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World Workshop on Oral Medicine VIII: Development of a core outcome set for dry mouth: a systematic review of outcome domains for xerostomia

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Objective. The purpose of this study was to identify all outcome domains used in clinical studies of xerostomia, that is, subjective sensation of dry mouth. This study is part of the extended project “World Workshop on Oral Medicine Outcomes Initiative for the Direction of Research” to develop a core outcome set for dry mouth.

Study Design. A systematic review was performed on MEDLINE, EMBASE, CINAHL, and Cochrane Central Register of Controlled Trials databases. All clinical and observational studies that assessed xerostomia in human participants from 2001 to 2021 were included. Information on outcome domains was extracted and mapped to the Core Outcome Measures in Effectiveness Trials taxonomy. Corresponding outcome measures were summarized.

Results. From a total of 34,922 records retrieved, 688 articles involving 122,151 persons with xerostomia were included. There were 16 unique outcome domains and 166 outcome measures extracted. None of these domains or measures were consistently used across all the studies. The severity of xerostomia and physical functioning were the 2 most frequently assessed domains.

Conclusion. There is considerable heterogeneity in outcome domains and measures reported in clinical studies of xerostomia. This highlights the need for harmonization of dry mouth assessment to enhance comparability across studies and facilitate the synthesis of robust evidence for managing patients with xerostomia. (Oral Surg Oral Med Oral Pathol Oral Radiol 2023;135:827–875)

Dry mouth is a common condition that can significantly impair oral health, daily oral functioning, and quality of life (QoL) and increase the economic burden associated with health care services.^{1,2} Previous clinical studies reported that the proportion of individuals with dry mouth in the population ranged from 5.5% to 46%.³ As the population ages, the prevalence of dry mouth is likely to increase, yet the condition appears to remain under-recognized and undertreated.^{1,4}

Dry mouth is usually referred to as xerostomia, salivary gland hypofunction, or hyposalivation. These terms are used interchangeably by clinicians, researchers, and

patients, although they convey a different meaning. Xerostomia is a self-reported subjective feeling of oral dryness. Salivary gland hypofunction is objectively

Statement of Clinical Relevance

There is high variability in outcome domains and measures used in the assessment of xerostomia, highlighting the need to develop a core outcome set to harmonize evidence better to inform clinical decision-making for dry mouth management.

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measured low saliva secretion, below normal secretion. In contrast, hyposalivation is a diagnosis when saliva secretion becomes pathologically low (i.e., low unstimulated whole saliva flow rate of ≤ 0.1 mL/min and/or a stimulated whole saliva flow rate of ≤ 0.5 to 0.7 mL/min).⁵ The exact nature of the relationship between xerostomia and salivary gland hypofunction has been shown to be inconsistent, and people complaining of xerostomia frequently do not show objective signs of salivary gland hypofunction, suggesting their symptoms may be secondary to change in the saliva composition.^{6,7} Similarly, patients with salivary gland hypofunction might not report xerostomia, as a previous report found that salivary gland hypofunction and xerostomia coincided in only one-sixth of those with either condition.⁸

Dry mouth has several causes that often overlap or interact. It can be primarily induced by several classes of medications (e.g., antidepressants, antipsychotics, bronchodilators, decongestants, benzodiazepines, and antihistamines, among many others), which are by far the most common contributing factors for chronic dry mouth.⁹ Independent of the class of medication being taken, polypharmacy on its own (which is very common in elderly patients) also increases the likelihood of developing dry mouth.¹⁰ Dry mouth often occurs after radiation therapy to the head and neck. Other conditions such as Sjögren's syndrome (also known as Sjögren's disease), diabetes mellitus, eating disorders, dehydration, mental illnesses, and normal aging can also cause a dry mouth.^{11,12}

Treatment options for dry mouth should be based on each affected individual's underlying condition or causative factors. Different therapeutic strategies for dry mouth can be broadly categorized into 3 domains: palliation, stimulation, and regeneration. Palliative treatment includes water and a myriad of salivary substitutes, such as oral lubricating gel, mouthwashes, and artificial saliva.¹³ Various local and systemic strategies have been used to stimulate salivary secretion, including topical salivary stimulants,¹⁴ pilocarpine,¹⁵ cevimeline,¹⁶ acupuncture,¹⁷ and electrostimulation.¹⁸ More recently, promising treatment strategies have been introduced for dry mouth in certain conditions that aim to regenerate and recover salivary gland function, including gene therapy,¹⁹ stem cell replacement therapy,²⁰ B-cell depletion,²¹ and inhibition of co-stimulation of T cells.²² Although multiple studies have evaluated these interventions, comparing their findings and drawing conclusions is difficult because of the lack of definition in the treatment outcomes and outcome measures. It is necessary to determine the minimal set of outcomes to evaluate the effectiveness of the different interventions to draw future conclusions about which treatment(s) are most effective for this condition.

A core outcome set (COS) is defined as an agreed minimum of outcome domains to be measured and reported in all trials of a particular treatment or condition.²³ There are 3 fundamental steps in developing a COS: identifying existing knowledge, patient involvement, and the consensus process.²⁴ To date, no COS has been developed for evaluating interventions in clinical trials on dry mouth. This study is part of the extended project "World Workshop on Oral Medicine Outcomes Initiative for the Direction of Research" to develop a COS for clinical trials assessing the effectiveness of interventions for dry mouth. Each step of the COS development from the "World Workshop on Oral Medicine Outcomes Initiative for the Direction of Research" project will be subsequently reported. For the first step, as dry mouth has both subjective (xerostomia) and objective (hyposalivation) components, for which many outcome domains and measures exist, we decided to perform 2 independent systematic reviews to facilitate the identification and analysis of the existing knowledge. Accordingly, this study aimed to identify and describe all the outcome domains measured in studies assessing xerostomia, that is, the subjective complaints of dry mouth.

METHODS AND MATERIALS

Registration and protocol

This systematic review was conducted according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (2020 statement).²⁵ The protocol was peer-reviewed and registered at The International Prospective Register of Systematic Reviews under number register: CRD42021279791 (available at https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021279791).

Inclusion and exclusion criteria

We defined the inclusion criteria for the literature search and questions using the population, intervention, control, outcome, and study design (PICOS): P, humans with a dry mouth; I, any active preventive, palliative, or curative pharmacologic or nonpharmacologic treatment/intervention for dry mouth administered topically or systemically; C, no restrictions to the comparison; O, all dry mouth-related outcomes (objectively and subjectively measured); S, clinical trials (randomized and nonrandomized) and observational studies (descriptive, cross-sectional, cohort, case-control).

All clinical and observational studies published in the literature investigating the management of dry mouth in humans were included. The present systematic review included studies that clearly reported at least 1 xerostomia or xerostomia-related outcome and/or outcome measure in the methods section. There was

no limitation on the nature of samples (e.g., convenience samples, population-based samples), type of interventions (e.g., pharmacologic, surgical, lifestyle modifications, psychosocial), or the aspects explored (patient-reported, clinician-reported). Secondary analysis studies or studies that used the same population as the initial population were included; however, duplicate outcomes were described only once.

Excluded from the study were conference abstracts, proceedings, commentaries, editorials, protocols, case reports, case series with <10 participants, animal or laboratory studies, and non-English language records. We also excluded studies where full text was not available.

Information sources and search strategy

The search strategy was developed in collaboration with an experienced bioinformatics specialist (S. vdW.) according to the syntax rules of each database. On September 15, 2021, a systematic search of the scientific literature was performed for articles published from January 2000 through September 2021 in the following bibliographic databases: MEDLINE (PubMed), EMBASE (Ovid), CINAHL (EBSCO), and Cochrane Central Register of Controlled Trials (CENTRAL). The reproducible search strategies for all databases are available in [Supplementary Table S1](#).

Selection process

Following the literature search, records from each database were exported into EndNote reference manager software (EndNote X7; Thomson Reuters, Philadelphia, PA, USA), and the duplicate articles were removed. Reviewer calibration was performed in 2 sessions on articles not included in this study before the initiation of the screening process. Cohen's κ was 0.7, with a percentage of agreement of 85 between the various observers. In the first phase, the study group (A.V., K.D., R.N.R., V.S., A.R.S.S., M.K.S., P.W., M.L.S., and S.N.) screened the titles and abstract for relevance independently. In the second phase, 5 reviewers (A.R.S.S., M.K.S., P.W., M.L.S., and S.N.) performed full-text reviews for the retained articles. Reasons for exclusion were not recorded for all because of the high number of studies ($n = 2700$). Any disagreement at both levels was resolved following a discussion with the section heads (A.V. and K.D.). Searches were re-run before the final analysis, and any additional studies identified were retrieved for assessment.

Data items and collection process

Reviewers (A.R.S.S. and M.K.S.) and assistant reviewers (P.W., S.N., and M.L.S.) extracted the following data: author; year of publication; country; type of study; the number of participants with a dry mouth;

mean, median, SD, and/or age range; percentage of female persons with a dry mouth; disease associated with a dry mouth; subjective (xerostomia) or objective (salivary gland hypofunction) outcome recorded; and level of outcome measurement (dichotomous, categorical, numerical/continuous, or unclear). All data were extracted and described in a spreadsheet (Office Excel 2016; Microsoft Corp., Redmond, WA, USA).

Effect measures

Primary xerostomia-related outcome domains were summarized using all the assessment methods applied across included studies. We also summarized the variability in the utilization of all subjective outcome measurements.

Synthesis methods

A qualitative analysis (not a quantitative synthesis) was considered because several different study designs were included, leading to potential heterogeneities across treatment interventions and outcomes reported in the xerostomia field. The findings of this review were presented in a table format along with a narrative summary of the outcome domains and respective measures.

RESULTS

Study selection

The systematic search initially retrieved 34,922 records. After removing duplicates and screening titles and abstracts, 2,700 potentially relevant articles were identified for full-text eligibility screening. At the end of the screening process, 688 studies were included for xerostomia outcome domain extraction. [Figure 1](#) visualizes the study selection process based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis flowchart.

Characteristics of the included studies

The study characteristics are outlined in [Table I](#). Nearly 3 times more studies were published from year 2011 onward than those between 2001 and 2010. The studies included 122,151 persons with xerostomia, with a large variation in sample size across studies (10 to 64,947 persons). The median age of study participants ranged from 33 to 69 years. There was heterogeneity in sex distribution among the included studies, with the proportion of female persons in mixed-sex studies ranging from 8% to 97%. Thirty and 7 xerostomia studies exclusively enrolled female and male persons, respectively.

More than one-third of the studies originated from Europe (259/688; 37.6%), followed by Asia (218/688; 31.7%) and North America (131/688; 19.0%). Most included studies were cohort studies, followed by

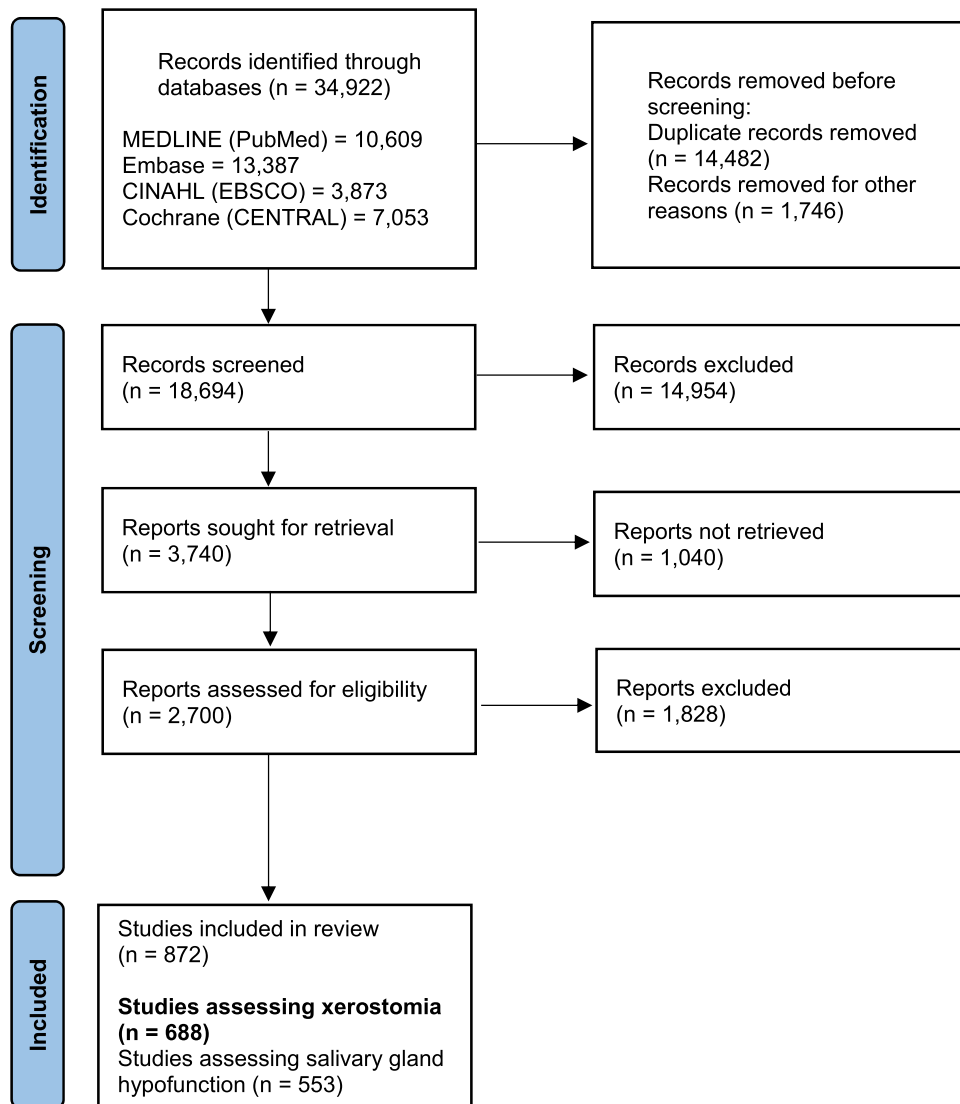


Fig. 1. Systematic review Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram for literature search on outcome domains related to dry mouth.

cross-sectional studies and randomized controlled trials. As for studied conditions related to xerostomia, most studies evaluated radiotherapy-induced xerostomia (RIX; 35.5%) and Sjögren’s syndrome (14.2%). Of the included studies, 380 assessed xerostomia and salivary gland hypofunction outcomes, whereas the remaining studies reported xerostomia outcomes alone (Table I).

Outcome domains assessing xerostomia

In total, there were 166 individual outcome measures, which were reviewed and categorized into 16 unique outcome domains mapped according to the Core Outcome Measures in Effectiveness Trials (COMET) taxonomy²⁶ (outlined in Table II).

The severity of xerostomia was the most frequently applied xerostomia outcome domain, measured in

more than two-thirds (482/688, 70.1%) of the included studies, followed by physical functioning (260/688, 37.8%) and the presence of xerostomia (163/688, 23.7%). The number of studies assessing different outcome domains of xerostomia is depicted in Figure 2.

The following section outlines the details of each outcome domain and respective outcome measures based on the core area and modes of administration of the outcome measures.

Xerostomia core area (COMET core area 8—gastrointestinal outcomes). The present review extracted 7 distinct outcome domains measuring different aspects of xerostomia, which include presence, severity, effect, frequency, duration, fluctuation, and location of xerostomia. The lists of patient-reported outcome measures and investigator-graded outcome

Table I. Characteristics of the included studies

Study characteristics	No. (%)
Year published	
2001-2005	68 (9.9)
2006-2010	104 (15.1)
2011-2015	233 (33.9)
2016-2020	236 (34.3)
2021	47 (6.8)
2001-2010	172 (25.0)
2011-2020	469 (68.1)
2021	47 (6.8)
Origin of the article	
Africa	2 (0.3)
Asia	218 (31.7)
Europe	259 (37.6)
Multiple	17 (2.5)
North America	131 (19.0)
Oceania	17 (2.5)
South America	44 (6.4)
Types of studies	
Case-control studies	48 (7.0)
Case series	10 (1.4)
Cohort	258 (37.5)
Cross-sectional	160 (23.3)
Mixed-method	1 (0.1)
Qualitative	4 (0.6)
Quasi-experimental	3 (0.4)
Randomized controlled trials	146 (21.2)
Other types of clinical trials	50 (7.3)
Nonrandomized	2 (0.3)
Noncontrolled comparative	14 (2)
Crossover	22 (3.2)
Single-arm	12 (1.7)
Validation	8 (1.2)
Conditions associated with dry mouth	
Older age	45 (6.5)
Polypharmacy	26 (3.8)
Radiation to the head and neck	244 (35.5)
Sjögren's disease	98 (14.2)
Other conditions	127 (18.5)
Several disease groups	76 (11.0)
Unknown etiology of dry mouth	72 (10.5)
What is the article assessing	
Xerostomia and salivary gland hypofunction	380 (55.2)
Xerostomia only	308 (44.8)

measures assessing each specific outcome domain in this core area are present in [Tables III](#) and [IV](#), respectively.

PRESENCE OF XEROSTOMIA. The presence of xerostomia is typically measured using single questions with binary responses (yes or no) by patients ([Table III](#)). Of 118 studies assessing the presence of xerostomia, 46 (39.0%) did not clearly describe how the outcome was measured in the method sections. For studies on Sjögren's syndrome, the standard question "Have you had a daily feeling of dry mouth for more than 3 months?" was used in 40 studies for assessing the presence of subjective oral dryness based on the 2002

Table II. Unique outcome domains assessing xerostomia mapped to the Core Outcome Measures in Effectiveness Trials taxonomy

<i>Physiologic/clinical core area, 8: Gastrointestinal outcomes (xerostomia core area)</i>
1. Xerostomia (presence/unspecified)
2. Severity of xerostomia
3. Affect of xerostomia
4. Frequency of xerostomia
5. Duration of xerostomia
6. Fluctuation of xerostomia
7. Location of xerostomia
<i>Life impact core area, 25: Physical functioning</i>
8. Physical functioning
<i>Life impact core area, 26: Social functioning</i>
9. Social functioning
<i>Life impact core area, 28: Emotional functioning/well-being</i>
10. Psychological functioning
<i>Life impact core area, 30: Global QoL</i>
11. Impact on oral health
12. Xerostomia-specific QoL
13. Oral health-related QoL
14. General health-related QoL
<i>Life impact core area, 32: Delivery of care</i>
15. Patient satisfaction
<i>Resource use core area, 34: Economic</i>
16. Economic

QoL, quality of life.

American-European Consensus Group classification criteria for Sjögren's syndrome²⁷ and the 2016 American College of Rheumatology/European League Against Rheumatism (Classification Criteria for primary Sjögren's syndrome.²⁸ The most commonly used single question to assess the presence of xerostomia in the non-Sjögren's syndrome literature was "Does your mouth usually feel dry?" (11 studies). The wordings of other single questions are inconsistent across the literature, particularly with variation in the use of xerostomia symptom descriptors (oral dryness sensation, little amount of saliva) and their duration (2 weeks, 3 months, and 6 months).

SEVERITY OF XEROSTOMIA. The severity domain encompasses the degree of subjective *patient-reported* symptoms related to xerostomia ([Table III](#); 362 studies), including the sensation of oral dryness or discomfort and *investigator-graded* severity of dry mouth ([Table IV](#); 120 studies), which incorporates the assessment of both subjective symptoms and objective clinical signs and assessment of dry mouth.

Patient-reported severity of xerostomia was rated using various response options, ranging from categorical verbal and numerical rating scales (NRS) to visual analog scales (VAS). The 100-mm VAS-xerostomia was the most predominantly adopted scale for measuring the severity of xerostomia, dominating in more

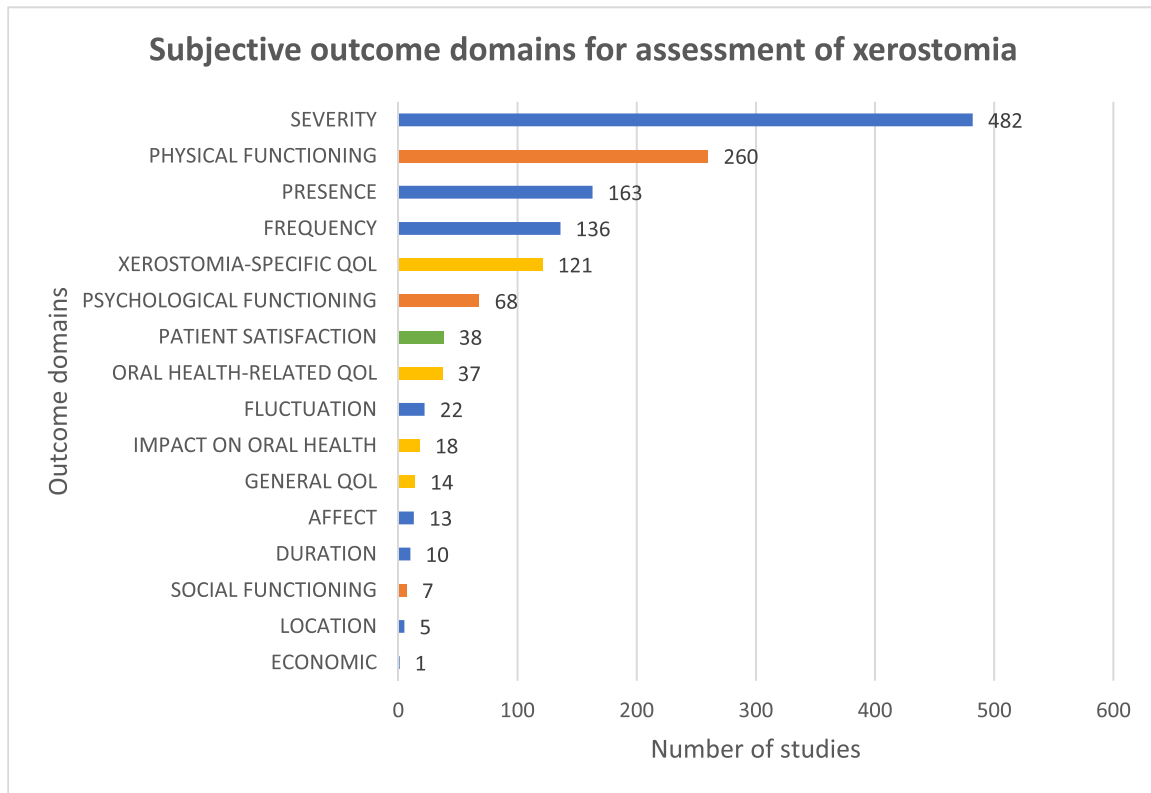


Fig. 2. Number of studies assessing different outcome domains of xerostomia. QoL, quality of life.

than one-quarter (94/362; 26%) of the studies reporting patient-rated severity of xerostomia. In Sjögren’s syndrome studies, the 0 to 10 dryness domain of the European Alliance of Associations for Rheumatology Sjogren’s Syndrome Patient Reported Index²⁹ was used in 33 studies. The 11-point (0 to 10) NRS-xerostomia was applied in 18 studies. As for the categorical verbal rating scale, there was variation in the response categories, with 3 or 4 response categories being the most commonly adopted measurement options (each used in 6 studies; usually with no/mild/moderate/severe word choices).

There are several established investigator-graded criteria for assessing both xerostomia and hyposalivation, as listed in Table IV. The Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) radiation morbidity scoring scheme for salivary gland toxicity was most frequently applied for assessing acute and RIX and used in 71 studies (8 acute radiation morbidity; 41 late radiation morbidity; 22 both acute and late). Aside from the RTOG/EORTC, the Common Terminology Criteria for Adverse Events radiation morbidity grading scale (41 studies) and the Late Effects in Normal Tissue-Subjective, Objective, Management and Analytical systems (6 studies) were also commonly used in

studies assessing the severity of xerostomia as a side effect of radiotherapy (Table III).

AFFECT OF XEROSTOMIA. Although the severity of xerostomia reflects the sensory component of the symptoms, the affect of xerostomia concerns immediate affective responses related to xerostomia. In other words, how unpleasant or disturbing xerostomia feels in affected individuals. This domain was less frequently explored in the literature than other xerostomia domains. The main instrument capturing the affect of xerostomia was the 1-item Bother Index.³⁰ The 1-item Bother Index assesses “how much of your dry mouth problem is bothering you?” on an 11-point (0 to 10) scale and has been applied in 3 studies. Other outcome measures of the affect of xerostomia were assessed with various ad hoc questionnaires across the studies (Table III).

FREQUENCY OF XEROSTOMIA. The frequency of xerostomia is typically evaluated by a well-established standard question, “How often does your mouth feel dry?” with the response options of never, occasionally, frequently, and always. This question was used in 20 studies in this review (Table III). This standard question has been used to assess the frequency of xerostomia and, after dichotomizing, to determine xerostomia prevalence,

Table III. Patient-reported unidimensional outcome measurements related to xerostomia core area

<i>Outcome domains</i>	<i>Outcome measures</i>	<i>Level of measurement/ response options</i>	<i>No. of studies</i>	<i>Reference</i>
Presence of xerostomia	Single question	Dichotomous		
	Are you normally aware of your dry mouth?	Yes/no	1	51
	Does your mouth (usually) feel dry?		11	52-62
	Does the amount of saliva in your mouth seem to be too little?		1	63
	Do you feel dryness of the mouth?		1	64
	Do you feel that your mouth is dry frequently?		1	65
	Do you often have dry mouth?		1	66
	Do you think you have a dry mouth?		1	67
	During the last 2 wk, have you at any time felt your mouth to be dry?		1	68
	During the last 2 wk, have you had a dry mouth?		1	69
	Have you had a dry mouth sensation every day for the last 3 mo?		1	70
	Have you had a dry mouth sensation every day for the last 6 mo?		2	71,72
	Have you had a persistent dry mouth for more than 3 mo?		1	73
	Have you ever been diagnosed by a dentist or doctor with dry mouth?		1	67
	Have you had a daily feeling of dry mouth for more than 3 mo?		40	74-113
	Have you suffered from a persistent dry mouth for the previous 3 mo?		1	114
	Has your mouth been abnormally dry, even if you have been drinking enough water?		1	115
	Is your mouth dry?		1	116
	Unspecified/ad hoc question	Yes/no		
	Presence of dry mouth complaint (ad hoc)		46	117-162
Do you think you have healthy saliva flow?	Categorical			
Does the amount of saliva in your mouth seem to be too little, too much, or you don't notice it?	Yes/no/don't know	1	67	
How would you describe the amount of saliva in your mouth?	Too little/too much/you don't notice it	1	163	
Patient's classification of one's own oral status	Few/normal/much	2	71,164	
	Moist (normal)/dry/do not notice	1	165	

(continued on next page)

Table III. Continued

<i>Outcome domains</i>	<i>Outcome measures</i>	<i>Level of measurement/ response options</i>	<i>No. of studies</i>	<i>Reference</i>
Severity of xerostomia		Categorical		
	Single question			
	Do you feel that you have enough saliva in your mouth?	No/mild/moderate/severe	1	166
	Does your saliva often feel thick?	No/mild/moderate/severe	1	166
	Have you had a dry mouth? Item from EORTC QLQ-H&N43	Not at all/a little/quite a bit/ very much	1	167
	Unspecified/ad hoc question			
	Level of discomfort from xerostomia	Extremely uncomfortable/ moderately uncomfortable/ little/no discomfort	1	115
	Severity of dry mouth (ad hoc)	Mild/moderate/severe	3	166,168,169
		None/mild/severe	1	170
		Never dry/moderate/severe	1	171
		None/a bit/quite a bit/a lot	1	172
		Not dry/somewhat dry/very dry	1	173
		1-5 (mild to severe xerosto- mia)	1	174
		0-4 (none/absent to severe)	2	175,176
		0-4 (absent/slight/moderate/ rather severe/ Maximum discomfort)	1	177
		0-3 (no feeling/slight/moder- ate/severe)	1	178
		<i>Numerical/continuous</i>		
	Validated/established scale			
	The Dry Mouth Inventory	Strongly disagree/disagree/ disagree a little/ Agree a little/agree/ strongly agree	1	179
	1. No moisture in the mouth			
	2. Lips sticking to roof of mouth			
	3. Tongue sticking to roof of mouth			
	4. Throat dry			
	How severe has your dryness been during the last 2 wk?	0-10	33	42,98,160,180-209
	The EULAR Sjogren's Syndrome Patient Reported Index			
	Your having a dry mouth at its worst	0-10	7	209-215
	The MD Anderson Symptom Inventory-Head and Neck Module			
	NRS for xerostomia	0-10	18	89,122,149,216-230
	VAS for xerostomia	0-100 mm/ 0-10 cm	94	18,19,42,62,190,196,199,201,206, 231-314

(continued on next page)

Table III. Continued

<i>Outcome domains</i>	<i>Outcome measures</i>	<i>Level of measurement/ response options</i>	<i>No. of studies</i>	<i>Reference</i>
	Semiquantal scale for xerostomia	0-6	1	315
	11-point colorimetric scale for xerostomia	0-10	1	316
	VAS for burning sensation	0-100 mm	4	235,242,272,276
	VAS for oral discomfort from dry mouth	0-100 mm	7	18,281,283,289,317-319
	11-point colorimetric scale for oral discomfort	0-10	1	316
	Severity of dry mouth	Unclear By interview	1	43
Affect of xerostomia		Categorical		
	Single question Do you have problems with dryness of the mouth?	No feeling/slight feeling/ severe feeling/ Troublesome feeling of dry mouth	1	320
	Validated/established scale Face scale on the feeling of oral dryness	7 drawings from smiley face (no feeling) to tearful face (severe feeling) Numerical/continuous	1	321
	Single question Bother 1 index On the scale of 0-10, how much of your dry mouth problem bothering you?	0-10	3	322-324
	Validated/established scale Unspecified/ad hoc question Effect of xerostomia	Unknown By interview	1	325
Frequency of xerostomia		Categorical		
	Single question Does your mouth feel dry? How often does your mouth feel dry?	No/occasionally/continuously Never/occasionally/fre- quently/always	1 20	326 1,18,31,171,281,302,314,327-340
	Unspecified/ad hoc question Daily frequency of oral dryness	Never/hardly ever/occasion- ally/fairly often/very often	1	177
	Pattern of xerostomia	Every day/intermittent/con- tinuous/once	1	169
	Frequency of xerostomia	Unknown By interview	2	174,341

(continued on next page)

Table III. Continued

<i>Outcome domains</i>	<i>Outcome measures</i>	<i>Level of measurement/ response options</i>	<i>No. of studies</i>	<i>Reference</i>
Duration of xerostomia		Categorical		
	Single question Since when have you experienced dryness in the mouth?	Recently/several months/several years/ ≥10 y	1	171
	Unspecified/ad hoc question Duration of xerostomia	Unknown By interview	3	97,123,174
Fluctuation of xerostomia		Dichotomous Yes/no		
	Unspecified/ad hoc question Comparison of dry mouth symptoms during the day and night		1	235
	Presence of dry mouth in the daytime		1	235
	Presence of dry mouth when eating		4	243,342-344
	Presence of dry mouth when waking		1	345
	Presence of nocturnal xerostomia: any symptoms of oral dryness during night-time and/or frequent waking up feeling thirst		2	235,346
		Categorical		
	Single question Do you have a dry mouth at night?	1-5 (no complaint to always present)	1	347
	Do you have a dry mouth during the day?	1-5 (no complaint to always present)	1	347
	Does your mouth usually feel dry at night?	Yes often/yes sometimes/no seldom/no never	3	4,348,349
	Does your mouth usually feel dry in the daytime?	Yes often/yes sometimes/no seldom/no never	3	4,348,349
	Unspecified/ad hoc question Presence of dry mouth during the day/nighttime xerostomia	Never/occasionally/quite often/always	1	350
		0-3 (no to severe oral dryness)	1	346
	Presence of dry mouth on waking up	Never/occasionally/quite often/always	1	350
		Numerical/continuous		
	Single question How comfortable does your mouth feel in the following situations: at night before bed, during the night, on waking	0-10 (no discomfort to extreme discomfort)	1	351

EORTC QLQ, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; *EULAR*, European Alliance of Associations for Rheumatology; *NRS*, numerical rating scale; *VAS*, visual analog scale.

Table IV. Investigator-graded outcome measurements related to xerostomia core area

<i>Outcome domains</i>	<i>Outcome measures</i>	<i>Level of measurement/response options</i>	<i>No. of studies</i>	<i>Reference</i>
Severity of dry mouth		Categorical		
	Single question			
	Validated/established criteria			
	The Common Terminology Criteria for Adverse Events radiation morbidity grading scale for dry mouth/salivary gland (xerostomia)	Grade 1 (mild)—symptomatic (dry or thick saliva) without significant dietary alteration Grade 2 (moderate)—moderate symptoms; oral intake alteration (e.g., copious water, other lubricants, a diet limited to purees and/or soft moist foods) Grade 3 (severe) —symptoms leading to inability to adequately aliment orally; intravenous fluids, tube feedings, or parenteral nutrition indicated	41	352-392
	The Late Effects in Normal Tissue-Subjective, Objective, Management, and Analytical systems for grading of dry mouth	1. Normal moisture 2. Scant saliva 3. Absence of moisture; sticky, viscous saliva 4. Absence of moisture; coated mucosa	6	379,380,382,387,388,393
	The Observer-Rated Xerostomia Scale	0-3 (no complaints or normal to severe discomfort or worse findings)	1	394
	Dryness of the oral mucosa			
	Redness of the oral mucosa			
	Oral ulcer			
	Coating of the tongue surface			
	Smoothing of the tongue surface			
	Wrinkles and creases on the tongue surface			
	Cracks on the tongue surface			
	Redness of the oral mucosa			
	Dryness of the mucosa of the oropharynx			
	The Oral Assessment Guide	Oral dryness 1-3 (normal to severe oral dryness)	1	342
	Oral dryness (lips, tongue, mucous membrane) Saliva	Saliva 1-3 (watery/thick or ropy/absent)		
	The Oral Assessment Protocol	Oral mucous membrane (pink and moist with firm gums/reddened or edema or radiation plaque/ulceration or bleeding)	1	395
	Oral mucous membrane			
	Comfort	Comfort (comfortable/discomfort/pain)		
	Lips/corners of mouth	Lips/corners of mouth (smooth, pink, moist/dry or cracked/ulcerated or bleeding/herpes simplex)		
	Tongue			
	Saliva/dry mouth			
	Swallow/chewing			

(continued on next page)

Table IV. Continued

<i>Outcome domains</i>	<i>Outcome measures</i>	<i>Level of measurement/response options</i>	<i>No. of studies</i>	<i>Reference</i>
	<i>Candida</i> infection Teeth/denture	Tongue (pink and moist/coated/blistered or cracked) Saliva/dry mouth (watery/thick and ropey/absent or dry mouth) Swallow/chewing (normal/unable to swallow normal diet/unable to swallow liquid diet/unable to swallow fluids/unable to swallow saliva) <i>Candida</i> /infection (no/yes) Teeth/denture (clean, no debris/loose teeth or ill-fitting dentures/debris/caries)		
	RTOG/EORTC acute radiation morbidity scoring scheme for salivary gland (acute xerostomia/salivary gland toxicity)	Grade 0—no change over baseline Grade 1—mild mouth dryness/slightly thickened saliva/may have slightly altered taste such as metallic taste/these changes not reflected in alteration in baseline feeding behavior, such as increased use of liquids with meals	30	396-425
	RTOG/EORTC late radiation morbidity scoring scheme for salivary gland (late xerostomia/salivary gland toxicity)	Grade 0—none Grade 1—slight dryness of the mouth; good response on stimulation Grade 2—moderate dryness of the mouth; poor response on stimulation Grade 3—complete dryness of mouth; no response on stimulation	63	45,359,383,387,388,396,397,399-407,409,410,415,417-421,423-462
	The Subjective Dry Mouth Grading by Eisbruch et al.	Grade I—no disability Grade II—dryness requiring additional fluids for swallowing Grade III—dryness causing dietary alterations or interference with sleep, speaking, or other Activities	5	463-467
	The Wang Zhong-He scoring criteria for xerostomia	0—none 1. Mild dryness of the mouth when sleeping at night or waking up in the morning. 2. Mild dryness, no effect on eating or speaking 3. Moderate dryness, drinking water necessary when eating or speaking. 4. Severe dryness, burning mouth, dysphasia, drinking water necessary.	1	468

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Table IV. Continued

Outcome domains	Outcome measures	Level of measurement/response options	No. of studies	Reference
	Unspecified/ad hoc question Severity of xerostomia	Mild—noticeable but does not influence daily activities and usually does not need intervention Moderate—sufficiently troublesome to make the person uncomfortable; it may influence performance of daily activities; and it may need intervention Severe—cause severe discomfort; it usually interferes with daily activities; it usually needs treatment or intervention	1	469

RTOG/EORTC, The Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer

especially for national survey estimates.^{1,31} In addition, the question itself has also been recommended to validate other self-reported instruments, including the Xerostomia Inventory (XI).³²

DURATION OF XEROSTOMIA. Duration of xerostomia refers to the time since the onset of xerostomia, which has been recorded inconsistently in the literature. Three studies reported the duration of xerostomia based on a patient interview, and 1 study used a nonstandardized question, “Since when have you experienced dryness in the mouth?” with arbitrary response categories of recently, several months, several years, and 10 years or more (Table III).

FLUCTUATION OF XEROSTOMIA. Fluctuation of xerostomia reflects a temporal pattern or variability in the presence and absence of xerostomia, together with changes in its intensity over different periods or daily activities. Differences in xerostomia fluctuation can reflect physiologic and pathologic changes in unstimulated and stimulated saliva production. Periods of the day that are frequently assessed in the present review were during the night (7 studies), during daytime (6 studies), while eating (3 studies), and on waking (3 studies). There appears to be no standardized unidimensional scale assessing this aspect of xerostomia, and various types of single questions with binary, 4-point, and 5-point categorical responses have been used in the literature (Table III).

LOCATION OF XEROSTOMIA. There is no unidimensional outcome measure specific to the location of xerostomia.

Life impact core area (COMET core area 25, 26, 28, 30, and 32). There are 5 major life impact core areas covering 8 different outcome domains for assessing xerostomia. These outcome domains include physical functioning, social functioning, psychologic functioning, impact on oral health, xerostomia-specific QoL, oral health-related QoL, and general health-related QoL. The lists of patient-reported outcome measures in each specific domain in this core area are summarized in Table V.

Physical functioning (COMET core area 25—physical functioning). The physical functioning domain includes the abilities or difficulties in performing daily physical functioning, including chewing, swallowing, speaking, and coping behavior related to xerostomia (e.g., the need to sip liquids to aid swallowing). The most frequently assessed dimension of physical functioning related to xerostomia was the ability/difficulty to swallow (16 studies), followed by the ability/difficulty to speak (10 studies), the ability/difficulty to chew/eat (9

Table V. Patient-reported unidimensional outcome measurements related to life impact core area

<i>Outcome domains</i>	<i>Outcome measures</i>	<i>Level of measurement/response options</i>	<i>No. of studies</i>	<i>Reference</i>
Physical functioning		Dichotomous		
	Unspecified/ad hoc question	Yes/no		
	Ability to chew apples/dried fruits/roast beef without difficulty		1	470
	Ability to chew French bread/rice crackers/pickled vegetables/peanuts without difficulty		1	60
	Difficulty with chewing		2	58,60
	Difficulty eating		1	52
	Difficulty speaking		2	58,60
	Difficulty swallowing		5	58,71,164,318,471
	Difficulty swallowing dry foods		2	151,472
	Need to drink liquids to aid in swallowing		4	71,164,318,471
		Categorical		
	Unspecified/ad hoc question			
	Difficulty swallowing/speaking for relatively long periods of time	No/mild/moderate/severe	1	166
	Satisfaction with the ability to chew/speak clearly	Satisfied/fairly satisfied/dissatisfied	1	470
	Need to drink water for speaking/swallowing/during ordinary time	Not at all/rather no/rather yes/very yes	1	473
	Validated/established scale	Continuous		
	Assessment of Intelligibility of Dysarthric Speech		1	474
	NRS for difficulty swallowing	0-10	1	220
	The Robertson Dysarthria Profile		1	474
	VAS for difficulty speaking	0-100 mm	8	18,232,235,242,244,276,281,289
	VAS for difficulty chewing	0-100 mm	5	232,235,242,272,276
	VAS for ability to swallow/difficulty swallowing	0-100 mm	8	18,235,242,244,272,276,281,289
	VAS for requirement to sip water when speaking, when chewing and swallowing, and even during sleep time	0-100 mm	1	270
	11-point colorimetric scale for difficulty eating, swallowing, need for additional water	0-10	1	316
		Unknown		
	Physical functioning	By interview	1	43

(continued on next page)

Table V. Continued

<i>Outcome domains</i>	<i>Outcome measures</i>	<i>Level of measurement/response options</i>	<i>No. of studies</i>	<i>Reference</i>	
Social functioning	Unspecified/ad hoc question Avoid speaking to people due to dry mouth Stay at home more due to dry mouth Visit people less frequently due to dry mouth	Dichotomous Yes/no	1	235	
		1	235		
		1	235		
	Psychologic functioning	Unspecified/ad hoc question Social interaction/social functioning	Unknown		
			By interview	2	43,325
		Unspecified/ad hoc question Difficulty in initiating sleep due to dry mouth at night? Unspecified/ad hoc question During the past week, how many times on average did you wake up in the night due to dryness of your mouth?	Categorical		
Not at all/rather no/rather yes/very yes			1	473	
Numerical/continuous					
Impact on oral health	Validated/established scale Hospital Anxiety and Depression Scale VAS for ability to sleep Unspecified/ad hoc question Psychologic response/psychologic functioning	Number of times	2	18,281	
		3	474-476		
		1	232		
	Unspecified/ad hoc question Changes in sweet, salty, sour, or bitter taste? Impact on denture retention Taste disturbance in the mouth Unspecified/ad hoc question Difficulty with taste Satisfaction with the ability to taste foods Suffer from dental caries Validated/established scale Global oral health rating Validated/established scale NRS for impact/alteration on taste VAS for difficulty wearing dentures	By interview	2	43,325	
		Dichotomous Yes/no			
		1	316		
		1	235		
		3	62,151,305		
		Categorical			
		No/mild/moderate/severe	1	166	
Satisfied/fairly satisfied/dissatisfied	1	470			
No/mild/moderate/severe	1	166			
0-4 (poor to excellent)	1	474			
Numerical/continuous					
0-10	1	220			
0-100 mm	2	244,276			

(continued on next page)

Table V. Continued

<i>Outcome domains</i>	<i>Outcome measures</i>	<i>Level of measurement/response options</i>	<i>No. of studies</i>	<i>Reference</i>
Xerostomia-specific QoL	VAS for impact/alteration on taste	0-100 mm	4	235,242,276,303
	VAS for severity of suffer from tooth decay	0-100 mm (hardly to highly)	1	244
	Unspecified/ad hoc question	Unknown		
	Impact on dental and oral health	By interview	1	174
		Categorical		
	Validated/established scale			
	EORTC QLQ-C30		32	355,357,360,369,391,405,410,411,428,429,475,477-497
	EORTC QLQ-H&N35		46	216,221,352,355,357,360,381,396,405,410,411,421,428,458,475,478,480,481,482,484-510
	EORTC QLQ-H&N43		1	391
	EORTC QLQ-OES18		3	493,511,512
	The Groningen Radiotherapy-Induced Xerostomia questionnaire		5	508,509,513-515
	The Head and Neck Quality of Life Questionnaire		2	389,516
	The Head and Neck Radiotherapy Questionnaire		2	259,517
	The RTOG-modified University of Washington Head and Neck Symptom Score		1	518
	The Sjögren's Syndrome Symptom Survey		1	519
The University of Washington Quality of Life Questionnaire		10	16,307,389,425,459,468,483,520-522	
The Xerostomia related Quality of Life Scale		15	202,222,385,520,521,523-532	
Oral health-related QoL	VAS for influence of dry mouth on general well-being	Numerical/continuous 0-100 mm	1	286
	Experience of xerostomia	Unknown By interview	1	418
		Numerical/continuous		
	The Geriatric Oral Health Assessment Index		4	266,533-535
	The OHIP-14		25	71,89,164,209,217,241,299,301,327,474,476,528,536-548
	The OHIP-49		2	16,220
	The Oral Health Related Quality of Life-UK		2	209,476
The Oral Impact on Daily Performance		4	124,209,349,474,549	

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Table V. Continued

<i>Outcome domains</i>	<i>Outcome measures</i>	<i>Level of measurement/response options</i>	<i>No. of studies</i>	<i>Reference</i>
General QoL	Validated/established scale Medical Outcomes study 8-Item Short Form Healthy Survey	Numerical/continuous	1	222
	Medical Outcomes study 36-Item Short Form Healthy Survey		10	146,239,240,478,519,533,550-553
	The Symptom Checklist-90-Revised		1	553
	VAS for general well-being	0-100mm	1	286
	VAS for quality of life	0-100mm	2	18,281
	The World Health Organization Quality of Life Instrument, Short Form questionnaire		1	476
	<i>Patient satisfaction</i>	<i>Unspecified/ad hoc questions</i>	<i>dichotomous</i> yes/no	
Easiness to use of the product			3	235,306,309
Symptom improvement after use of the product			4	235,306,309,472
Willingness to take medication for a long- term basis			1	533
<i>Single question</i>		<i>categorical</i>		
How did your dry mouth feel after the treat- ment?		worse/no change/better/much better	2	168,251
<i>Validated/established criteria</i>				
Change from baseline symptoms related to dry mouth sensation		worse/no change/better	4	232,289,554,555
		worsening/unchanged/slight improvement/ significant improvement	1	177
		better/slightly better/unchanged/slightly worse/ worse	1	303
Product Performance and Attribute Questionnaire			2	179,556
Product Performance Questionnaire			1	557
<i>Unspecified/ad hoc questions</i>				
Comparison between the effect of treatment		the effect of both experiments was similar/ the first had a better effect on my dryness/ the second had a better effect on my dryness	1	53
<i>Validated/established criteria</i>	<i>numerical/continuous</i>			
VAS for easiness to use the product	0-100mm	1	558	
VAS for effect of the product on symptom relief	0-100mm	8	235,289,306,309,533,558-560	

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Table V. Continued

Outcome domains	Outcome measures	Level of measurement/response options	No. of studies	Reference
	VAS for pleasantness of the taste of the product	0-100mm	4	235,306,309,558
	Unspecified/ad hoc questionnaires			
	Patient satisfaction		4	550,561-563
	Change in symptoms with treatment	unknown		
		By interview	2	174,267

NRS, numerical rating scale; VAS, visual analog scale; QoL, quality of life; EORTC QLQ, European Organization for Research and Treatment of Cancer Quality of Life questionnaire; RTOG, Radiation Therapy Oncology Group; OHIP, Oral Health Impact Profile.

studies), and need to drink liquids to aid swallowing (6 studies). Most studies assessed aspects of physical functioning using single dichotomous questions (10 studies), followed by the VAS (9 studies; [Table V](#)).

Social functioning (COMET core area 26—social functioning). Only 3 studies assessed social functioning as distinct outcomes. Two studies used patient interviews to elicit information on social functioning, whereas 1 study applied 3 yes/no questions asking if patients avoided speaking to people, stayed at home more, or visited people less frequently because of dry mouth ([Table V](#)).

Psychologic functioning (COMET core area 28—emotional functioning/well-being). The psychologic functioning domain includes changes in emotional functioning and sleep disturbance related to xerostomia. The Hospital Anxiety and Depression Scale was used for the evaluation of both anxiety and depression of patients in 3 studies. Three studies evaluated different sleep disturbance dimensions, including sleep ability at night, difficulty initiating sleep because of xerostomia, and the number of night waking episodes because of xerostomia ([Table V](#)).

Impact on oral health (COMET core area 30—global QoL). Eleven studies assessed different dimensions of impact on taste, including the level of taste disturbance (4 studies using the VAS; 1 using a Likert-type scale; 1 using the NRS), presence of taste disturbance (4 studies using dichotomous scales), and satisfaction with the ability to taste foods (1 study using a Likert-type scale; [Table V](#)). The impacts of dry mouth on denture retention and the development of dental caries were evaluated in 3 and 2 studies, respectively. One study used a global oral health rating (5 grades; poor to excellent) to assess the overall impact of xerostomia on oral health.

Xerostomia-specific QoL (COMET core area 30—global QoL). Quality-of-life domains related to the assessment of xerostomia can be divided into xerostomia-specific QoL, oral health-related QoL, and general health-related QoL based on the specificity of the construct. Xerostomia-specific QoL encompasses QoL specific to the symptoms and/or conditions associated with xerostomia. The 15-item Xerostomia-Related Quality-of-Life Scale³³ was the most frequently used xerostomia-specific QoL measurement instrument (15 studies), which evaluates 4 different QoL dimensions, including physical functioning, psychologic functioning, social functioning, and pain/discomfort. The 14-item Groningen Radiotherapy Induced Xerostomia questionnaire is the only condition-specific QoL instrument emphasizing the impact of xerostomia and sticky

saliva during the day and night in patients with RIX³⁴ and has been used in 5 studies assessing RIX.

Four modules of the EORTC Quality of Life Questionnaire (EORTC QLQ), which aims to measure cancer-specific QoL, have been identified for use in studies assessing xerostomia outcomes. These include the core module (EORTC QLQ-C30, used in 32 studies), the 35-item and 43-item Head and Neck Cancer (HNC) modules (EORTC QLQ-H&N35, used in 46 studies; EORTC QLQ-H&N43, used in 1 study), and the esophageal cancer module (EORTC QLQ-OES-18). Apart from the core module, other EORTC QLQ modules have certain items related to xerostomia, including the presence and severity of dry mouth and sticky saliva and limitation in oral function. Other Head and Neck Cancer–specific measures with items assessing xerostomia identified in this systematic review include the University of Washington Quality of Life Questionnaire (10 studies), the Head and Neck Radiotherapy Questionnaire (2 studies), the Head and Neck Quality of Life instrument (2 studies), and the RTOG-modified University of Washington Head and Neck Symptom Score (1 study; [Table V](#)).

Oral health–related QoL (COMET core area 30–global QoL). Overall, the 14-item Oral Health Impact Profile was the most frequently adopted oral health–related QoL measure, used in 25 included studies. This was followed by the Geriatric Oral Health Assessment Index (4 studies), the Oral Impact on Daily Performance (4 studies), the 49-item Oral Health Impact Profile (2 studies), and the Oral Health-Related Quality of Life-UK (2 studies; [Table V](#)).

General health–related QoL (COMET core area 30–global QoL). General QoL measures applied in studies of xerostomia include the Medical Outcomes study 36-Item Short Form Healthy Survey (10 studies), the VAS for QoL (2 studies), and the following measures, each of which is used in 1 study: The Medical Outcomes study 8-Item Short Form Healthy Survey, the Symptom Checklist-90-Revised, the VAS for general well-being, and the World Health Organization Quality of Life Instrument, Short Form questionnaire ([Table V](#)).

Patient satisfaction (COMET core area 32–delivery of care). The domain of patient satisfaction in the present study encompasses preference and satisfaction with symptom relief, functioning, and perception related to products used for xerostomia. The 100-mm VAS for symptom improvement, used in 8 of the included studies, was the most frequently used scale for measuring symptom relief from the xerostomia products. The categorical scale for assessing changes in symptoms from

baseline, the so-called Global Rating of Change, has been adopted with the response ranging from 3 (worse/no change/better; 4 studies) to 5 categories (with added slightly worse/slightly better; 1 study; [Table V](#)).

Outcome measurements assessing multidomain of xerostomia assessment

The present study identified 26 validated outcome measures assessing multiple aspects of xerostomia in the literature ([Table VI](#)); in addition, 68 articles used ad hoc instruments to measure xerostomia unique to their studies. Within validated multidomain outcome measures, physical functioning was the most commonly included domain of xerostomia assessment (23/26), followed by severity (17/26) and psychologic functioning (10/26). The most frequently used multidomain xerostomia instrument was the XI by Thomson et al. (68 studies),³² followed by the Xerostomia Questionnaire by Eisbruch et al. (31 studies),³⁵ the VAS-Xerostomia Questionnaire by Pai et al. (21 studies),³⁶ and the Summated XI by Thomson et al. (15 studies).³⁷

Regarding the number of domains assessed, the Multidisciplinary Salivary Gland Society questionnaire³⁸ and the xerostomia assessment based on the study of Suh et al.³⁹ measured the highest number of domains of xerostomia assessment, with each evaluating 8 unique outcome domains. The location of the xerostomia domain, which has no specific unidimensional outcome measures in the literature, has been included for assessment in a number of the recently developed multidomain outcome instruments, including the Regional Oral Dryness Inventory,⁴⁰ the Multidisciplinary Salivary Gland Society questionnaire, and the New York University Bluestone Mouthfeel Questionnaire.⁴¹

Resource use core area (COMET core area 34–economic). There is a lack of studies assessing the economic aspect of having xerostomia. Only 1 study⁴² was identified to use the EuroQol 5-domain 3L to calculate the quality-adjusted life-year, which aids in cost-effectiveness analysis of disease or treatment burden.

DISCUSSION

This systematic review revealed the diversity and variability in the domains and outcome measures used in clinical research on xerostomia. This is in accordance with the increasing recognition that insufficient attention has been paid to the choice and harmonization of outcome assessment in clinical studies, which might indicate methodologic flaws in the synthesis of evidence-based clinical practice as a whole. The present study is a crucial prerequisite to systematically identifying existing knowledge on outcome domains and measures for evaluating xerostomia before the future

Table VI. Patient-reported multi-domain outcome measurements for the assessment of xerostomia

Outcome measures	Outcome domains							Level of measurement							No. of studies	References		
	Xerostomia core area							Life impact core area										
	Presence	Severity	Affect	Frequency	Duration	Fluctuation	Location	Physical functioning	Social functioning	Psychological functioning	Impact on oral health	Xerostomia-specific QoL	Oral health related QoL	General health related QoL			Patient satisfaction	
Dry Mouth Questionnaire Part 1: Xerostomia assessment How dry is your mouth? <i>very dry-not dry</i> For the following items: <i>Very severe-never</i> Are you suffering from oral dryness during daytime? Are you suffering from oral dryness at night? Do you have a nasty taste in your mouth? Is sleeping/swallowing/eating impeded? Part 2: Effectiveness of treatment How frequently do you apply the substitute? <i>...times per day</i> For how long is your mouth moist after applying the substitute? <i>...min</i> Is the extent of oral dryness reduced when applying the substitute? <i>highly-not reduced</i> How dry is your mouth when applying the substitute? <i>very severe-not dry</i> How do you appreciate the taste of the substitute? <i>very palatable-nasty</i> What complaints are reduced when using the substitute? For the following items: <i>Very severe-never</i> Dryness during daytime/dryness at night/burning mouth/nasty taste/sleeping difficulties/difficulties with speech/difficulties with swallowing/difficulties with eating		X				X		X			X	X			X	0-4	5	564-567
Dry Mouth Symptom Score The following 2 questions are applied to each symptom: In the past week, how often have you had these problems? In the past week, how bothered were you by these problems? dry mouth/difficulty in speaking/difficulty in swallowing/difficulty in sleeping/bad breath/difficulty in wearing dentures/dry throat			X	X				X		X	X					1-7 (never-always)	1	568
		X	X					X								0-100 mm/0-10	4	137, 250, 517, 569

(continued on next page)

Table VI. Continued

Outcome measures	Outcome domains				Level of measurement				No. of studies	References									
	Xerostomia core area				Life impact core area														
	Presence	Severity	Affect	Frequency	Duration	Fluctuation	Location	Physical functioning			Social functioning	Psychological functioning	Impact on oral health	Xerostomia-specific QoL	Oral health related QoL	General health related QoL	Patient satisfaction		
My saliva feels thick and pasty I have difficulty swallowing I have plenty of saliva My mouth feels sticky Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events for dry mouth Please think back over the past 7 d. How often did you have dry mouth? (never/rarely/occasionally/frequently/almost constantly) What was the severity of your dry mouth at its worst? (none/mild/moderate/severe/very severe) How much did dry mouth interfere with your usual or daily activities? (not at all/a little bit/somewhat/quite a bit/very much) Profile of Fatigue and Discomfort—Xerostomia Symptoms Inventory (short form) 19 items with 5 items on oral dryness (full questionnaire is not available online) Regional Oral Dryness Inventory upper lip, lower lip, inside of the cheeks, front part of the palate, back part of the palate, front part of the tongue, back part of the tongue, floor of the mouth, throat	X		X								X					1	378		
Xerostomia Symptom Inventory 42 items with 24 items related to dry mouth Rate the frequency of experience of each symptom item over the last 2 wk (0-4 never/all the time) Rate the overall severity of each group of symptoms over the last 2 wk (0-7 no problem at all-as bad as imaginable) Difficulty eating (oral facet 1): mouth felt dry when eating/difficulty eating certain food/difficulty swallowing dry food/liquid helps to swallow/food stuck in	X		X					X									1	181	
Regional Oral Dryness Inventory upper lip, lower lip, inside of the cheeks, front part of the palate, back part of the palate, front part of the tongue, back part of the tongue, floor of the mouth, throat	X							X									2	46, 322	
Sticca Symptom Inventory 42 items with 24 items related to dry mouth Rate the frequency of experience of each symptom item over the last 2 wk (0-4 never/all the time) Rate the overall severity of each group of symptoms over the last 2 wk (0-7 no problem at all-as bad as imaginable) Difficulty eating (oral facet 1): mouth felt dry when eating/difficulty eating certain food/difficulty swallowing dry food/liquid helps to swallow/food stuck in	X		X					X		X							4	572, 187, 191, 208, 573	

(continued on next page)

Table VI. Continued

Outcome measures	Outcome domains				Level of measurement					No. of studies	References					
	Xerostomia core area				Life impact core area											
	Presence	Severity	Affect	Frequency	Duration	Fluctuation	Location	Psychological functioning	Social functioning			Physical functioning	Xerostomia-specific QoL	Oral health related QoL	General health related QoL	Patient satisfaction
Xerostomia assessment by Arico et al. Have you had a daily feeling of dry mouth for more than 3 mo? Have you been experiencing difficulty in swallowing dry foods? Do you frequently drink liquids to aid swallowing dry foods? Do you wake up at night to drink water?	X								X					yes/no	2	93, 95
Xerostomia assessment by Bertin-Couto et al. Does your mouth feel dry? Do you experience any difficulties chewing dry foods? Do you experience any difficulties swallowing dry foods? Are you aware of any recent increase in the frequency of liquid intake?	X								X					yes/no	3	598-600
Xerostomia assessment by Campisi et al. Do you feel your mouth is dry? Do you have difficulty eating certain foods? Do you have difficulty swallowing certain foods? Do you use water to help when swallowing certain foods? Do you use water to rinse away debris?	X								X					not at all/a little/quite a bit/very much	1	601
Xerostomia assessment by Fox et al. (5 item version) Does your mouth usually feel dry? Does your mouth feel dry when eating a meal? Do you have difficulties swallowing any foods? Do you sip liquids to aid in swallowing dry foods? Does the amount of saliva in	X		X			X			X					yes/no	5	275, 546, 564, 602-609 91, 282, 343, 425, 610

(continued on next page)

Table VI. Continued

Outcome measures	Outcome domains							Level of measurement							No. of studies	References		
	Xerostomia core area							Life impact core area										
	Presence	Severity	Affect	Frequency	Duration	Fluctuation	Location	Physical functioning	Social functioning	Psychological functioning	Impact on oral health	Xerostomia-specific QoL	Oral health related QoL	General health related QoL			Patient satisfaction	
certain foods																		
The skin of my face feels dry																		
My eyes feel dry																		
My lips feel dry																		
The inside of my nose feels dry																		
Xerostomia Questionnaire by Dirix et al.	X						X				X	X				Different response options in each item/part	5	237, 238, 301, 309, 497
Part 1: Grading of intensity of symptoms of xerostomia and related symptoms																		
Xerostomia: no xerostomia/now and then, partial/always, partial, completely dry, disturbing																		
Pain: no/seldom, minimal/always, strong/unbearable																		
Taste loss: no change/seldom, minimal/now and then, considerable/always																		
Dysphagia: no swallowing problems/solid food/soft food/liquid																		
Part 2: quality of life																		
Part 3: VAS for xerostomia																		
Xerostomia Questionnaire by Eisbruch et al.	X						X			X						0-10	31	35, 45, 174, 215, 298, 305, 373, 386, 388, 407, 446, 456, 457, 458, 507, 516, 522, 620, 635, 651-662
Rate your difficulty in talking due to dryness																		
Rate your difficulty in chewing due to dryness																		
Rate your difficulty in swallowing solid food due to dryness																		
Rate the frequency of your sleeping problems due to dryness																		
Rate your mouth or throat dryness when eating food																		
Rate your mouth or throat dryness while not eating																		
Rate the frequency of sipping liquids to aid swallowing food																		
Rate the frequency of sipping liquids for oral comfort when not eating																		
Ad hoc scales for the assessment of xerostomia																Different response options in each scale	68	10, 67, 168, 224, 242, 252, 265, 286, 303, 394, 459, 471, 477, 563, 557, 651, 563, 574, 652, 653, 663-711

VAS, visual analogue scale; QoL, quality of life.

establishment of a promising COS specific for dry mouth.

The reporting of outcome domains and instruments varied considerably across studies assessing xerostomia. Among the 688 included studies, 16 unique outcome domains, and 166 outcome measures were extracted in the present systematic review. No single outcome domains or measures were consistently used across all included studies. Surprisingly, 137 different outcome measures were reported by ≤ 3 studies. This profoundly impedes evidence synthesis because of the lack of comparability across studies. Nearly half of all clinical studies did not adequately describe or unclearly report the domain of outcome assessment, reflecting that researchers often underestimate the importance of prespecifying the outcome of interest in clinical studies.

Regarding unique outcome domains, the severity of xerostomia, physical functioning, and presence of xerostomia were the 3 most reported domains of xerostomia. However, the most frequently reported domain does not necessarily imply that the domain itself is important to the patients, nor should it be included in all clinical studies of xerostomia. Also, apart from the localized symptoms, xerostomia can substantially impact other aspects of affected individuals' lives, including emotional and social functioning,⁴³ which were found as an individual outcome in only 3 and 9 studies in the xerostomia literature, respectively, and thus under-represented. In addition, certain outcome domains were rarely examined in persons with xerostomia, particularly the economic aspect and location of symptoms.

Apart from wide variation across reporting outcomes, diversity within the assessment of each outcome domain was also observed. For instance, the severity of xerostomia was assessed in various points of interest, including average and worst severity ratings, whereas the clinical relevance of each subdomain in the management of this condition remains underinvestigated. The use and combination of outcome domains were heterogeneous between studies, implying that designing and reporting of xerostomia outcomes in clinical trials is more or less based on specific intentions of researchers or subjective decisions of "what to measure" rather than having a systematic approach using inputs or engagement from investigators and more importantly patients, who are recipients of the intervention.

There was also significant variation in adopting outcome measures for assessing each outcome domain. For example, there were 23 different outcome measures for assessing the severity of xerostomia. The most extensively used outcome measure within the literature of xerostomia was the VAS (94 studies), followed by

the XI (68 studies), and the RTOG/EORTC late radiation toxicity scoring for salivary gland (63 studies). Although widely used in the literature, the RTOG/EORTC has some unclear scoring schemes, including whether "response on stimulation" requires chairside application of an acid or mechanical stimuli⁴⁴ or whether the investigator can subjectively grade this without additional clinical procedures.⁴⁵ This might result in difficulties interpreting the findings and drawing conclusions from such outcome measures.

Different types of multidomain questionnaires assessing xerostomia were used in the literature, each assessing various combinations of outcome domains of xerostomia. However, without knowledge of which outcome domains are considered important and relevant for the patients, health care providers, and other stakeholders to be included in clinical studies assessing intervention of xerostomia, the actual benefits of using these outcome measures remain to be elucidated.

The current assessments of xerostomia appear to lack a standardized approach, particularly regarding operational definitions of xerostomia specific to clinical trials. This includes a description of symptoms (e.g., oral dryness sensation, feeling lack of saliva, and mouth stickiness) and temporal reference points (e.g., 2 weeks or 3 or 6 months). The ambiguity and variation of how xerostomia and its outcomes were described make analysis across studies challenging.

Certainly, inconsistencies in reporting outcomes and selecting outcome measures hinder the comparison and synthesis of robust evidence in systematic reviews and meta-analyses, which can be reliably performed only when clinical studies assess the same outcomes and measure them in the same way.⁴⁶ The outcome domains of xerostomia generated in the present review, together with those of salivary gland hypofunction published in a separate systematic review,⁴⁷ can be taken forward to form a complete list of candidate outcome domains for dry mouth for further consensus processes in the development of COS by a multiprofessional panel including patient representatives.⁴⁸ Clarification of "what to measure" and "how to measure" dry mouth in a set of outcomes validated by various stakeholders will improve consistency in outcome domains and measures applied, minimize outcome reporting bias, improve quality and comparability between studies, and provide recommendations for clinical practice.

To the best of our knowledge, this systematic review is the first study to provide a detailed, comprehensive summary of outcome domains and measures applied to assess xerostomia in relevant clinical studies over the last 2 decades. The extensive variation in the range of outcomes applied in the literature of xerostomia has been underlined in previous Cochrane reviews.^{49,50} With the broad scope of search strategies and 4

databases searched, the results of this study are relevant and can apply to various treatments or interventions for xerostomia rather than confining itself to a single study type, treatment modality, or etiologies of xerostomia. The methodologic process of this study was guided by good practice as recommended by the COMET handbook.⁴⁶ The core area and outcome domains extracted in the present study were mapped to the recently developed standard taxonomy for outcome classifications.²⁶

The present study has several limitations. Despite our broad search strategies, this systematic review included only articles written in English to lessen issues associated with translating terms and thus may potentially fail to identify certain outcome domains reported in non-English publications. Additionally, to capture the diversity of outcomes and outcome measures available in the literature, included studies were not assessed on their scientific rigor. Because of the large number of publications related to xerostomia, we did not exhaustively include all the published articles, but our literature search was narrowed down to a period of the last 20 years. We assume, however, that any clinically relevant, important outcome measures would be carried over to the evaluated period. Nonetheless, these limitations are unlikely to change this study's main findings and conclusions.

CONCLUSION

There is considerable heterogeneity in outcome domains and measures reported in clinical studies of xerostomia. This systematic review is the first step toward developing a COS for assessing dry mouth to homogenize outcome reporting, standardize the conduct of individual trials, facilitate comparison across trials, and minimize research waste. This will ultimately support informed clinical decisions in the management of dry mouth.

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DECLARATION OF INTEREST

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SUPPLEMENTARY MATERIALS

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