World Workshop on Oral Medicine VIII: Development of a Core Outcome Set for Dry Mouth: A Systematic Review of Outcome Domains for Salivary Hypofunction

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Abstract

Objective: To identify all outcome measures used to assess salivary gland hypofunction (i.e.: objective measures used to determine actual changes in saliva quantity or to assess response to treatment of salivary gland hypofunction) and to group these into domains.

Study Design: A systematic review including clinical trials, and prospective or retrospective observational studies involving human participants with dry mouth, with any type of intervention where objective assessment of salivary gland hypofunction was described.

Results: Five hundred fifty-three studies involving 31,507 participants were identified. The majority assessed both salivary gland hypofunction and xerostomia (68.7%), whilst 31.3% assessed salivary gland hypofunction alone. The majority of studies investigated 'amount of saliva' and the highest number of outcome measures was within the domain 'clinical/objective signs of salivary gland hypofunction'.

Conclusions: Seven domains encompassing 30 outcome measures were identified, confirming the diversity in outcomes and outcome measures used in research regarding salivary gland hypofunction. Identified items will be used in conjunction with those identified regarding xerostomia to create a COS for dry mouth quantification for use in future clinical trials, with the overall goal of improving the standardization of reporting, leading to the establishment of more robust evidence for the management of dry mouth and improving patient care.

1. Introduction

Dry mouth is a debilitating condition which can have a significant impact on quality of life. It is a ubiquitous problem worldwide, yet despite this, management options remain limited, and there is no strong evidence that treatments are effective.[1] Prevalence ranges from 5.5%- 46%[2] with a slight female preponderance[3,4] However, the precise global prevalence is difficult to determine due to differing study methodology and diagnostic or inclusion criteria used.[5-7]

The term 'dry mouth' encompasses xerostomia, salivary gland hypofunction, and hyposalivation. Xerostomia is defined as 'the subjective feeling of oral dryness',[8,9] whilst salivary gland hypofunction is objectively decreased saliva secretion, i.e. below normal secretion. Hyposalivation refers to a diagnosis when saliva secretion becomes pathologically low, as measured objectively,'[10] i.e. unstimulated whole saliva flow rate ≤0.1 mL/min, and/or stimulated whole saliva flow rate ≤0.5-0.7 mL/min.[11,12] The terms xerostomia, salivary gland hypofunction, or hyposalivation are therefore not synonymous and should not be used interchangeably. Unfortunately, however, these terms are often combined in the dry mouth literature, limiting the interpretation of study results.

Xerostomia (the subjective *feeling* of dry mouth) due to salivary gland hypofunction (an objective reduction in saliva secretion) is typically apparent once ≥50% of unstimulated salivary function has been lost.[13] Conversely, patients may experience xerostomia (*subjective* dry mouth) in the absence of objective reduction of salivary secretion. It is postulated that this may be due to mouth breathing causing evaporation of saliva[14] and/ or due to changes in the composition of saliva (a qualitative change) to a more viscous production, resulting in a *feeling of dryness*, even though the

quantity of saliva production remains unchanged.[15-17] Xerostomia has also been proposed to be psychogenic in aetiology.[3,18]

Salivary gland hypofunction may be due to a variety of reasons, including medication intake and polypharmacy (a multitude of medications, most commonly those that are anti-cholinergic, sympathomimetic, or diuretic in action), damage to salivary glands (e.g. radiation, radioactive iodine), diseases of the salivary glands (e.g. Sjögren's syndrome (also known as Sjögren's disease) either primary or secondary to connective tissue diseases), sarcoidosis, human immunodeficiency virus, hepatitis C virus, chronic graft versus host disease, primary biliary cholangitis, cystic fibrosis, amyloidosis, hemochromatosis, vasculitis), developmental abnormalities (aplasia or agenesis), diabetes mellitus, eating disorders, dehydration and/or renal failure, amongst others.[2,17,19-35] It is reported in the literature that older age does not result in salivary gland hypofunction,[12,36-38] but rather that as ageing occurs and health declines, there is an increase in polypharmacy with xerogenic medications, which often results in a reduction in saliva secretion, and/or xerostomia.[39-41] However, a previous meta-analysis has concluded that the aging process is in fact directly associated with a reduction in salivary flow rate.[42]

A range of objective special investigations can be employed to assess if there is a quantitative reduction in salivary flow rate or disease or damage to the salivary glands, including sialometry, salivary gland imaging and sialadenoscopy, amongst others. To assess the subjective feeling of dry mouth it is fundamental to obtain the patient's opinion by questioning the patient about their dry mouth, or using any number of validated scales and tools,[43-47] some of which may have direct

relation to or predictive ability for the presence of salivary gland hypofunction or even hyposalivation.[8]

Within the healthcare setting, an outcome measure reflects "a change in current or future health status that can be attributed to the antecedent intervention".[48] A plethora of outcome measures relating to the assessment of both xerostomia and salivary gland hypofunction are cited in the literature and the majority of these focus on the subjective element of dry mouth through patient-reported outcome measures (PROMS). Outcome measures for dry mouth and the definitions/terminology to which they relate are heterogeneous across the literature, which can introduce imprecision when interpreting the collective results and conclusions regarding the efficacy of interventions. Furthermore, this translates to challenges creating evidence-based guidelines and clinical decision making. With this in mind, the aim of the World Workshop on Oral Medicine Outcomes Initiative for the Direction of Research (WONDER) was to address these difficulties by creating core outcome measures for effectiveness trials. A core outcome set (COS) is an agreed *minimum* of outcome domains to be measured and reported in all trials of a particular treatment or condition.[49] As part of this process, all subjective and objective outcome measures need to be systematically reviewed, to allow consensus to be reached by a panel of experts regarding which outcomes should be part of the COS.

The purpose of this systematic review was to identify all the different outcome measures used to assess salivary gland hypofunction (i.e. the objective measures used to diagnose an actual reduction in saliva quantity or to assess response to treatment of salivary gland hypofunction) and

to group these into domains. The outcome measures relating to xerostomia are the subject of a separate systematic review.[50]

2. Materials and Methods

This systematic review was conducted as part of the World Workshop on Oral Medicine VIII (WWOM VIII). The research method was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement guidelines.[51] The protocol for this systematic review was registered at the International Prospective Register of Systematic Reviews (PROSPERO), University of York Centre for Review and Disseminations, with identification number CRD42021279791 (available at: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021279791).

2.1. Search Strategy

The research question "what are the outcome measures used in studies for dry mouth?" was formulated to direct the search strategy. The search strategy was developed with the help of a bioinformation specialist (SvdW) according to the syntax rules of each database. On 15 September 2021, a systematic search of the scientific literature was performed for articles published from January 2000 up to 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 provided as a supplementary document (Supplement 1). A total of 34,922 citations were retrieved from the four databases. A total of 1,746 records not meeting the publication date restrictions were removed

before screening. After removal of duplicates, a total of 18,694 were retained for screening (**Figure 1**).

2.2. Eligibility Criteria

This manuscript focused on outcome measures used to assess salivary gland hypofunction. In a separate manuscript, we address outcome measures relating to xerostomia.[50] The Population, Intervention, Control, Outcome, and Study Design (PICOS) approach was adopted as follows: P – humans with a dry mouth; I – any active preventive, palliative, or curative pharmacological or non-pharmacological 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 non-randomized) and observational studies (descriptive, cross-sectional, cohort, case-control).

Inclusion criteria were as follows: Clinical trials and prospective or retrospective observational studies involving human participants with dry mouth and describing any types of intervention or objective assessment of dry mouth. Studies must have had at least one objective dry mouth-related outcome and/or outcome measures clearly designated in the methods section. Exclusion criteria were as follows: Animal and/or in vitro studies, publications not available in full text, conference proceedings, commentaries, editorials, study protocols, case reports, review articles, studies published before the year 2001, and records which did not have an English version. Studies using a cohort of less than ten participants were further excluded to ensure a representative sample of the general population. No age restriction was applied.

2.3. Study Selection and Data Extraction Process

Reviewer calibration was performed in two sessions on articles not included on this study prior to the initiation of the screening process. The Cohen's Kappa was 0.7 with a percentage of agreement of 85 between the various observers. The titles and abstracts obtained from the initial electronic searches were screened for relevance by the study group (AV, KD, RNR, VS, ARSS, MKS, PW, MLS, SN). Papers retained were screened by full text review by the five reviewers (ARSS, MKS, PW, MLS, SN). A total of 2,700 studies were found to be relevant and considered for comprehensive review and data extraction. Data extracted included the type of the study and the target population as well as the number of patients included. All objective outcome measures/instruments relating to dry mouth were recorded and classified within domains (paragraph 3.2; figure 2).

3. Results

A total of 553 studies assessing salivary gland hypofunction, comprising 31,507 patients met the inclusion criteria. Of these, 173 (31.3%) studies assessed salivary gland hypofunction alone, whilst 380 (68.7%) assessed both salivary gland hypofunction and xerostomia (**Table I**). Most studies (n=303, 54.8%) assessed one outcome measure for salivary gland hypofunction, with only 43 and 25 of studies assessing three and four different outcome measures, respectively. The rest of the studies assessed two outcome measures for salivary gland hypofunction, each (n=182, 32.9%).

3.1. Characteristics of Studies Included

As depicted in Table I, the proportion of studies assessing salivary gland hypofunction increased over the years, with almost double the number of studies published between the years 2011-2020

compared with 2001-2010. Most studies originated from Europe (n=206, 37.3%), followed by Asia (n=190, 34.4%) and North America (n=85, 15.4%). Cohort studies were the most represented study type (n=160; 28.9%). The most common condition studied was salivary gland hypofunction due to head and neck radiotherapy (n=123, 22.2%), closely followed by Sjögren's syndrome (n=115, 20.8%). A total of 60 studies (10.8%) did not specify the condition evaluated.

3.2. Identified Domains

Seven domains were identified (**Figure 2**). The domain most frequently explored, based on the number of studies including at least one outcome measure used for this domain, was 'Amount of Saliva,' with 481 (87.0%) studies. Domains that were less frequently studied were 'Saliva Properties,' 'Saliva Composition,' and 'Biomarkers,' with a total of 11, 11, and two studies evaluating at least one related outcome measure, respectively.

As one study could include outcome measures for more than one domain simultaneously, each study could be retrieved once per domain but also be reported in several domains.

3.3 Main Outcome Measures Within Each Domain

The highest number of outcome measures were recorded within the two subdomains of Domain 3 (Clinical/Objective Signs of Salivary Gland Hypofunction), despite there being a relative paucity of papers within this domain (**Table II)**. Domain 5 (Imaging Modalities Assessing Salivary Gland Dysfunction) and Domain 6 (Properties of Saliva) looked at five outcome measures each. Despite having the largest number of papers evaluating this domain, only four outcome measures, two in each subdomain, were identified in Domain 1 (Amount of Saliva). Only 3 outcome measures were identified for Domain 2 (Salivary Biomarkers).

3.3.1 Domain 1: Amount of Saliva

Domain 1 considered salivary gland flow rate and/or saliva weight. This was divided into two subdomains: Whole mouth saliva and gland/region specific saliva. Each subdomain included outcome measures looking at both stimulated and unstimulated saliva.

Within the outcome measure of stimulated whole saliva flow rate/weight, 276 studies used seven different instruments (**Table III**). All instruments used a scale (numerical/continuous) as the level of measurement. The most common method of assessing stimulated whole saliva flow rate/weight was stimulation by chewing (n=63). Chewing materials included paraffin wax,[52-92] gum,[93-106] rubber,[107,108] and silicone.[109-111] Other instruments to specifically assess stimulated whole saliva flow rate/weight included gustatory stimulation (n=23) with gustatory stimulants including citric acid and lime juice.[47,62,77, 85, 102,112-129] Less commonly used methods were the Saxon test; where saliva production is quantified by weighing a gauze before and after chewing it for a set time[130] (n=10),[98,131-139] biscuit test; the amount of time taken to chew and swallow a dry cracker biscuit,[140] electrostimulation,[141] and medication such as pilocarpine oral solution or tablets.[142,143] One study specifically compared the stimulated salivary flow rate induced by an alcohol-based and non-alcohol-based mouthwash.[144]

Within the outcome measure of unstimulated whole saliva flow rate/weight, 368 studies used 11 instruments (**Table III**). The most common instrument to assess unstimulated whole saliva flow rate/weight was passive drooling or spitting (n=150),[39, 57, 60, 62, 64, 67, 69, 70, 72, 77, 79, 82, 83, 85, 86, 90, 92, 93, 99, 100, 106, 107, 109, 111, 113, 114, 118-120, 122, 129, 135, 137, 141-257] followed by spitting at timed intervals (n=

30),[47, 56, 78, 87, 117, 126, 258-281] and weighing cotton balls/rolls (n=10).[116, 282-290] Other methods of measuring unstimulated whole saliva flow rate/weight included the Saxon test,[104, 291-295] Oral Schirmer's test; a strip of filter paper is placed on the floor of mouth for 5 minutes and the wetted length is measured in millimeters,[112, 296-299] Modified Schirmer's test,[283, 300, 301] and weighing gauze placed in the mouth.[302-304]

A total of 58 papers evaluated the subdomain of gland/region specific saliva (**Table III**). This included investigating specific major and/or minor glands (e.g. parotid gland, labial glands) either alone or in combination, or specific regions/locations of the oral cavity (e.g. floor of mouth, palate, labial mucosa). Outcome measures evaluated both stimulated and unstimulated saliva, and great variability was recorded in terms of the different glands and/or regions of the mouth assessed.

The most common individual gland to be investigated (i.e. not investigated in combination with any other glands) was the parotid gland. Twenty-seven studies used stimulated parotid saliva as the outcome measure[78, 305-327] with methods of stimulation of the gland including acidic sweets, 1% ascorbic acid solution, and 2%, 4% or 6% citric acid, and methods of collection including devices such as the Carlsson-Crittenden Cup, Lashley cup and the modified Crittenden-Lashley cup method. Nine studies also measured unstimulated parotid saliva alongside stimulated parotid saliva.[305, 306, 311, 315, 319, 322, 324, 325, 327]

The next most common outcome measure was unstimulated saliva from the floor of mouth (n=9)[270, 329-336] measured most frequently by the modified Schirmer's test. The submandibular and sublingual glands were assessed together, investigating both unstimulated,[236, 312, 322, 337-339] and

stimulated salivary flow rate.[317, 321, 322, 338, 340] Several papers also investigated stimulated and unstimulated saliva from the parotid and submandibular glands.[69, 341-343]

Minor glands were investigated by several authors. Some investigated these as specific, individual regions/locations of the mouth; unstimulated labial gland saliva (n=6),[100, 206, 226, 344-346] unstimulated buccal saliva,[206, 344] or unstimulated palatal saliva,[206, 347] whilst some investigated more than one individual location; palatal and upper labial glands[109] or labial and buccal glands.[73]

3.3.2 Domain 2: Salivary Biomarkers

Two studies used a total of three salivary biomarkers and the use of all these methods was ad hoc. Biomarkers recorded were inflammatory cytokines, proteins, and immunoglobulins. Specifically, chromogranin A and IgA[135] and extracellular microRNA.[348]

3.3.3 Domain 3: Clinical or Objective Signs of Hyposalivation

Domain 3 considered clinical or objective signs of hyposalivation as rated by a physician. The domain was divided into individual clinical signs of hyposalivation and multiple clinical signs of hyposalivation. Eight studies used individual clinical signs of hyposalivation as their outcome measure. The most common method used was for the physician to assess for clinical signs of dryness of the oral mucosa or specific mucosal sites such as the dorsum of the tongue[349, 350] and palate.[351] Other methods included use of the mirror test,[335, 350, 352] scoring dryness from clinical examination (giving a score between 1-10 depending on presence of clinical signs of hyposalivation e.g.: cervical caries, debris on palate),[314] and the tongue blade test.[274]

Eighteen studies used multiple clinical signs of hyposalivation as their outcome measure. The most common outcome measure used was the Clinical Oral Dryness Score (CODS) (colloquially known as the 'Challacombe Scale of Clinical Oral Dryness'),[77, 78, 85, 105, 213, 218, 255, 278, 353] followed by a physician carrying out a clinical evaluation to assess for multiple signs of dry mouth.[39, 169, 177, 261, 298, 354, 355] Other methods included scoring methods such as the Objective Oral Mucosa Scale (OOMS)[356] and a dichotomous objective dry mouth score.[353]

3.3.4 Domain 4: Mucosal Hydration

Domain 4 considered mucosal hydration, specifically moisture, wetness, and residual saliva. While most authors refer to these terms interchangeably to describe the level of mucosal hydration, some use the term 'moisture' to describe the water content of the oral mucosal surface and intramucosal layer, 'wetness' to describe the water content of the mucosal surface only, and 'residual saliva' to specifically describe the saliva remaining on mucosal surfaces after swallowing.

In total, 20 studies used outcome measures relating to this domain. The most common outcome measure was moisture, with 13 papers considering this outcome measure.[137, 204, 357-367] Five of these studies specifically investigated this via a checking device such as a Periotron™ (Pro-Flow TM Incorporated, Amityville, NY, USA). [137, 362, 364, 366, 367] Wetness was the outcome measure for four studies.[177, 190, 368, 369] Three papers used residual saliva as the outcome measure.[67, 213, 218]

3.3.5 Domain 5: Imaging Modalities Assessing Salivary Gland Dysfunction

Domain 5 considered salivary gland dysfunction (a change in quality and/or quantity of saliva)[370] assessed by a variety of different imaging modalities comprising ultrasonography, scintigraphy,

sialography, magnetic resonance imaging (MRI) and computed tomography (CT). Twenty-four studies used five individual outcomes measures involving ultrasonography of the salivary glands (parenchymal structure, colour or power doppler signal, a scoring system, tissue elasticity and not specified).[123, 293, 295, 323, 328, 371-388]

The most common outcome measure involving ultrasonography used a scoring system[123, 328, 375, 377, 379-382, 384-386, 388] such as that of Hočevar et al.[389] Six studies investigated parenchymal structure (e.g.: homogeneity, echogenicity) via ultrasonography.[293, 295, 371-373, 387] One study looked specifically at intraglandular power doppler signal.[381] Forty-four studies considered salivary gland hypofunction by scintigraphy.[134, 157, 170, 225, 268, 283, 293, 320, 355, 376, 390-423] Five studies used MRI as an outcome measure,[132, 291, 371, 403, 416] two used sialography,[371, 424] and only a single paper assessed salivary gland hypofunction by CT.[425]

3.3.6 Domain 6: Properties of Saliva

Domain 6 looked at saliva properties. The most common property considered was pH[115, 196, 221, 280] followed by buffering capacity.[196, 209, 426] Two studies used lubrication as an outcome measure, specifically looking at the level and concentration of the salivary mucin MUC5B (originally named MG1).[91, 427] Two studies used saliva stringiness (Spinnbarkeit) as an outcome measure.[213, 218] A single study looked at viscosity using the inclined plane test; the faster the velocity of the saliva on a glass slide, the less viscous ('sticky') it is.[250]

3.3.7 Domain 7: Saliva Composition

Domain 7 considered the composition of saliva. Two studies considered individual components of saliva; salivary IgA (alongside pH)[221] and calcium concentration.[427] Nine papers used multiple outcome measures regarding the composition of saliva via biochemical and sialochemical analysis.[67, 178, 195, 201, 277, 280, 311, 428, 429]

4. Discussion

Following the first of four steps outlined by the Core Outcome Measures in Effectiveness Trials (COMET) Initiative,[430] this systematic review sought to identify domains and outcomes that have been used by clinicians from varied backgrounds and settings for the evaluation of salivary gland hypofunction (i.e., *what* to measure). Combined with Part I which reviewed the outcome domains used to assess xerostomia[50] we assessed all domains used in dry mouth research.

A total of seven domains encompassing 30 outcome measures were identified for salivary gland hypofunction based on the 553 studies included. By far, the most common domain was 'Amount of Saliva', retrieved from a total of 485 studies. This finding may indicate an overall agreement among clinicians and researchers that these are the most important, or clinically relevant outcome measures for salivary gland hypofunction. In addition, this may reflect the availability of instruments for evaluation of salivary flow rate/weight in daily practice, rendering related outcome measures feasible and relatively reproducible. Alluding to the latter is the finding that within the 'Amount of Saliva' domain, most studies (n=368, 76%) evaluated unstimulated whole saliva flow rate/weight, an outcome for which instrumentation is minimal. With the passive drooling or spitting method, the most common instrument used, all that is needed is a receptacle (e.g., cup or

a tube) and a precision scale. This may also explain why only a small number of studies investigated the domains of 'Saliva Properties', 'Saliva Composition' and 'Biomarkers'; outcome measures within these domains often require expensive laboratory equipment and appropriately trained personnel to provide and interpret results, and therefore these are less readily available. Although outcome measures within the domain 'Imaging Modalities Assessing Salivary Gland Dysfunction' require expensive imaging equipment, these are usually easily accessible in most hospital settings, reflected in the fact that this domain was the second most common to be investigated. The number of different outcomes assessed and the inconsistency in assessment methods is problematic. For example, while 'Saliva Properties' were used in only 13 of the 553 studies evaluating salivary gland hypofunction, five different outcome measures were used across the 13 studies, making comparison of studies and aggregation of results difficult.

Salivary gland hypofunction secondary to radiation to the head and neck was the most common condition/disease to be investigated (n=123). This was closely followed by Sjögren's syndrome, investigated in 115 papers, with outcome measures across a range of domains. Outcome measures included unstimulated and stimulated salivary flow rate, physician assessment of clinical dryness, including use of the CODS, ultrasonography, scintigraphy and MRI. In addition to having outcome measures within the identified domains, fourteen studies looked specifically at histological analysis of lymphocytic infiltrates (focus scores) in salivary gland biopsies.[195, 309, 371, 394, 404, 431-439] Overall, outcome measures used in studies assessing Sjögren's syndrome were relatively homogeneous, likely the results of the efforts made in recent years to move towards less invasive methods to diagnose this condition [440, 441] and to improve the understanding of the disease and to standardize the evaluation and monitoring of disease activity; starting with the 2016 International

Consensus to endorse the ACR-EULAR set of criteria for the classification of primary Sjögren's syndrome,[442] through the development of indices such as the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) and the Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS),[443] addressing different aspects of the disease.

This systematic review has several limitations. By focusing on articles published after the year 2000, this study may have missed outcome measures used to assess salivary gland hypofunction before this date. We assume, however, that any clinically relevant, important outcome measures would be carried over to the evaluated time period. Additionally, with the aim to capture the diversity of outcomes and outcome measures available in the literature, included studies were not assessed on their scientific rigor. Due to the volume of results, the data extraction on outcomes was limited and information concerning the timing and implementation method(s) of the various outcome measure instruments was not retrieved. Finally, this review included English-language literature only, and relevant research published in other languages may have been left out (language bias).

The strengths of this review in our view, however, outweigh its limitations. With over 34,000 records screened, the inclusion of a large number of studies to summarize information on outcome domains and outcome measures for the evaluation of salivary gland hypofunction resulted in a comprehensive data set ranging across clinical settings, patient populations, and geographical locations. Additional strengths include the international team of reviewers, and the rigour and consistency of the screening process.

This systematic review revealed the diversity and variability in the outcomes and outcome measures used in clinical research regarding salivary gland hypofunction. The lack of standardised outcome measures for the assessment of dry mouth contributes to the heterogeneity between studies and makes it difficult to compare results, synthesize findings, or guide clinicians on management strategies. The WONDER initiative aims to address these difficulties by developing a COS for dry mouth, encompassing both the findings regarding salivary gland hypofunction as identified in this manuscript, as well as those identified for xerostomia.[50] Once available, a dry mouth COS would improve the standardization of reporting, and facilitate meta-analyses, leading to the establishment of more robust evidence for the management of dry mouth and, eventually, improved patient care. This systematic review was thus designed to identify existing outcomes and outcome measures for salivary gland hypofunction in order to inform the next steps in ranking and selecting items that would be most relevant to be included in a COS for dry mouth and to highlight potential gaps. Building on the current findings, future work is planned to further evaluate the identified outcome measures for their specific properties (i.e., *how* to measure). The next steps of the WONDER initiative are to complement the results of this systematic review with the results of focus groups regarding the most important or bothersome domains from the perspective of patients with dry mouth and to identify any gaps between priorities of clinicians/researchers and the patients' perspective.

5. Conclusion

There is considerable diversity and variability in the outcomes and outcome measures used in clinical research regarding salivary gland hypofunction. The identified seven domains, which encompass 30 outcome measures, are the first step towards development of a COS for dry mouth within the WONDER initiative.

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7. Figure Legends

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline flowchart detailing article selection process.

Figure 2. Identified Outcome Domains for Assessment of Salivary Gland Hypofunction.

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Table I. Characteristics of the Included Studies

Study characteristics	Number (%)
Year published	***Total n=553***
2001-2010	180 (32.5)
2011-2020	331 (59.9)
2021	42 (7.8)
Origin of the article	
Europe	206 (37.3)
Asia	190 (34.4)
North America	85 (15.4)
South America	51 (9.2)
Multiple	15 (2.7)
Oceania	4 (0.7)
Africa	2 (0.4)
Types of studies	
Cohort	160 (28.9)
Randomized controlled trials (RCTs)	119 (21.5)
Case-control studies	50 (9.0)
Case series	8 (1.4)
Other types of study Cross-sectional Clinical trial Comparative Randomized crossover Qualitative (questionnaire/survey) Validation Crossover Observational Chart review	216 (39.1) 140 30 16 12 6 5 3 3 1
Number of patients	31,507
Range of age (years)	5 – 99
Conditions associated with dry mouth	
Salivary gland hypofunction secondary to radiation to the head and neck	123 (22.2)
Sjögren's syndrome	115 (20.8)
Other conditions	112 (20.3)
Several disease groups	89 (16.1)
Unknown etiology of dry mouth	60 (10.8)
Older age	32 (5.8)
Polypharmacy	22 (4.0)
What is the article assessing	

Salivary gland hypofunction and xerostomia	380 (68.7)
Salivary gland hypofunction only	173 (31.3)

Table II: Outcome Measures Represented Within Each Domain

DOMAIN	SUBDOMAINS	OUTCOME MEASURES
DOMAIN 1: AMOUNT OF SALIVA (please also see Table III)	**Whole-mouth saliva**	a) Stimulated whole saliva flow rate/weight b) Unstimulated whole saliva flow rate/weight
	Gland/region-specific saliva	a) Stimulated gland/region-specific saliva b) Unstimulated gland/region-specific saliva
DOMAIN 2: SALIVARY BIOMARKERS	**Laboratory biomarkers**	a) Inflammatory cytokines b) Protein and immunoglobulins c) Extracellular microRNA
DOMAIN 3: CLINICAL/OBJECTIVE SIGNS OF HYPOSALIVATION	**Individual physician-rated signs of hyposalivation**	a) Physician-assessment of individual clinical signs of dryness of the oral mucosa or specific mucosal sites b) Mirror test c) Scoring oral dryness d) Tongue blade test
	Multiple physician-rated signs of hyposalivation	a) Clinical Oral Dryness Score (CODS) b) Physician-assessment of multiple clinical signs of dryness of the oral mucosa or specific mucosal sites c) Scoring oral dryness
DOMAIN 4: MUCOSAL HYDRATION	**N/A**	a) Moisture b) Wetness c) Residual saliva
DOMAIN 5: IMAGING MODALITIES ASSESSING SALIVARY GLAND DYSFUNCTION	**Salivary gland imaging**	Outcome measures per imaging modality: a) Salivary gland ultrasonography b) Salivary gland scintigraphy c) Sialography d) Salivary gland MRI (Magnetic Resonance Imaging) e) Salivary gland CT (Computerized Tomography)
DOMAIN 6: SALIVA PROPERTIES	**N/A**	a) Lubrication b) Stringiness c) pH d) Viscosity e) Buffering
DOMAIN 7: SALIVA COMPOSITION	**Individual components of saliva**	Salivary proteins Inorganic components
	Multiple components of saliva	Biochemical and sialochemical analysis

Table III: Domain 1: Amount of Saliva

DOMAIN	SUBDOMAIN	OUTCOME MEASURES	INSTRUMENTS/METHODS
DOMAIN 1: AMOUNT OF SALIVA	**Whole-mouth saliva**	Stimulated whole saliva flow rate/weight	1. Biscuit 2. Chewing 3. Electrostimulation 4. Gustatory stimulant 5. Medication 6. Mouthwash 7. Saxon test 8. Not specified
		Unstimulated whole saliva flow rate/weight	1. Biscuit test 2. Blotting mucosa 3. Frequency of swallow (by electromyography) 4. Modified Schirmer's test 5. Passive drooling or spitting 6. Saxon test 7. Schirmer's test 8. Spitting at timed intervals 9. Wafer test 10. Weight of cotton balls/roll 11. Weight of gauze 12. Not specified
	Gland/region-specific saliva	**OUTCOME MEASURES**	**ANATOMICAL LOCATION**
		a) Stimulated gland/region-specific saliva	1. Parotid 2. Parotid and submandibular 3. Submandibular and sublingual saliva 4. Floor of mouth
		b) Unstimulated gland/region-specific saliva	1. Parotid 2. Parotid and submandibular 3. Submandibular and sublingual 4. Labial mucosa 5. Buccal mucosa 6. Palate 7. Floor of mouth 8. Labial and buccal minor glands 9. Palatal and upper labial glands

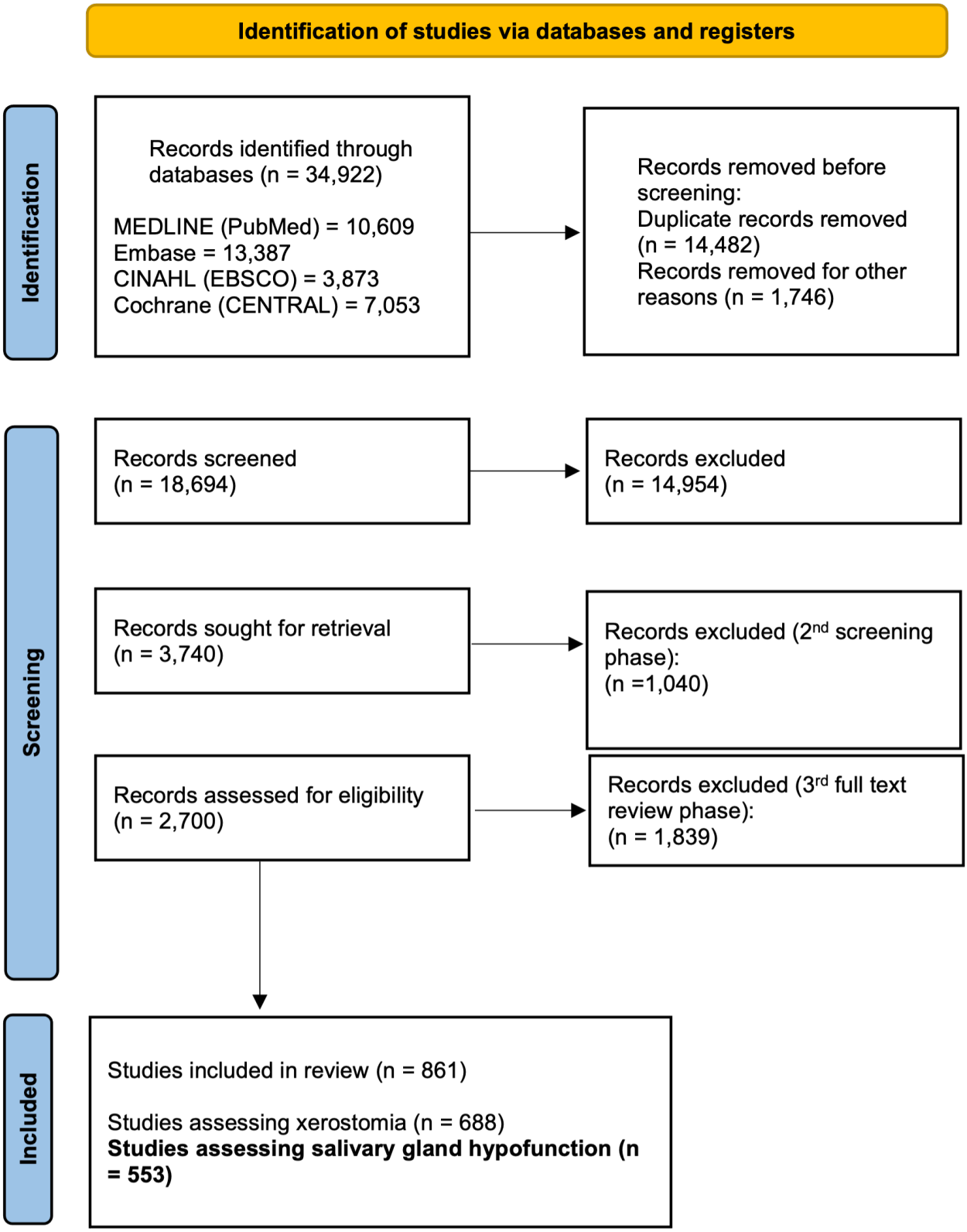
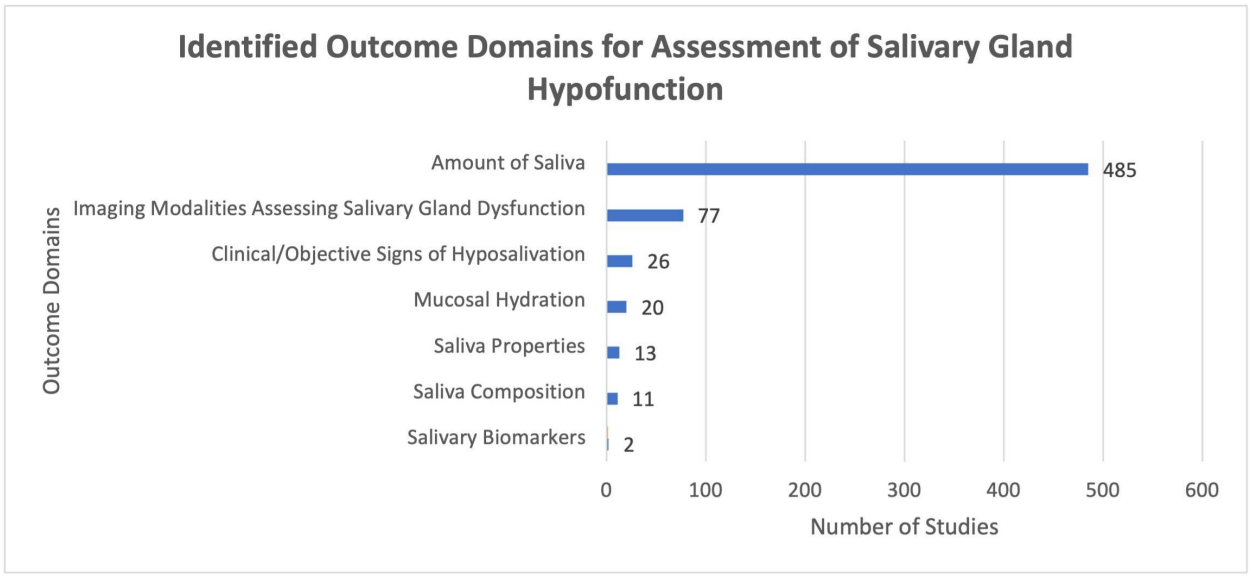

Identification of studies via databases and registers
Identification
Records identified through databases (n = 34,922)
MEDLINE (PubMed) = 10,609
Embase = 13,387
CINAHL (EBSCO) = 3,873
Cochrane (CENTRAL) = 7,053
Records removed before screening:
Duplicate records removed (n = 14,482)
Records removed for other reasons (n = 1,746)
Screening
Records screened (n = 18,694)
Records excluded (n = 14,954)
Records sought for retrieval (n = 3,740)
Records excluded (2nd screening phase): (n =1,040)
Records assessed for eligibility (n = 2,700)
Records excluded (3rd full text review phase): (n = 1,839)
Included
Studies included in review (n = 861)
Studies assessing xerostomia (n = 688)
Studies assessing salivary gland hypofunction (n = 553)

Figure 1


Identified Outcome Domains for Assessment of Salivary Gland Hypofunction
Outcome Domains
Amount of Saliva
Imaging Modalities Assessing Salivary Gland Dysfunction
Clinical/Objective Signs of Hyposalivation
Mucosal Hydration
Saliva Properties
Saliva Composition
Salivary Biomarkers
485
77
26
20
13
11
2
0
100
200
300
400
500
600
Number of Studies

Supplementary Material

MEDLINE (PubMed) 8-9-2021

("Xerostomia"[Mesh] OR xerostomia*[tiab] OR hyposaliv*[tiab] OR dry-mouth[tiab] OR mouth-dryness[tiab] OR oral-dryness[tiab] OR sjogren*[tiab] OR hyposiali*[tiab] OR salivary-gland-dysfunct*[tiab] OR salivary-gland-hypofunct*[tiab] OR reduced-saliv*[tiab])
AND
("Clinical Trial" [Publication Type] OR "Clinical Trials as Topic"[Mesh] OR "Epidemiologic Studies"[Mesh] OR "Surveys and Questionnaires"[Mesh] OR "Outcome Assessment, Health Care"[Mesh] OR "Quality of Life"[Mesh] OR "Visual Analog Scale"[Mesh] OR "Biomarkers"[Mesh] OR intervention*[ti] OR treatment*[ti] OR therap*[ti] OR management*[ti] OR study[ti] OR random*[tiab] OR trial*[tiab] OR controlled-study[tiab] OR clinical-study[tiab] OR cohort[tiab] OR case-control[tiab] OR prospectiv*[tiab] OR follow-up[tiab] OR followed-up[tiab] OR retrospectiv*[tiab] OR crosssectional*[tiab] OR cross-sectional*[tiab] OR questionnair*[tiab] OR inventory[tiab] OR patient-reported[tiab] OR outcome*[tiab] OR survey*[tiab] OR tool[tiab] OR tools[tiab] OR tooling[tiab] OR scale*[tiab] OR scaling[tiab] OR index[tiab] OR "Visual Analog Scale"[tiab] OR VAS-scale[tiab] OR clinician-reported[tiab] OR marker*[tiab] OR biomarker*[tiab] OR indicator*[tiab])
NOT
(("Animals"[Mesh] NOT "Humans"[Mesh]) OR "Review" [Publication Type] OR "Comment" [Publication Type] OR "Editorial" [Publication Type])
AND
("2000/01/01"[pdat] : "3000"[pdat])
10,588 results 8-9-2021

Embase (embase.com) *n.b. copy/paste the search in 'Advanced'. Clear selections.*
('xerostomia'/exp/mj OR (xerostomia* OR hyposaliv* OR 'dry mouth' OR 'mouth dryness' OR 'oral dryness' OR sjogren* OR hyposiali* OR 'salivary gland dysfunct*' OR 'salivary gland hypofunct*' OR 'reduced saliv*'):ab,ti)
AND
('clinical study'/exp OR 'questionnaire'/exp OR 'quality of life'/exp OR 'treatment outcome'/exp OR 'visual analog scale'/exp OR 'biological marker'/exp OR (intervention* OR treatment* OR therap* OR management* OR study):ti OR (random* OR trial* OR 'controlled study' OR 'clinical study' OR cohort OR 'case control' OR prospectiv* OR 'follow-up' OR 'followed up' OR retrospectiv* OR crosssectional* OR 'cross-sectional*' OR questionnair* OR inventory OR 'patient reported' OR outcome* OR survey* OR tool OR tools OR tooling OR scale* OR scaling OR index OR 'Visual Analog Scale' OR 'VAS-scale' OR 'clinician-reported' OR marker* OR biomarker* OR indicator*):ab,ti)
NOT
((('animal'/exp OR 'in vitro study'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp) OR 'conference abstract'/it OR 'conference paper'/it OR 'editorial'/it OR 'review'/it)
AND
[2000-2021]/py

13,371 titles 8-9-2021

CINAHL (EBSCO)
((MH "Xerostomia+") OR TI (xerostomia* OR hyposaliv* OR “dry mouth” OR “mouth dryness” OR “oral dryness” OR sjogren* OR hyposiali* OR “salivary gland dysfunct*” OR “salivary gland hypofunct*” OR “reduced saliv*”) OR AB (xerostomia* OR hyposaliv* OR “dry mouth” OR “mouth dryness” OR “oral dryness” OR sjogren* OR hyposiali* OR “salivary gland dysfunct*” OR “salivary gland hypofunct*” OR “reduced saliv*”))
AND
((MH "Nonexperimental Studies+") OR (MH "Experimental Studies+") OR (MH "Quasi-Experimental Studies+") OR (MH "Questionnaires+") OR (MH "Visual Analog Scaling") OR (MH "Outcomes (Health Care)+") OR (MH "Biological Markers+") OR (MH "Quality of Life+") OR **TI** (intervention* OR treatment* OR therap* OR management* OR study OR random* OR trial* OR “controlled study” OR “clinical study” OR cohort OR “case control” OR prospectiv* OR “follow-up” OR “followed up” OR retrospectiv* OR crosssectional* OR “cross-sectional*” OR questionnair* OR inventory OR “patient reported” OR outcome* OR survey* OR tool OR tools OR tooling OR scale* OR scaling OR index OR “Visual Analog Scale” OR “VAS-scale” OR “clinician-reported” OR marker* OR biomarker* OR indicator*) OR **AB** (random* OR trial* OR “controlled study” OR “clinical study” OR cohort OR “case control” OR prospectiv* OR “follow-up” OR “followed up” OR retrospectiv* OR crosssectional* OR “cross-sectional*” OR questionnair* OR inventory OR “patient reported” OR outcome* OR survey* OR tool OR tools OR tooling OR scale* OR scaling OR index OR “Visual Analog Scale” OR “VAS-scale” OR “clinician-reported” OR marker* OR biomarker* OR indicator*))
AND
PT (Letter OR Masters-Thesis OR Meta-analysis OR Review OR Editorial OR Commentary OR Book OR Book-chapter OR Book-review)
Published Date: 20000101-30001231

3,866 titles 8-9-2021

Cochrane Library, CENTRAL (Trials)
([mh Xerostomia] OR xerostomia*:ti,ab OR hyposaliv*:ti,ab OR dry-mouth:ti,ab OR mouth-dryness:ti,ab OR oral-dryness:ti,ab OR sjogren*:ti,ab OR hyposiali*:ti,ab OR salivary-gland-dysfunct*:ti,ab OR salivary-gland-hypofunct*:ti,ab OR reduced-saliv*:ti,ab)
4451 Trials 8-9-2021 (total result 4547 titles: 93 Cochrane reviews, 2 Protocols, 4451 Trials, 1 Editorial)