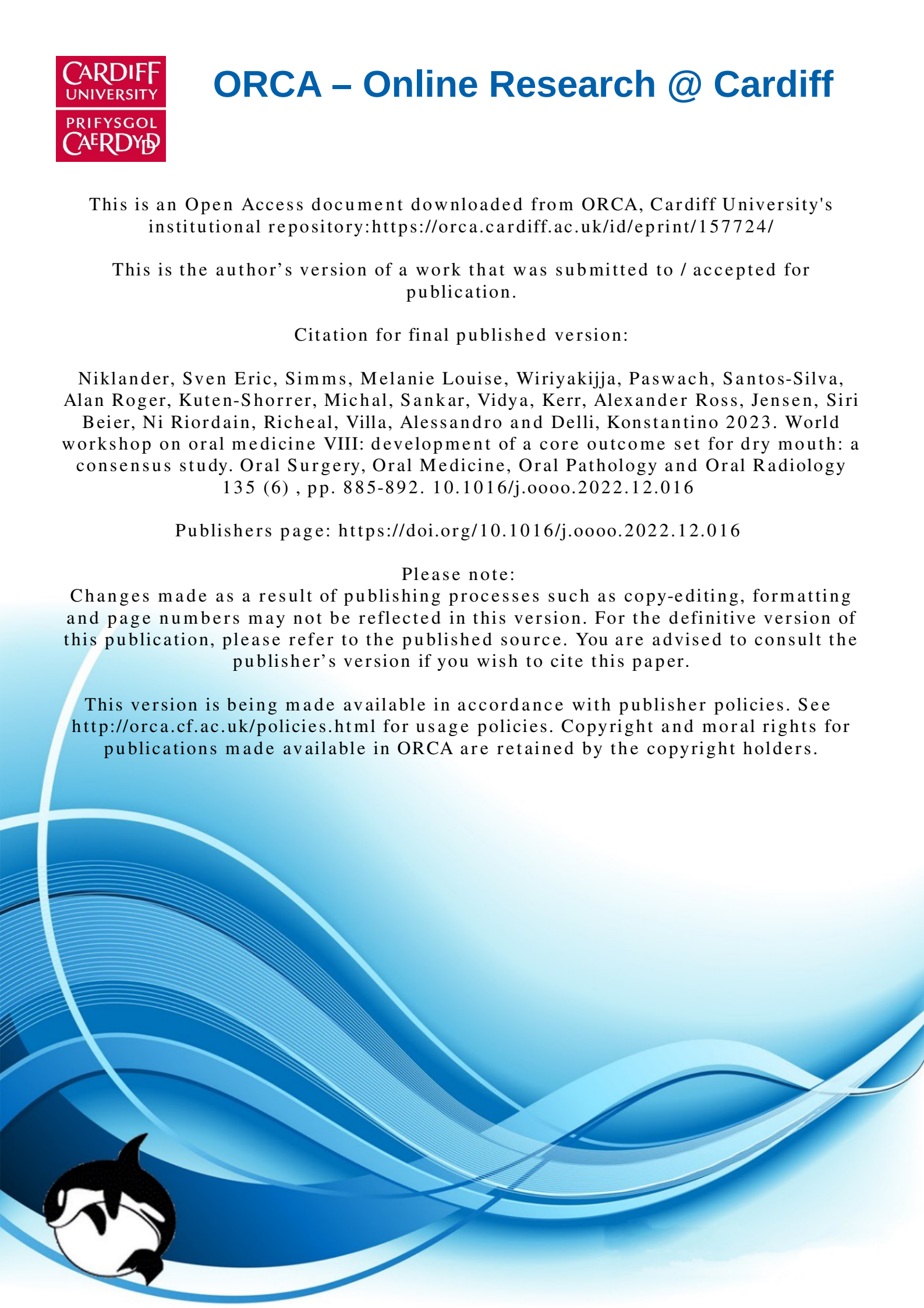

World Workshop on Oral Medicine VIII: Development of a core outcome set for dry mouth: A Consensus Study

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ABSTRACT

Objective: To develop a consensus-based core outcome set (COS) to be used in clinical trials assessing dry mouth interventions.

Study design: Through two systematic reviews of the literature and interviews with dry mouth patients we identified relevant outcome domains for dry mouth assessment. A Delphi survey was presented to health care providers attending the American Academy of Oral Medicine annual meeting in Memphis, Tennessee, USA, May 2022 (n = 104) and ten dry mouth patients at Cork University Dental School and Hospital, Republic of Ireland. Outcome domains for which no consensus was reached were subsequently discussed in a second consensus process led by a virtual Special Interest Group (SIG) of 11 oral medicine experts from the World Workshop on Oral Medicine VIII dry mouth working group.

Results: After the two-step consensus process, consensus was reached for 12 dry mouth outcome domains (salivary gland flow, signs of hyposalivation, mucosal moisture/wetness, severity of xerostomia, duration of xerostomia, overall impact of xerostomia, impact on physical functioning, impact of hyposalivation on general health, impact on social activities, quality of life, economic impact of dry mouth, patient satisfaction) to be included in the final COS.

Conclusion: We propose a consensus-based COS to assess dry mouth interventions in clinical trials. This COS includes the minimum, but mandatory set of domains that all clinical trials evaluating dry mouth treatments should assess.

INTRODUCTION

Dry mouth is one of the most common oral conditions reported worldwide. Dry mouth sensation or 'xerostomia' corresponds to the *subjective* feeling of dry mouth, which may or may not be accompanied by an actual reduction in salivary flow rate. Salivary gland hypofunction and hyposalivation, are the recommended terms to refer to an *objective* decrease in the salivary output.[1] Salivary gland hypofunction designates a saliva flow rate below normal secretion, whilst hyposalivation refers to a diagnosis when saliva secretion becomes pathological low[2] as measured objectively below a cutoff value, i.e. unstimulated whole saliva flow rate ≤0.1 mL/min, and/or stimulated whole saliva flow rate ≤0.5-0.7 mL/min.[2, 3] Although in many cases xerostomia is the consequence of salivary gland hypofunction, these two terms should not be used interchangeably, and should be assessed differently. Not all patients with xerostomia will suffer from salivary gland hypofunction as their symptoms may be secondary to other issues, e.g. changes in the composition of saliva.[4] Equally, patients with salivary gland hypofunction might not experience xerostomia,[5] likely due to habituation.

Over the last few decades, hundreds of clinical trials assessing the effect of different treatment modalities for the improvement of xerostomia and/or salivary gland hypofunction have been carried out. These trials have been analyzed in numerous systematic reviews with or without meta-analysis, and most of them report the same difficulties in comparing results between studies due to the heterogeneity and lack of consistency of the outcomes being measured.[6-10] This problem in dry mouth-related clinical trials is therefore compounded in subsequent clinical recommendations because these often reflect the results and conclusions drawn from systematic reviews and meta-analyses.[11]

To address this issue, the development of a core outcome set (COS) has been recommended.[12] COS are an agreed minimum list of outcome domains to be measured and reported in all trials of a particular treatment of a condition.[13] This does not mean that other outcomes cannot be collected, but the COS defines a minimum standard, with the expectation that the primary outcomes will be contained in the COS.[14] Consequently, the core domains that form part of the COS will be measured consistently in all trials assessing a specific field, e.g., treatment of dry mouth. This will facilitate the combination of trials

in systematic reviews and meta-analyses, improving the quality and validity of the conclusions obtained from these types of studies[11] and consequently specific treatment recommendations could be put into practice.

The Core Outcome Measures in Effectiveness Trials (COMET) Initiative (www.comet-initiative.org), published in 2012, aims to facilitate the development of COS.[14] Once the COS have been defined, it is important to achieve consensus on how these COS should be measured according to the **CO**nsensus-based **S**tandards for the selection of health **M**easurement **IN**struments (COSMIN) initiative (http://www.cosmin.nl/). This project is part of the World Workshop on Oral Medicine (WWOM) Outcomes Initiative for the Direction of Research (WONDER), exploring core outcome measures in effectiveness trials. We aimed to develop a consensus-based COS to be used in clinical trials assessing treatments for dry mouth based on outcome domains used in previous dry mouth studies and on patients' perspectives.

MATERIAL AND METHODS

To develop a COS for reporting dry mouth, we followed the methodology reported by Williamson et al.,[14] which included: Identifying existing knowledge, patient involvement, and consensus process (Figure 1). This study represents the two final stages of a mixed methods study consisting of i) semi-structured interviews, (Santos-Silva et al., under submission) ii) an iterative consensus Delphi survey and iii) a virtual Special Interest Group (SIG) session for discussion. The study was registered in COMET (https://www.cometinitiative.org/Studies/Details/1557).

Identifying existing knowledge

To build a potential list of outcomes to be part of the COS, we conducted two systematic reviews of the literature to identify the outcome domains used in interventional studies to report objective (hyposalivation/salivary gland hypofunction) and/or subjective (xerostomia) dry mouth. Both systematic reviews are reported independently. (Wiriyakijja et al., under submission; Simms et al., under submission)

Patient involvement

To gain patients' perspectives on the outcomes to be incorporated in the COS, we invited patients with dry mouth to participate in focus groups. A total of 20 patients with a diagnosis of dry mouth, older than 18 years, were randomly selected and contacted by telephone between March and April 2022. Only English speakers were considered for the study. There were no other inclusion or exclusion criteria. Out of the 20 patients, 10 consented to take participate to study. Two became unwell the day of the focus groups interviews, thus 8 patients were able to attend the session and were divided in two groups of 4 participants each. The interviews were semi-structured using a specific topic guide and the domains identified from the literature review were discussed at each focus group to ascertain patient feedback and suggestions of missing domains. The result of those interviews is reported in a separate manuscript. (Santos-Silva et al., under submission) In addition, the same 10 patients were later invited to participate in the voting process (see below). The focus groups and patients' voting were conducted at Cork University Dental School and Hospital, Republic of Ireland.

Consensus process

For the Delphi survey, we followed a predefined protocol, based on relevant guidelines.[15, 16] During the WWOM VIII held on May 2nd and 3rd 2022 in Memphis, USA, the outcome domains obtained from the systematic reviews of the literature and patients' interviews were merged to form a Delphi survey with proposed possible outcome domains. A voting process was held on May 6th during The American Academy of Oral Medicine (AAOM) annual meeting in an interactive clicker session using the software Mentimeter (VPAT® Version 2.4).

Using their own mobile phones, each member of the audience was instructed to scan a QR code and access the dry mouth consensus session. Participants were asked to vote on the importance of measuring each of the proposed outcome domains for *every* future trial testing a treatment for dry mouth on a scale of 1-9. Specifically, 1 was considered 'of limited importance', and 9 'of critical importance'. Participants were instructed to vote 7, 8 or 9 if they felt the outcome was essential to assess the treatment

efficacy for dry mouth and that it should be incorporated in the outcome set (i.e. it is an outcome that must be measured in every future dry mouth trial), or to vote in the middle (4, 5 or 6) or low (1, 2 or 3) if they felt the outcome was less important and does not need to be measured in every trial. Scores 1-3 were grouped under the category 'limited importance' (exclude), 4-6 'slight importance' (unsure), and 7-9 'critical importance' (include).[14] The same voting process was repeated later with the same group of ten patients with dry mouth that participated in the focus groups at Cork University Dental School and Hospital in a separate session.

Both patients' and health care providers' response percentages were averaged, and a final score for each category was calculated. Consensus to include an outcome was achieved when at least 70% of the voters (average between patients and stakeholders) agreed that that specific outcome was of critical importance (score 7 or higher) and less than 15% rated it of limited importance (3 or lower).[14] Consensus to exclude an outcome was achieved when 70% or more of the voters considered it of limited importance (score 3 or lower), and less than 15% rated it 7 or higher. All other distributions scores indicated a lack of agreement.[14]

Outcomes for which no consensus was reached during the first voting process (whether to include or exclude) were subsequently analyzed and discussed by a virtual SIG of 11 oral medicine experts from the WWOM VIII dry mouth working group (SEN, MLS, MKS, PW, ARSS, VS, ARK, SBJ, AV, RNR, KD). This second stage of the consensus process was held online on August 29th 2022. The outcome domains where no consensus was previously achieved were discussed by the SIG. Consensus to include an outcome was achieved when 70% or more of the SIG agreed it should be included. Outcomes with an agreement of lower than 70% were not included in the final COS.

The study was carried out in accordance with the Declaration of Helsinki. Ethical approval for this study was granted by the Clinical Research Ethics Committee of the Cork Teaching Hospitals (ECM 3 (rrr) 01/06/2021). Written informed consent was given by all participants.

RESULTS

Twenty-two outcome domains emerged from two systematic reviews (where data from more than 700 papers was extracted and analyzed) (Wiriyakijja et al., under submission; Simms et al., under submission) and from the two patient focus groups. (Santos-Silva et al., under submission) The data was reviewed by the dry mouth working group of the WWOM VIII between June 2021 and May 2022 and the domains were agreed by all members of the group. The proposed list of domains included a large variety of objective and subjective aspects of dry mouth, such as: Salivary gland flow rate, saliva composition and saliva properties, biomarkers, different aspects of xerostomia (severity, duration, and frequency), quality of life, economic impact, among many others (Table I).

The survey was first presented to members ($n \approx 30$) of the WWOM VIII during the World Workshop held in May 2022, and mock voting was performed in order to obtain feedback and adjust terminology or clarify definitions before presenting the domains to a general audience for voting. Minor textual changes were applied, and afterwards the domains were presented to the attendees of the AAOM annual meeting held in Memphis, USA, in May 2022. One hundred and four health care providers took part in this first voting process. Most of the health care providers were from North America (76%), followed by Europe (12%) and Asia (7%). In terms of their occupation, most of the voters were oral medicine specialists (60%), followed by general dental practitioners (12%), practitioners within other dental specialties (12%) and oral medicine trainees (9%) (Table II). The same Delphi survey with the 22 domains was also presented to a group of ten dry mouth patients. After this process, seven domains were voted 7 or higher by more than 70% of the participants, with less than 15% of the remaining votes being 1, 2 or 3, thus consensus to include was achieved and these domains were directly included in the final COS (Table III). No consensus (whether to include or exclude) was obtained with the remaining 15 outcome domains. These domains were analyzed and discussed by the virtual SIG and consensus was reached to include five of the remaining 15 outcome domains (severity of xerostomia, duration of xerostomia, overall impact of xerostomia, impact on physical functioning and quality of life), with 100% of agreement between the panel members (Supplementary Table SI). Thus, the final COS for assessing dry mouth in clinical trials consisted of 12 outcome domains (Table IV).

DISCUSSION

The dry mouth research field is vast and keeps growing rapidly. Just in the US there is an estimate of 24 million persons suffering from dry mouth, with an average cost of $1-$2/person/day.[17] In our recent systematic reviews, we identified over 700 studies that have assessed dry mouth. (Wiriyakijja et al., under submission; Simms et al., under submission) We found a large variety of different outcome measures, which were grouped under more than 20 different outcome domains. No single outcome was found to be consistently reported across all studies. This is a good reflection of the great heterogeneity present in terms of the outcomes assessed in trials reporting dry mouth, highlighting the need for the development of a COS for the study of this condition, which would help in generating more comparable results across studies, minimizing bias and eventually will assist in the development of clinical recommendations.

The availability of COS for assessing oral conditions in clinical trials is very limited. Available COS assess periodontal diseases,[18] symptoms of head and neck cancer treatment,[19] adult oral health,[20] endodontic,[21] and orthodontic treatments,[22] but there are no COS available for reporting dry mouth. The present study, part of the World Workshop on Oral Medicine Outcomes Initiative for the Direction of Research (WONDER) Initiative, has produced a clinician and patient consensus proposal of the outcome domains to be assessed in clinical trials assessing dry mouth.

The validity of this COS is strengthened by the fact that it was developed by an international group of oral medicine experts, following the methodology recommended by COMET and Williamson et al.[14] When averaging the voting results of domains of relevance, patients' and clinicians' results were given the same weight, to make sure that the voice of the patients is not underrated when making treatment decisions, as patients are the final receivers of the interventions clinicians prescribe.[14, 23, 24]

With the employed methodology, it was ensured that the views from every stakeholder, i.e. clinicians, patients, and researchers, were included when making the final decision regarding the COS, therefore, the domains included in this COS adequately represent what clinicians and patients believe is of

importance to assess in clinical trials of dry mouth interventions. For several domains, such as salivary gland flow rate, signs of hyposalivation, mucosal moisture and patient satisfaction, there was direct agreement between patients and health care providers from the first round of consensus that these domains should be included in the final COS. Other domains, such as economic impact of dry mouth and impact on social activities, usually not considered as outcome measures by clinicians in clinical trials (Wiriyakijja et al., under submission) were considered very important by patients as evidenced during the focus groups. (Santos-Silva et al.,) These domains were included in the final COS due to averaging the results and to the equal weight given to patients and health care professionals votes. Similarly, domains such as severity, duration, overall impact of xerostomia, impact on physical functioning and quality of life, commonly assessed in dry mouth trials and voted to be included by health care providers, were not considered by patients. These domains were also finally included into the COS due to the importance given to them by clinicians.

There could be other domains that might be of importance for specific dry mouth trials, but these were not included in this COS. This COS defines a minimum set of outcomes that every clinical trial should report to reduce heterogeneity across studies, but this does not mean that any other domains cannot be measured in addition to the ones from the COS. Domains such as biomarkers, impact of hyposalivation on oral health, saliva properties, among others, might be of importance for specific studies and should then be reported if appropriate, but were considered too specific for their assessment in every clinical trial.

Intentionally, we did not describe in the COS how these domains should be measured. In our systematic reviews, hundreds of different instruments were identified to measure these outcome domains. Many of these instruments have been validated through robust validation processes, but others have not. Several have been used by many studies and are well known by the scientific community, but others have been used by only a small number of studies and/or ad hoc. Many have been translated and validated in different languages, whereas others are only available in their original languages, or the translational process has not been validated. (Wiriyakijja et al., under submission; Simms et al., under

submission) The selection of the measurement instruments is a complex process and should follow a structured methodology considering the available literature, stakeholders views, and a consensus process. There are specific guidelines that have been developed for this purpose,[13, 25] and will be part of the future work of the WONDER Initiative.

Despite the rigorous development process of this COS, this study had some limitations. Involving patients in the process is a major strength and an important part of data collection. However, all patients came from a single institution and therefore the generalizability of the findings may be limited as it can be argued that patients' answers can vary between institutions. Nevertheless, this is unlikely to have any global effect when applying this COS in clinical trials, as the other stakeholders' views were also considered, and the final decision whether to include or exclude, where no consensus was reached, was made by the SIG in unanimous decision. Furthermore, patients were well represented, accounting for 50% of the weight of the final score. In addition, the proposed COS can be considered lengthy, as it includes 12 outcome domains to measure. Assessing these 12 outcome domains in a single trial, however seems feasible, since all domains included in this COS can be expeditiously measured in routine clinical settings using visual analogue scales (VAS),[26-28] validated questionnaires,[29-33] simple saliva collecting techniques,[27, 34, 35] among others, without the need of special training or special equipment. Therefore, the application of this COS in clinical trials should be feasible for either dental or non-dental health care professionals. Nevertheless, COS should be reviewed periodically as a form of validation to ensure outcomes are still relevant and to evaluate how successful implementation has been.[14, 22] If implementation of this COS is found to be difficult due to its length, it can be subsequently revised.

CONCLUSION

This project, part of the WONDER Initiative, has produced the first consensus-based core outcome set to be used in clinical trials assessing treatments for dry mouth. Its development was an international expert collaboration following a strict methodological process. This core outcome set includes the minimum, but mandatory set of domains that all future clinical trials evaluating dry mouth should

assess. It will contribute to assure that the most relevant aspects of this condition are evaluated in all trials, which would make trials more comparable and facilitate data synthesis in meta-analyses, with the final aim of improving treatment recommendations for patients.

DISCLOSURE OF CONFLICT OF INTEREST

The authors state that they have no conflict of interest.

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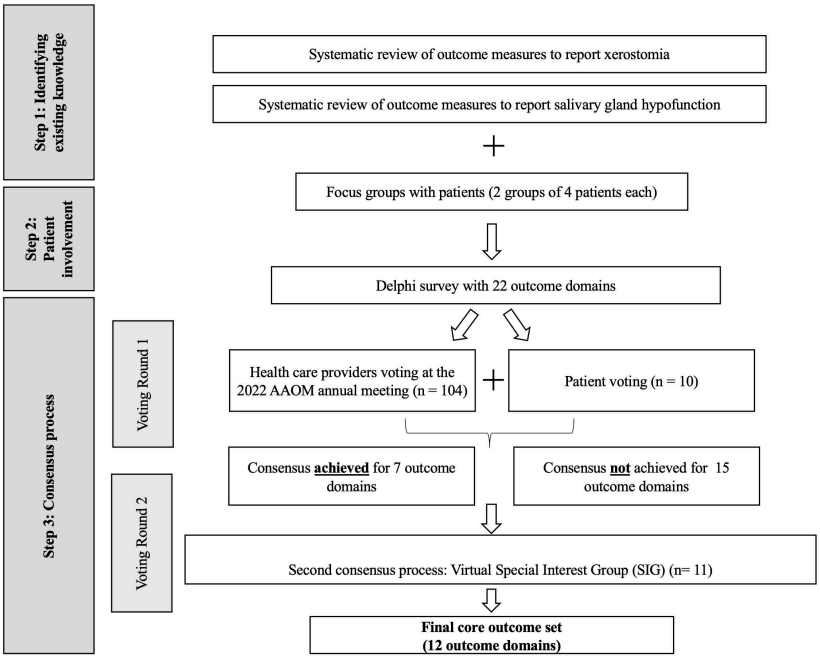
Figure 1. Flow diagram for the development of a core outcome set (COS) for reporting dry mouth in clinical trials.



AAOM: American Academy of Oral Medicine.

Table I. Preliminary domains identified from two systematic reviews of the literature and patient interviews. (Wiriyakijja et al., under submission; Simms et al., under submission; Santos-Silva et al., under submission)

Domain	**Examples**
Salivary gland flow rate	
Gland-specific or region-specific saliva	
Saliva composition	Electrolytes, enzymes
Saliva properties	Stringiness, stickiness
Signs of hyposalivation	Depapillation of the tongue
Mucosal moisture/wetness	
Salivary gland abnormalities via imaging	
Biomarkers	Blood and salivary biomarkers
Severity of xerostomia	
Duration of xerostomia	
Frequency of xerostomia	
Presence and variability/fluctuation of xerostomia over time	
Location of xerostomia	
Overall impact of xerostomia	
Impact on physical functioning	
Impact on social activities	
Impact on psychological functioning	Mood
Quality of life	Interference with daily activities
Patient satisfaction	
Impact of hyposalivation on oral health	Caries
Impact of hyposalivation on general health	
Economic impact (costs) of dry mouth	

Table II. Demographics of health care providers that participated in the voting process during AAOM 2022 annual meeting.

	N	%
Location[#]		
North America	72	75.8
South America	3	3.2
Europe	11	11.6
Asia	7	7.4
Africa	1	1.1
Australia	1	1.1
Professional position[*]		
Oral Medicine Specialist (in university or hospital setting)	50	50.5
Oral Medicine Specialist (private practice)	9	9.1
Oral Medicine Trainee/Resident	9	9.1
General dentist/practitioner	12	12.1
Other dental specialty	12	12.1
Allied healthcare (e.g., dental hygienist)	2	2.0
Industry/Pharma	0	0.0
Researcher in other specialty	1	1.0
Other	4	4.0

95/104 participants responded
* 99/104 participants responded
AAOM: American Academy of Oral Medicine

Table III. Voting results from health care providers attending the AAOM 2022 annual meeting and dry mouth patients.

	AAOM voting				Patients' voting				Average		
Consensus to include	**Exclude (%)**	**Unsure (%)**	**Include (%)**	**Nº**	**Exclude (%)**	**Unsure (%)**	**Include (%)**	**Nº**	**Exclude (%)**	**Unsure (%)**	**Include (%)**
Salivary gland flow rate	0.0	6.9	93.1	102	0	2	80	10	0.0	4.4	86.6
Signs of hyposalivation	5.9	9.8	84.3	102	0	10	90	10	2.9	9.9	87.2
Mucosal moisture/wetness	6.9	11.9	81.2	101	0	10	90	10	3.5	10.9	85.6
Patient satisfaction	3.0	8.9	88.1	101	0	10	90	10	1.5	9.5	89.1
Impact of hyposalivation on general health	12.0	21.0	67.0	99	0	0	100	10	6.0	10.5	83.5
Economic impact of dry mouth	22.2	31.5	46.3	54	0	0	100	10	11.1	15.74	73.15
Impact on social activities	8.8	24.5	66.7	102	0	20	80	10	4.4	22.25	73.35
No consensus to include or exclude											
Saliva composition	29.1	29.1	41.8	103	50	20	30	10	39.6	24.55	35.9
Salivary gland abnormalities via imaging	35.9	39.8	24.3	103	40	50	10	10	38.0	44.9	17.15
Location of xerostomia	44.7	31.1	24.3	103	70	30	0	10	57.4	30.55	12.15
Severity of xerostomia	1.0	4.0	95.1	101	0	70	30	10	0.5	36.98	62.525
Duration of xerostomia	4.9	18.5	76.7	103	30	70	0	10	17.4	44.225	38.35
Overall impact of xerostomia	1.0	12.5	86.5	104	20	50	30	10	10.5	31.25	58.27
Impact on physical functioning	2.9	8.7	88.4	103	10	80	10	10	6.5	44.37	49.175
Quality of life	2.0	7.8	90.2	102	20	40	40	10	11.0	23.92	65.1
Gland-specific or region-specific saliva	17.5	37.9	44.7	103	80	10	10	10	48.8	23.95	27.35
Saliva properties	11.8	24.5	63.7	102	40	50	10	10	25.9	37.25	36.85
Biomarkers	24.3	29.1	46.6	103	40	50	10	10	32.2	39.55	28.3
Frequency of xerostomia	5.8	24.0	70.2	104	60	40	0	10	32.9	32	35.1
Presence and variability/fluctuation of xerostomia over time	5.9	34.3	59.8	102	60	40	0	10	33.0	37.15	29.9
Impact on psychological functioning	8.8	26.5	64.7	102	40	50	10	10	24.4	38.25	37.35
Impact of hyposalivation on oral health	12	21	67	99	0	40	60	10	6.0	30.5	63.5

№: Number of voters, AAOM: American Academy of Oral Medicine. The discrepancies observed in the numbers of AAOM voters between domains is because not all 104 participants answered all questions during the voting process.

Table IV. Final core outcome set (COS) (in alphabetical order) to be included in all clinical trials assessing dry mouth.

Outcome domain
Duration of xerostomia
Economic impact of dry mouth
Impact of hyposalivation on general health
Impact on physical functioning
Impact on social activities
Mucosal moisture/wetness
Overall impact of xerostomia
Patient satisfaction
Quality of life
Salivary gland flow rate
Severity of xerostomia
Signs of hyposalivation

Supplementary Table SI. Results of the consensus process (second voting) conducted by a SIG of experts of the WWOM VIII dry mouth working group of the domains that did not achieve consensus after the voting process during the AAOM 2022 meeting.

Domains	Include Nº	Exclude Nº	Total Nº
Consensus to include			
Severity of xerostomia	11	0	11
Duration of xerostomia	11	0	11
Overall impact of xerostomia	11	0	11
Impact on physical functioning	11	0	11
Quality of life	11	0	11
Consensus to exclude			
Frequency of xerostomia	0	11	11
Location of xerostomia	0	11	11
Gland-specific or region-specific saliva	0	11	11
Impact of hyposalivation on oral health	0	11	11
Saliva properties	0	11	11
Impact on psychological functioning	0	11	11
Presence and variability/fluctuation of xerostomia over time	0	11	11
Biomarkers	0	11	11
Saliva composition	0	11	11
Salivary gland abnormalities via imaging	0	11	11

Nº: Number of voters, WWOM: World Workshop on Oral Medicine