all people. For example, development of cancer is a rare and long-term outcome. To include it as a core outcome, all LS trials would need to continue for sufficient duration to identify cancer development. Sexual function is not relevant to children or adults who are not sexually active and is likely to be captured when measuring quality of life.

Discussion

CORALS followed methodology in line with accepted best practice for COS development and as such, used a robust and accepted process to obtain international consensus.[19] After three rounds of e-Delphi surveys and two online consensus meetings, there was international agreement for three core domains to be included in all future LS clinical trials: Symptoms, Clinical (visible) signs and quality of life – LS specific.

Using bespoke software to manage the e-Delphi consensus process was beneficial in tracking participants and individualising communications to maximise participation. However, as Delphi manager was unable to allow ranking, a separate software was needed for round 3. An attrition of 38% participants was seen between e-Delphi round 1 and round 3. This is higher than experienced in other similar COS projects which report between 9-20% dropout[28-30] but lower than in a recently published COS development project.[31] The cause is likely to be multifactorial but is particularly attributable to workplace and life pressures faced during the COVID 19 pandemic.

Face-to-face consensus meetings, as traditionally used for previously published COSs, were not feasible due to challenges faced during and after the COVID-19 pandemic. Guidance issued through the COMET initiative was consulted to support the smooth running of the meetings and give the greatest chance of success.[32] We found that engagement from international stakeholders across the four virtual meetings was strong and potentially led to better attendance than an in-person event. Earlier meetings reported for other COS groups had fewer participants overall despite the disease areas being more common.[33-36]

Preparing participant resources that were circulated two weeks in advance was beneficial in meeting preparation. Test voting at the beginning of the meetings helped to identify technical issues that some participants were experiencing and most of these could be resolved prior to the real voting. Having a

backup questionnaire to send out immediately to participants who couldn't vote live was also helpful to maximise votes.

There was good geographical representation overall, but participants from the far East and Africa/India were not represented. CORALS must work to engage participants from these locations in future. In the e-Delphi surveys, there was also minimal representation from researchers and none from histopathologists. This led to concern at the consensus meetings that the domain 'histological changes' was voted out too early as a result. However, a greater number of researchers were present at the virtual meetings and this concern was not shared. To agree that histological changes should be a core outcome would mean that ALL clinical trials in LS would need to take serial biopsies, e.g. from the genital site (vulva /penis), as part of their protocol. This is not practical to implement and would likely limit uptake of the COS.

Representation of minority groups (male patients and representatives of children) was relatively low during the e-Delphi surveys. A similar pattern of under-representation has been reported previously and reasons cited are that males are less willing than women to engage with health-related surveys and that LS is less common in children.[17] The numbers of these groups were proportionately higher in the virtual consensus meetings suggesting greater motivation to attend a meeting rather than enter a survey, or that CORALS had succeeded in promoting the initiative more widely.

Challenges to consider moving forward with the next stages of this COS are whether the different groups affected by LS - males, females, and children - can be kept together when identifying core outcome measure instruments. A COS that is applicable to greater numbers of people is likely to generate more powerful evidence longer-term than one that used for groups separately, however, it may not be practicable or possible to agree on instruments that are applicable to all. For example, capturing QoL in different age groups is challenging as instruments designed for adults are not tailored for the needs of children. However, this has been overcome in other COS initiatives as certain QoL tools, such as the dermatology life quality index (DLQI) has versions validated in different age groups.[37]

CORALS has agreed upon a small number of core domains which we hope will encourage researchers to adopt the final set more easily. Some COS groups have a larger number of domains – for example acne[38] (six core domains), capillary malformations[39] (11 core domains), but CORALS is similar to eczema[30] (four core domains). There are similarities in the chosen domains to other initiatives; hidradenitis suppurativa[29], eczema and acne have chosen general clinical signs, whereas vitiligo have specified repigmentation as the important clinical sign to measure. Condition-specific QoL was agreed in HS and eczema. 'Symptoms' were agreed upon for eczema but not for HS nor vitiligo.

The domains 'clinical signs' and 'symptoms' are broad and may possibly need further breaking down. Further discussion on 'QoL-LS specific' is also needed to ascertain whether an overall genital QoL tool is acceptable, as it would potentially have greater use across other genital disease COS in the long-term. Other initiatives, such as the incontinence associated dermatitis group[40], have chosen domains that are specific to the disease state. There is no published guidance on how broad or specific to be.

Although outcome measure instruments for LS are not identified as yet, we recommend that implementation of the core domains should start with immediate effect. Trialists and researchers should include these three domains in their protocols and systematic reviewers should report these domains in their work.

The next steps are to generate international working groups for each of the domains. The groups will identify existing outcome measurement instruments and evaluate the quality of evidence regarding their measurement properties. These will then be discussed at further international consensus meetings to form the final LS COS. CORALS should work to increase global participation, particularly from under-represented geographical regions and minority groups.

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Conflicts of interest: There are no conflicts of interest to declare from any members of the Steering Group

Data availability: Data available on request.

Ethics statement: Not applicable

What's already known about this topic?

- Agreement of outcomes is an international priority area for lichen sclerosus research.
- Core outcome sets reduce research waste by ensuring that outcomes measured in randomised controlled trials (of a specific condition) can be compared and combined in meta-analyses to provide a stronger treatment evidence base.
- There is currently no core outcome set for genital lichen sclerosus trials.

What does this study add?

- CORALS provides international multi-stakeholder consensus on core outcome domains for clinical trials in genital lichen sclerosus.
- The core domains are relevant to all people with genital lichen sclerosus – males, females, adults and children.
- The three internationally agreed core domains are: Clinical (visible) signs, symptoms and quality of life specific to lichen sclerosus.

What are the clinical implications of this work?

- Implementation of the core domains into the protocols of randomised controlled trials and systematic reviews will ensure that outcomes of importance to both patients and health professionals are measured in future lichen sclerosus research.

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Supporting information

Appendix S1:Facilitator pack for CORALS domain meeting

S2: COS-STAR reporting checklist

Figure legends

Figure 1: Electronic Delphi survey round 3- ranking results. Bars demonstrate the ranking for the 11 outcome domains ('y' axis) that met consensus in by at least 1 stakeholder group in the first 2 Electronic Delphi rounds. The answer choice with the largest average ranking ('x' axis, 0=low; 9=high ranking)) represents the most preferred choice.

DOMAIN	EXPLANATION OF DOMAIN
Clinical (visible) signs	Examples include skin colour change, skin texture change, damage to surface of the skin, changes in the anatomy of the genital area
Control of disease	Includes length of time without flares, frequency of flares, progression of the disease
Development of vulval/penile cancer	Development of cancer
Extent of disease	Which parts of the genitals or anus are affected?
Histological changes	Changes seen when skin sample taken and specimen reviewed under the microscope by specialist doctor
Impact on important relationships	For example, relationships with partners, family relationships, interactions with friends, forming new relationships
Quality of life – general health	A more general measure looking at overall quality of life (i.e., someone's overall health and wellbeing both physical and psychological
Quality of life-lichen sclerosus specific	Activities of daily living specific to genital lichen sclerosus
Sexual functioning	Including ability to enjoy closeness/tenderness, sexual desire or sexual interest, arousal during sexual activity or intercourse, ability to have an orgasm, satisfaction with sexual life and sexual relationships, pain/soreness (related to sexual activity), inability to tolerate or enjoy sex play or penetrative sex
Societal/resource use	Costs related to healthcare use and overall cost to society
Symptoms	Examples include itch, burning, irritation, pain/soreness (unrelated to sexual activity), feeling of dryness, fragile skin / splitting of skin (loss of elasticity of skin), bleeding, constipation, difficulty passing urine/pain when passing urine

Table 1: *Long-list of LS outcome domains identified from review of literature (domains are presented in alphabetical order)*

1

Demographic	Delphi Round 1 N (%)	Delphi Round 2 N (%)	Delphi Round 3 N (%)	Consensus meetings 1+2 N (%)	Consensus meetings 3+4 N (%)
Total participants	199	141	123	42	29
Stakeholder group					
Health care professionals	71 (36)	54 (38)	44 (35)	21 (50)	14 (48)
Patients/patient representatives	126 (63)	85 (60)	77 (63)	15 (36)	9 (31)
Researchers	2 (1)	2 (1)	2 (2)	6 (14)	6 (21)
Minority group representation					
Representatives of children	41 (21)			19 (45)	10 (34)
Representatives of male patients	17 (9)			14 (33)	9 (22)
Geographical representation – country where participants came from					
Australia	9				1
Austria	2				
Brazil	2				
Canada	26			4	1
Chile	0			1	
Czech Republic	1				
Denmark	27			2	5
Germany	26			6	2
Finland	1				
France	2			1	1
Israel	3				
Italy	3			4	
Jersey	1				
Lithuania	1			1	1

Luxembourg	1			1	1
Mexico	1				
Netherlands	6			2	1
Northern Ireland	1				
New Zealand	3				1
Portugal	1				
Russia	1				
Scotland	1			1	1
Spain	1				
Switzerland	8				
Taiwan	1				
United Kingdom	35			11	8
USA	35			8	6

Table 2: *Demographics of participants during 3 rounds of e-Delphi surveys and virtual consensus meetings*

Domain	Patients	Health care professionals/ researchers
Quality of life-lichen sclerosus specific	93%	96%
Control of disease	95%	89%
Symptoms	94%	88%
Development of vulval/penile cancer	84%	91%
Sexual functioning	84%	84%
Extent of disease	84%	77%
Emotional impact	86%	73%
Clinical (visible) signs	78%	75%
Quality of life – general health	84%	50%
Negative events of treatment	79%	61%
Treatment acceptability	71%	59%
Impact on important relationships	67%	68%
Histological changes	43%	32%
Societal/resource use	17%	10%

Table 3: *Proportion of voters rating outcomes as 'critical' on 9-point Likert scale after 2 rounds of voting in the e-Delphi surveys. GREEN = domain met consensus across all stakeholder groups as being critical, AMBER = domain met consensus with one stakeholder group as being critical, RED = domain not voted as critical by any stakeholder groups.*

DOMAIN (Total number of voters for that domain)	Yes % (n)	No % (n)	Not sure % (n)	Didn't vote
Symptoms (n=39)	**100** (39)	0	0	3
Quality of life-lichen sclerosus specific (n=39)	**92** (36)	5 (2)	3 (1)	3
Control of disease (n=40)	65 (26)	15 (6)	20 (8)	2
Clinical (visible) signs (n=39)	64 (25)	18 (7)	18 (7)	3
Sexual functioning (n=39)	31 (12)	56 (22)	13 (5)	3
Extent of disease (n=39)	15 (6)	77 (30)	8 (3)	3
Treatment acceptability (n=39)	13 (5)	77 (30)	10 (4)	3
Negative effects of treatment (n=40)	10 (4)	75 (30)	15 (6)	2
Development of vulval/penile cancer (n=39)	8 (3)	74 (29)	18 (7)	3
Emotional impact (n=40)	8 (3)	75 (30)	17 (7)	2
Quality of life – general health (n=38)	5 (2)	95 (36)	0	4

Table 4: *Results of virtual consensus meetings January 2022. Green = consensus met for domain to be in the final core outcome set. Amber = consensus close and for further voting. White = consensus not met.*

DOMAIN (Total number of voters for that domain)	Yes % (n)	No % (n)	Not sure % (n)	Didn't vote
Control of disease (n=29)	17 (5)	45 (13)	38 (11)	0
Clinical (visible) signs (n=29)	97(28)	0 (0)	3 (1)	0

Table 5: *Results of virtual consensus meetings May/June 2022. Green = consensus met. White = consensus not met.*

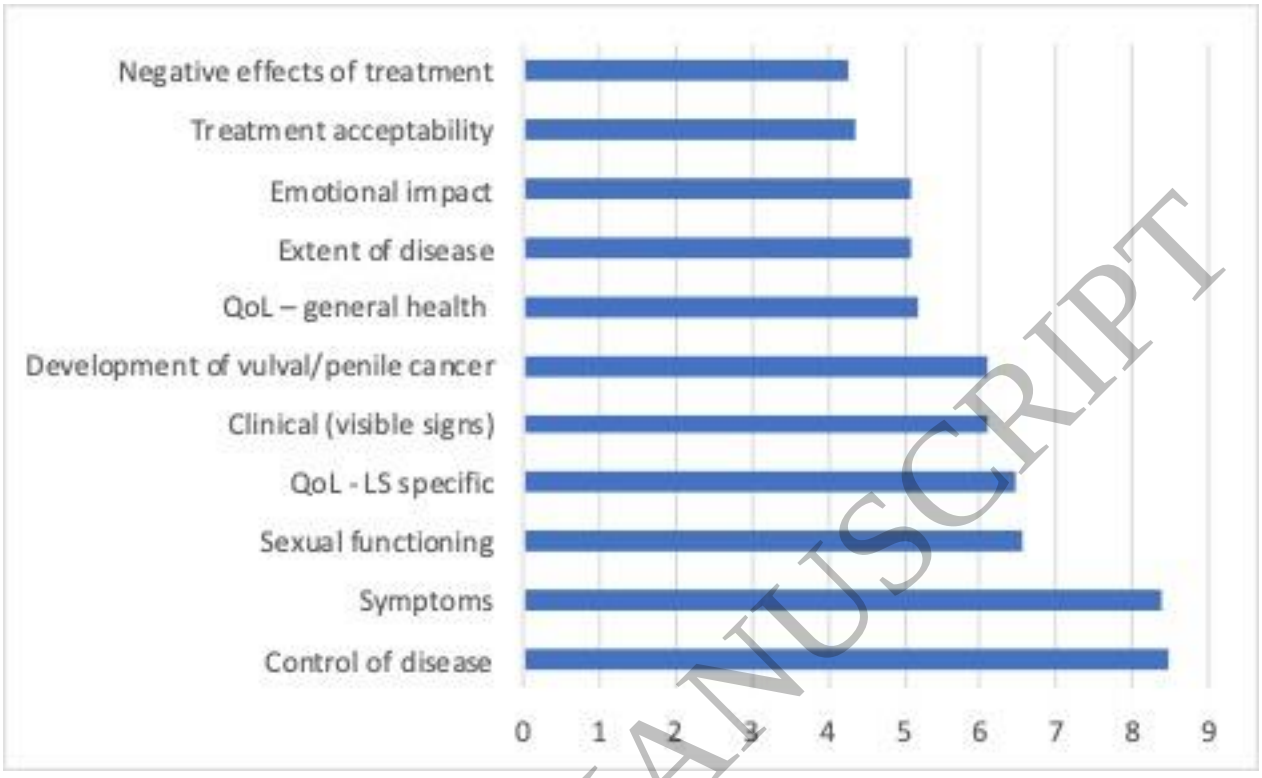

Figure 1
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