Journal Pre-proof

World Workshop on Oral Medicine VIII: Development of a Core Outcome Set for Oral Lichen Planus: A Systematic Review of Outcome Domains

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PII: S2212-4403(23)00070-6
DOI: https://doi.org/10.1016/j.oooo.2023.01.014
Reference: OOOO 5028

To appear in: *Oral Surg Oral Med Oral Pathol Oral Radiol*

Received date: 7 November 2022
Revised date: 20 December 2022
Accepted date: 5 January 2023

Please cite this article as: Rosa María López-Pintor DDS, PhD , Márcio Diniz-Freitas DDS, PhD , Shilpa Shree Kuduva Ramesh BDS, MDS , J Amadeo Valdéz DDS, MAS , HongxiaDan DMD , Caroline Bissonnette DMD, MS , Catherine Hong BDS, MS , Arwa Farag BDS, DMSc , Martin S Greenberg DDS, FDS, RCSEd , Michael T Brennan DDS, MHS , Nancy W Burkhart EdD, MEd, BSDH , Jane F Setterfield BDS, DCH, MD, FRCP , Sook-Bin Woo DMD, MMSc, FDSRCS , Thomas P Sollecito DMD, FDS, RCSEd , Richeal Ni Riordain MBBS, BDS, MA (Higher Ed), PhD, MFD, FFD, FDS Jennifer Taylor BDS, MBChB, MFDSRCS, FDS(OM), PhD , Jairo Robledo-Sierra DDS, MSc, PhD , World Workshop on Oral Medicine VIII: Development of a Core Outcome Set for Oral Lichen Planus: A Systematic Review of Outcome Domains, *Oral Surg Oral Med Oral Pathol Oral Radiol* (2023), doi: https://doi.org/10.1016/j.oooo.2023.01.014

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World Workshop on Oral Medicine VIII: Development of a Core Outcome Set for Oral Lichen Planus: A Systematic Review of Outcome Domains

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ABSTRACT

Objective: There is a lack of consensus regarding clinician- and patient-reported outcomes for oral lichen planus (OLP). The World Workshop on Oral Medicine Outcomes Initiative for the Direction of Research (WONDER Project) aims to develop a core outcome set (COS) for OLP, which would inform the design of clinical trials, and importantly, facilitate meta-analysis, leading to the establishment of more robust evidence for the management of this condition and hence improved patient care.

Study Design: Ovid MEDLINE, Embase, CINAHL, CENTRAL, and Clinicaltrials.gov were searched for interventional studies (randomized controlled trials, controlled clinical trials, and case series including ≥5 participants) on OLP and oral lichenoid reactions published between January 2001 and March 2022 without language restriction. All reported primary and secondary outcomes were extracted.

Results: The searches yielded 9,135 records, and 291 studies were included after applying the inclusion criteria. A total of 422 outcomes were identified. These were then grouped based on semantic similarity condensing the list to 69 outcomes. The most frequently measured outcomes were pain (51.9%), clinical grading of the lesions (29.6%), lesion size/extension/area (27.5%), and adverse events (17.5%).

Conclusion: As a first step in developing a COS for OLP, we summarized the outcomes that have been used in interventional studies over the past two decades, which are numerous and heterogeneous.

KEYWORDS

Core outcome set; oral lichen planus; outcome measures; outcome domains.

INTRODUCTION

Oral lichen planus (OLP) is a common, immune-mediated condition that affects nearly 1% of the global population.[1] Although the exact etiology remains unknown, the development of OLP is hypothesized to be the result of an interplay between the immunologic system, environmental factors, and genetic predispositions.[2] OLP typically presents with bilaterally symmetric white reticular striations involving the oral mucosa. Variable degrees of severity and extent of erythema, erosions, and ulcerations may also be present.[3,4] These features are characterized by pain, burning sensation, and discomfort, which decrease the patient's quality of life.[5] Given the chronic nature of this condition, currently, the primary goal of treatment is to alleviate patient discomfort. In many individuals, achieving long-term complete resolution of symptoms and lesions is not feasible or realistic.

In addition to measuring the impact of therapeutics on symptomatology, interventional studies on OLP have used a wide variety of outcome measures, both clinician and patient-reported, rendering meta-analysis of data across these studies difficult. A recent Cochrane review on interventions for treating OLP highlighted the lack of

standardization in the primary outcome measures evaluated and methods used to measure them.[6] Outcome measures used in trials were traditionally selected by investigators alone. Initiatives such as Outcome Measures in Rheumatology (OMERACT) have served a critical role over the past 20 years in the development of core outcome sets (COS) and the development and validation of clinical and radiographic outcome measures in several rheumatic diseases.[7] A COS is an agreed standardized set of outcomes that should be measured and reported, as a minimum, in all clinical trials of a specific condition.[8] They do not imply that outcomes in a particular study should be restricted to those in the COS. Instead, there is an expectation that the core outcomes will be collected and reported to allow the results of trials and other studies to be compared, contrasted, and combined as appropriate and that researchers will continue to collect and explore other outcomes. Notably, COS must be developed with the input of different stakeholders, including clinicians, researchers, and patients.

Currently, the use of COS in oral mucosal disease research is practically non-existent. The World Workshop on Oral Medicine Outcomes Initiative for the Direction of Research (WONDER Project) was launched in January 2020 aiming to develop COS for different oral conditions such as OLP. The development of a COS for OLP would standardize the results to be reported, reduce investigator bias, and facilitate meta-analysis, leading to the establishment of more robust evidence for the management of OLP and hence improved patient care. Once the need to develop a COS has been established, the first step of the process consists of the identification of outcomes used in previous interventional studies. For this purpose, we conducted a systematic review

to identify all primary and secondary outcomes reported in interventional studies on OLP over the past two decades.

MATERIALS AND METHODS

The protocol was registered in the International Prospective Registry of Systematic Reviews (PROSPERO) (Registration number: CRD42021266357) and the COMET Database (https://www.comet-initiative.org/Studies/Details/1558). This systematic review was conducted following the Core Outcome Measures in Effectiveness Trials (COMET) Handbook[8] and reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA) statement.[9]

Eligibility Criteria

Inclusion criteria

We included all interventional studies (e.g., randomized controlled trials [RCTs], controlled clinical trials [CCTs], and case series including five or more participants) published in any language between January 1st, 2001, and March 8th, 2022, investigating any active treatment (preventive, palliative, or curative, either pharmacological or non-pharmacological) administered topically or systemically in patients with OLP or oral lichenoid reactions (OLRs). The latter group of oral mucosal diseases was included as their associated symptoms, and clinical and histopathological features resemble those of OLP. Only the outcomes related to the oral lesions were extracted for interventional studies of mucocutaneous disease. The patients must have been diagnosed clinically with or without histopathological confirmation. All comparators/controls were included: usual treatment, alternative treatment, placebo, or no treatment to assess the effectiveness of the investigated intervention.

Exclusion criteria

We excluded non-interventional studies and studies involving patients with malignant comorbidity (e.g., graft-versus-host disease and paraneoplastic autoimmune multiorgan syndrome) or histopathologically diagnosed with oral epithelial dysplasia. Also, studies investigating treatments for extraoral involvement only were excluded.

Information sources and search strategy

An exhaustive search was performed by a librarian on July 15th, 2021, and March 8th, 2022, in the following electronic databases: Ovid MEDLINE, Embase, CINAHL, CENTRAL, and Clinicaltrials.gov. The search strategy used on each electronic database is shown in Table 1.

Selection process

The search records were exported into EndNote™ 20. After removing the duplicates, RML-P, SSKR, JAV, HD, CB, CH, RNiR, JT, and JR-S screened full titles and abstracts independently using Microsoft© Excel for Mac to identify the studies that met the inclusion criteria. Then, RML-P, MD-F, SSKR, JAV, HD, and CB independently read the identified studies in full text. Each reference was screened by one investigator. Any disagreements were resolved by discussion with JR-S and JT.

Data collection process and data items

RML-P, MD-F, SSKR, JAV, HD, and CB independently extracted the data from the selected studies using a tool designed in Google Forms (Google LLC) specifically for this purpose (Supplementary file 1). One investigator extracted the following data from

each study: reference number, title, names of the authors, journal, year of publication, country of origin, study design (RCT, CCT, or case series), language, the primary outcome, and the secondary outcome(s). All studies not written in English were translated to extract the study design and the primary and secondary outcomes. Any doubts were resolved with JT and JR-S. Finally, the collected data were exported into Microsoft© Excel for Mac.

Study quality assessment

Since all interventional studies reporting outcome measures were included and the results of these were not considered, the studies were not assessed regarding their risk of bias or graded.

Statistical Analysis

The descriptive analyses (frequency distribution) were performed using IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp, Armonk, NY).

RESULTS

The database searches yielded 9,135 records, of which 3,045 were duplicates (Figure 1). After screening 6,090 references by title and abstract, 5,405 were excluded for not meeting the inclusion criteria. Of the remaining 685 studies, 18 could not be retrieved, and 667 were evaluated in full text. Of these, 374 did not meet the inclusion criteria, and two were duplicated. Therefore, 291 studies were included in this systematic review (Supplementary file 2).

One hundred and two studies (35%) were published between 2001 and 2010, 158 (54.3%) between 2011 and 2020, and 31 (10.7%) between 2021 and March 8th, 2022. The studies were published in 135 different journals in various fields, such as dentistry, maxillofacial surgery, medicine, dermatology, otorhinolaryngology, and laser therapy. Most studies were conducted in Asia (47%), followed by Europe (34.3%), America (11.3%), Africa (6.8%), and Australia (0.6%) (Figure 2). Only two studies had a multicenter approach, of which one was conducted across different continents (Europe and North America). Regarding the study design, 155 (53.3%) were RCTs, 39 (13.4%) CCTs, 90 (30.9%) case series, and 7 (2.4%) were retrospective studies of clinical records. Finally, 270 (92.8%) were published in English, 13 (4.5%) in Mandarin Chinese, 4 (1.4%) in Persian, 2 (0.7%) in Russian, 1 (0.3%) in French, and 1 (0.3%) in German.

After removing the duplicates, 422 outcomes were identified (Supplementary file 3). Three investigators (RML-P, MD-F, JR-S) grouped the synonyms or semantically related outcomes, obtaining a final list of 69 items (Table 2). "Pain" was the most frequent outcome, measured in 51.9% of the studies. Other types of symptoms such as burning sensation (12.4%), discomfort (4.1%), xerostomia (1.4%), itching (1%), taste disorders (1%), pruritus (0.7%), irritation (0.3%), and soreness (0.3%), were also identified. Forty-three studies (14.8%) measured symptoms without specifying the type. Other commonly measured outcomes included "clinical grading of the lesions" (29.6%), "lesion size/extension/area" (27.5%), "adverse events/side effects" (17.5%), "clinical response to treatment" (14.1%), "type of lesion" (13.4%), "recurrence" (11.7%), "disease severity" (10%), and quality of life (8.6%).

Outcomes such as complete blood count, glucose, and coagulation tests were grouped into the "biochemical analyses" category. Outcomes such as bleeding on probing, plaque index, and probing depth were grouped into the "clinical periodontal parameters" category.

DISCUSSION

The development of a COS is a multi-stage process aimed at standardizing the selection, measuring, and reporting of treatment outcomes to facilitate study comparison and data pooling in systematic reviews and meta-analyses, thus leading to more robust evidence-based interventions.[8] The first step in developing a COS involves identifying the outcomes used in previous interventional studies for a specific condition (Figure 3). Then, focus groups of patients with this condition are incorporated to identify other relevant outcomes through synergistic discussions between individuals with different disease experiences.[10] Thereafter, the individual outcomes identified through these two processes are gathered into outcome domains by various working groups. Finally, a consensus is achieved among the stakeholders, i.e., clinicians, researchers, and patients, on the domains to be included in the COS through various voting procedures.[11-13] Thus, as the first step in developing a COS for OLP, this study summarizes the outcomes that have been used in interventional studies for this disease over the past two decades.

Through a comprehensive scientific literature search, we identified 422 unique terms used as treatment outcomes for OLP. This finding highlights the lack of standardized terminology and the wide variety of outcomes used in interventional studies to measure the efficacy of OLP treatments. As many of these outcomes were synonyms or semantically related, we grouped these terms into a condensed list of 69 outcomes,

which was central for constructing the outcome domains in the later stages of the process. As the primary goal of the treatment of OLP is to alleviate symptoms, patient-reported outcomes (PROs) are a critical component of assessing whether clinicians are improving patients' health.[14] In this systematic review, “pain” was the most frequently used outcome, but other PROs, such as “burning sensation”, “discomfort”, “xerostomia”, “itching/pruritus”, “taste disorders”, “irritation”, and “soreness”, were also identified. Altogether, symptoms were used as an outcome in a cumulative of 253 studies.

Clinician-reported outcomes (ClinROs) related to the appearance and severity of the lesions were also frequently used and included “clinical grading of the lesions”, “lesion size/extension/area”, “type of lesion”, “disease severity”, “clinical signs”, “clinical characteristics of the lesions”, “number of erosions”, “number of lesions”, “color”, “erythema size”, and “surface texture”. Altogether, these outcomes were used in a cumulative of 296 studies.

Exacerbations and remissions characterize the clinical course of OLP.[15] Furthermore, the treatment response between patients is highly variable. Therefore, it is essential for a clinical trial to measure the behavior of lesions and symptoms over time. A cumulative of 108 studies used timeline-related outcomes, such as “clinical response to treatment”, "recurrence of lesions/relapse", “resolution of lesions”, "period between the start of treatment and remission", "complete healing time", “stability of the result/effect”, and “lesion-free period”.

In contrast, some PROs and ClinROs were reported in a remarkably low number of studies. For example, adverse events were only measured in a cumulative of 58 studies. Of these, nine reported "clinical diagnosis of candidiasis" and "malignant transformation" as adverse events of topical corticosteroids, although little is known about the role of these medications in the promotion of carcinogenesis. Other outcomes related to the psychosocial impact, such as "quality of life", "oral function", "anxiety and depression", "interference with daily activities", "maximum mouth opening", "breath odor and oral freshness", and "psychological recovery" were used in a cumulative of 46 studies. Also, only one study used the "need for rescue medication" as a secondary outcome.

Interestingly, a cumulative of 59 studies measured crevicular fluid, cytological, salivary, serological, or histopathological biomarkers in patients with OLP before and after treatment. Currently, no biomarker or biochemical analysis has been shown to accurately assess the patient's symptoms, the clinical or histopathological changes of the lesions, or the malignant progression.[16] Furthermore, many of these investigations are invasive and expensive. Therefore, these outcomes are unlikely to be included in the COS.

A recent review of the outcome measures used in RCTs on OLP since 2004 showed diversities in outcome selection, high heterogeneity of outcome measures, low degree of consensus on measurement methods, inadequate reporting of adverse effects, and little focus on oral health-related quality of life.[17] The methodological limitation of many trials is the lack of standardized outcome measures, which has been emphasized since the early 2000s.[18] Our systematic review aimed to collect information on the reported

outcomes and not on the measurement instruments or timing of measurements, as this is a future stage of COS development.[19]

The strength of this systematic review is the comprehensive screening of all interventional studies published on OLP and OLRs in the past 21 years. Firstly, the search was not limited to RCTs but included all other types of interventional studies, such as CCTs and case series (including ≥5 participants), investigating any active treatment administered topically or systemically in patients with OLP and OLRs. Secondly, we included all interventional studies on OLRs, e.g., oral lichenoid contact reactions, oral lichenoid drug reactions, and oral lichenoid lesions of graft-versus-host-disease, because these conditions may occasionally represent a diagnostic challenge for their clinical and histopathologic similarity to OLP. Furthermore, the symptoms associated with OLRs are indistinguishable from those of OLP. Therefore, by increasing the number of studies, we ensured that all potential outcomes were included. Thirdly, the search included all studies involving patients without a histopathologically confirmed diagnosis, not to limit the number of studies. In many trials, the diagnosis of OLP or OLRs was made based on the clinical features of the lesions only. Finally, no language restriction was applied.

The first limitation of this review is related to the year limit applied to the searches. We decided not to include articles published before 2001 because a preliminary PubMed search of RCTs and clinical trials on OLP showed that more than 70% were published after 2001. In addition, due to the large number of studies elicited (9,135), each abstract was screened only by a single investigator, which could have resulted in selection bias.

In summary, this systematic review presents a list of 69 outcomes that have been used in interventional studies over the past two decades and highlights the lack of standardized terminology and the wide variety of outcomes that have been used to measure the efficacy of OLP treatments. These outcomes will be discussed in focus groups of patients with OLP (cross-reference the second paper) and other working groups, including oral medicine experts (clinicians and researchers) at the 2022 American Academy of Oral Medicine (AAOM) Annual Conference (cross-reference the third paper) in Memphis, TN, USA, to achieve a consensus on the domains to be included in the COS for OLP.

STATEMENT OF CLINICAL RELEVANCE

As a first step in developing a core outcome set for oral lichen planus, this systematic review summarizes the outcomes that have been used in interventional studies for this condition over the past two decades.

Disclosures

The authors declare no financial disclosure or conflicts of interest.

SUPPLEMENTARY MATERIALS

Supplementary file 1. Data extraction tool.

Supplementary file 2. Included references sorted by publication date.

Supplementary file 3. Outcomes used in interventional studies on oral lichen planus.

ACKNOWLEDGMENTS

We want to thank Paul Cannon, Librarian in the Faculty of Medicine, Veterinary and Life Sciences at the University of Glasgow, Scotland, for conducting the database

searches, and Anna Yuan, Assistant Professor at Tufts University, USA, for her support in the study selection process.

The World Workshop on Oral Medicine (WWOM) VIII Steering Committee provided the conceptual framework and logistical support to produce the WWOM VIII Conference in May 2022 in Memphis, Tennessee, USA. In addition, the Steering Committee provided scientific and editorial critiques of this manuscript. The Steering Committee is listed below, in alphabetical order: Arwa M. Farag (Saudi Arabia/USA), Timothy A. Hodgson (UK), Catherine Hong (Singapore), Siri Beier Jensen (Denmark), A. Ross Kerr (USA), Giovanni Lodi (Italy), Richeal Ni Riordain (Ireland), Thomas P. Sollecito (USA).

The WWOM VIII Steering Committee gratefully acknowledges the following organizations, companies, and individuals that provided financial support for WWOM VIII: American Academy of Oral Medicine, European Association of Oral Medicine, Church & Dwight Co. Inc., Colgate Palmolive, and patients of Dr. Ross Kerr.

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FIGURE LEGENDS

Figure 1. Flow diagram of the literature search according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA).

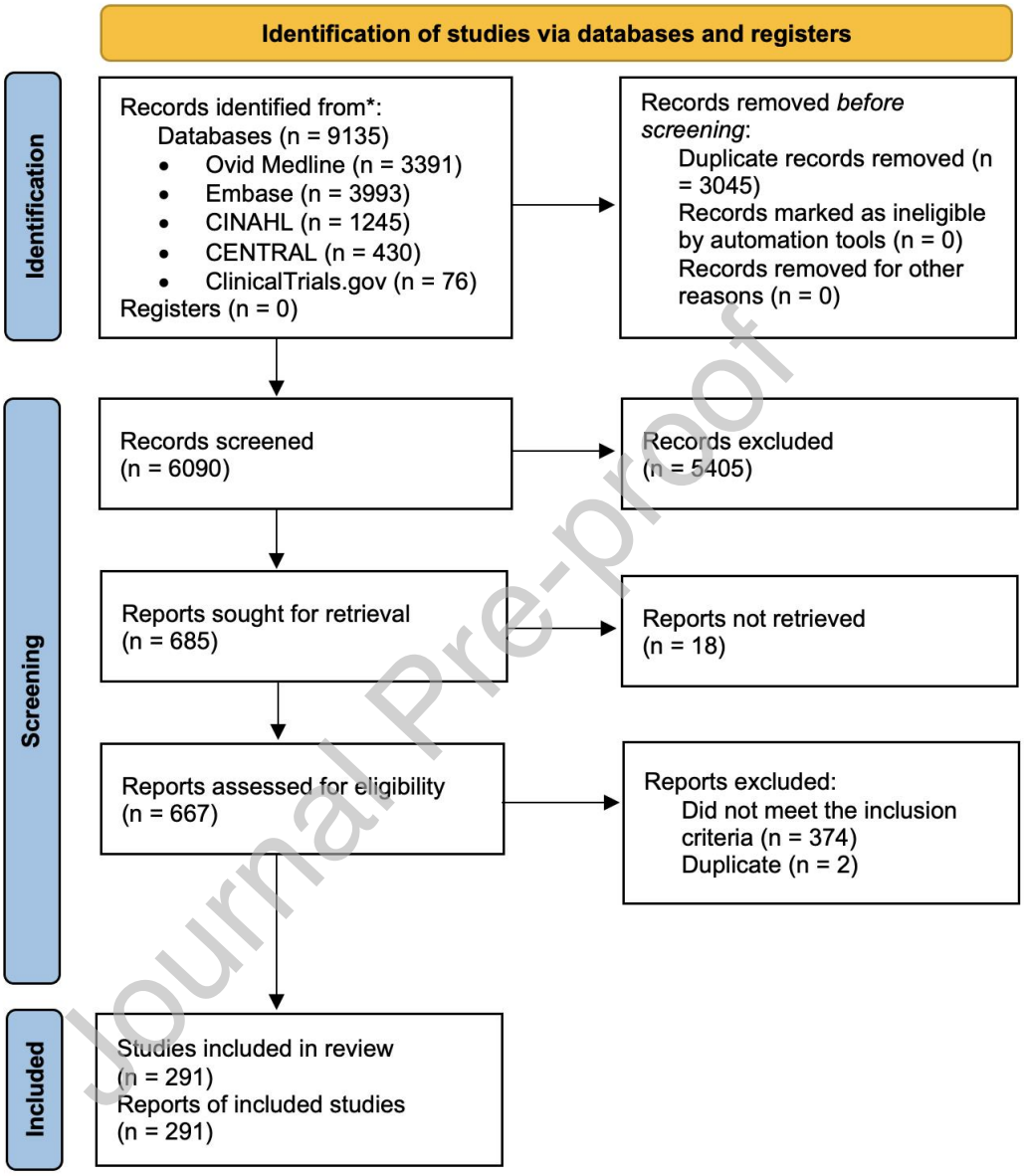

Figure 2. Number of studies included by country and continent.

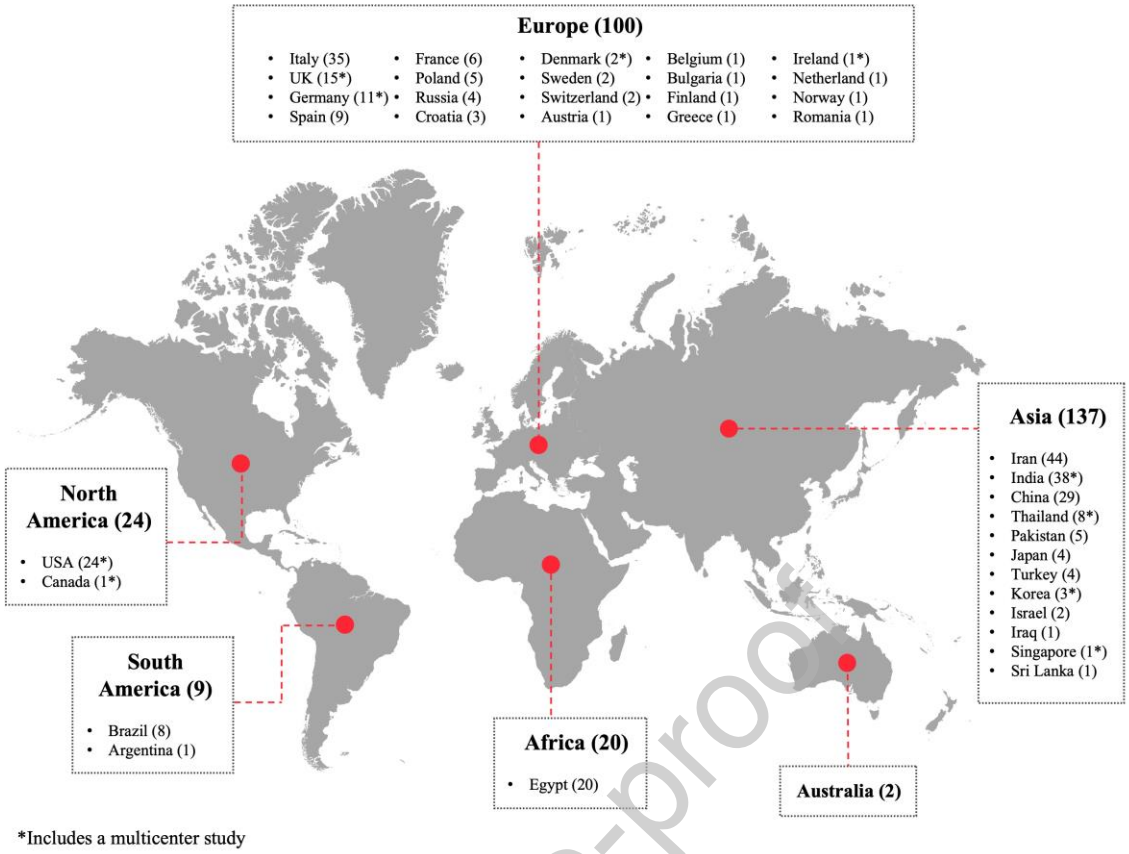

Figure 3. Three-stage approach for developing a core outcome set for oral lichen planus (OLP) (Adapted from Taylor et al., 2017).

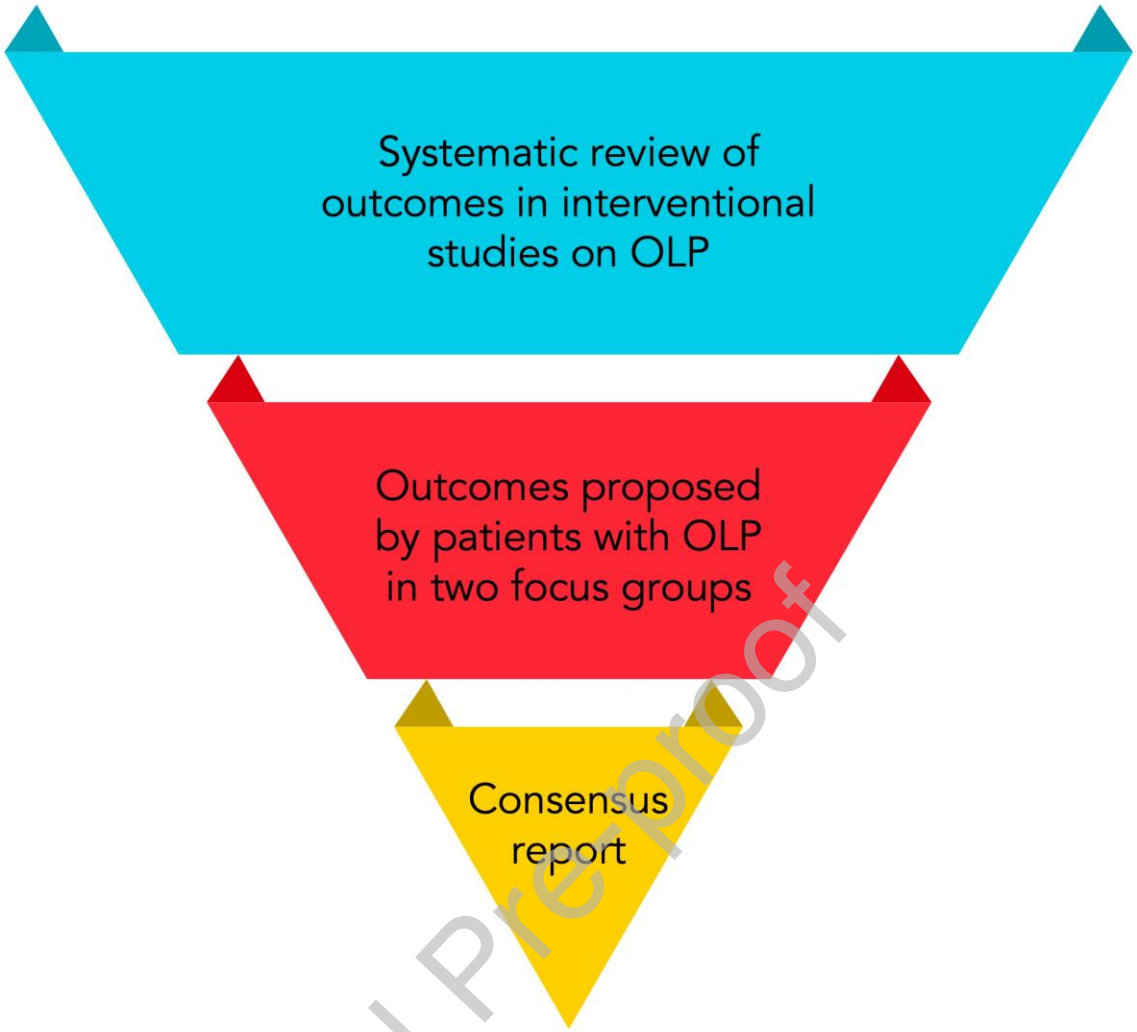

Table 1. Search strategy used on each electronic database

Source	Interface	Search Strategy	Retrieved records
MEDLINE	OvidSP	1 Lichen Planus, Oral/ (2604) 2 ("lichen planus" and (mouth or oral)).tw. (3984) 3 (OLP and (oral or mouth)).tw. (1623) 4 or/1-3 (4476) 5 (lichenoid and reaction* and (oral or mouth)).tw. (360) 6 (OLR and (oral or mouth)).tw. (48) 7 or/5-6 (369) 8 4 or 7 (4624)	3391
EMBASE	OvidSP	1 ("lichen planus" and (mouth or oral)).tw. (5086) 2 (OLP and (oral or mouth)).tw. (1872) 3 or/1-2 (5125) 4 (lichenoid and reaction* and (oral or mouth)).tw. (525) 5 (OLR and (oral or mouth)).tw. (54) 6 or/4-5 (538)	3993

		7 3 or 6 (5419)	
CINAHL	EBSCOhost	S1 (MH "Lichen Planus, Oral") (980) S2 TI ((("lichen planus") and (mouth or oral))) OR AB ((("lichen planus") and (mouth or oral))) (1,051) S3 TI ((OLP and (oral or mouth))) OR AB ((OLP and (oral or mouth)))(497) S4 S1 OR S2 OR S3 (1,283) S5 TI (((lichenoid and reaction*) and (oral or mouth))) OR AB (((lichenoid and reaction*) and (oral or mouth))) (97) S6 TI ((OLR and (oral or mouth))) OR AB ((OLR and (oral or mouth))) (19) S7 S5 OR S6 (100) S8 S4 OR S7 (1,315)	1245
CENTRAL	Cochrane Library/Wiley Interscience	#1 MeSH descriptor: [Lichen Planus, Oral] explode all trees (186) #2 (("lichen planus") and (mouth or oral)):ti,ab (457) #3 (OLP and (oral or mouth)):ti,ab (228) #4 {or #1-#3} (483) #5 ((lichenoid and reaction*) and (oral or mouth)):ti,ab (13) #6 (OLR and (oral or mouth)):ti,ab (3) #7 {or #5-#6} (15)	430
Clinicaltrials.gov	https://clinicaltrials.gov/	Condition or disease: Oral Lichen Planus or Oral Lichenoid Reaction	76

Table 2. Summary of the outcomes used in interventional studies on oral lichen planus

Outcome	**Number of studies**	%
Pain	151	51.9
Clinical grading of the lesions/clinical score/clinical index	86	29.6
Lesion size/extension/area	80	27.5
Adverse events/side effects	51	17.5
Symptoms	43	14.8
Clinical/treatment response	41	14.1
Type of the lesion	39	13.4
Burning	36	12.4
Recurrence of lesions/relapse	34	11.7

Disease severity	29	10.0
Quality of life	25	8.6
Treatment efficacy	24	8.2
Clinical improvement	23	7.9
Serological biomarkers	20	6.9
Clinical signs	18	6.2
Clinical assessment of the disease (e.g., site, severity, activity)	17	5.8
Resolution of lesions	16	5.5
Extension of lesions	15	5.2
Assessment of the clinical presentation of the lesions	14	4.8
Remaining disease	13	4.5
Clinical characteristics of the lesions	12	4.1
Discomfort	12	4.1
Biochemical analyses (e.g., CBC, glucose, fibrinogen, SGOT, SGPT, PT, PTT, TT)	11	3.8
Safety	10	3.4
Clinical evaluation	9	3.1
Number of erosions	9	3.1
Salivary biomarkers	9	3.1
Period between the start of treatment and remission	8	2.7
Histological biomarkers	8	2.7
Periodontal parameters (plaque index, bleeding on probing)	8	2.7
Color	7	2.4
Number of lesions	7	2.4
Oral function	7	2.4
Histopathologic features	7	2.4
Erythema size	6	2.1
Anxiety and depression	6	2.1
Complete healing time	6	2.1
Interference with daily activities	5	1.7
Clinical diagnosis of candidiasis	5	1.7
Xerostomia	4	1.4
Compliance	4	1.4
Treatment satisfaction	4	1.4
Malignant transformation	4	1.4
Resolution of symptoms	4	1.4
Lesion location	3	1.0
Surface texture	3	1.0
Itching	3	1.0
Taste disorders	3	1.0
Tolerance to treatment	3	1.0
Candida carriage	3	1.0
Pruritus	2	0.7
Treatment success	2	0.7

Toxicity	2	0.7
Stability of the result/effect	2	0.7
Cytological biomarkers	2	0.7
Salivary flow rate	2	0.7
Detection of salivary bacteria	2	0.7
Irritation	1	0.3
Soreness	1	0.3
Maximum mouth opening	1	0.3
Breath odor and oral freshness	1	0.3
Psychological recovery	1	0.3
Cost	1	0.3
Cost-effectiveness/benefit	1	0.3
Lesion-free period	1	0.3
Use of rescue medication for pain management	1	0.3
Crevicular fluid biomarkers	1	0.3
Total volume of gingival crevicular fluid	1	0.3
Salivary consistency	1	0.3

CBC, complete blood count; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; PT, prothrombin time; PTT, partial thromboplastin time; TT, thrombin time