Research Study Protocol Synopsis

Study title	A retrospective observational study on characteristics, treatment patterns, and healthcare resource use of patients with xerostomia in primary care settings using Optimum Patient Care Research Database in United Kingdom.
Protocol number	COGA2002
Version & Date	V1.1 19 November 2021
Study Sponsor	Colgate Palmolive (UK) Limited
Chief Investigator	Professor David Price dprice@opri.sg
Study Management Company	OPEN Health The Weighbridge, Brewery Courtyard High Street Marlow, SL7 2FF
Country of study	UK
PASS?	No

Rationale and background

Xerostomia, also known as dry mouth, is defined as a subjective complaint of dry mouth that may result from a decrease in the production of saliva(1,2). It is more prevalent in older populations over 60 years of age. The prevalence of xerostomia in population-based studies ranges from 10% to 46%, with a generally lower prevalence in men (9.7% –25.8%) than women (10.3% –33.3%) (1,3,4). Symptoms of xerostomia include halitosis, oral soreness and burning, difficulty swallowing and talking, and altered taste (1).

Besides being associated with ageing (5), xerostomia sometimes occurs as an adverse effect of certain medications i.e., anticholinergic agents, antidepressant and antipsychotic agents, diuretic agents, antihypertensive agents, sedative and anxiolytic agents, muscle relaxant, analgesic agents, antihistamines, chemotherapy, and immunotherapy (5–7); or as a consequence of radiation therapy of the head and neck regions for cancer (6). Xerostomia can also be associated with underlying conditions such as Alzheimer's, stroke, Sjogren's syndrome, connective tissue diseases, human immunodeficiency virus infection (HIV)/ acute immunodeficiency syndrome (AIDS), and diabetes mellitus (4). Moreover, recreational drug use (i.e., methamphetamine) can cause severe xerostomia (8). Less often, xerostomia may be caused by conditions that directly affects the salivary glands, i.e., salivary gland hypofunction (SGH) (1,6).

Saliva helps prevent tooth decay by neutralising acids produced by bacteria, limiting bacterial growth and washing away food particles. Xerostomia significantly increases the risk of experiencing dental caries, demineralisation, tooth sensitivity, candidiasis, and other oral diseases that may negatively affect quality of life (6,9). Despite the significant prevalence of xerostomia in the general population, no standard treatment guidelines exist (10).

Currently, xerostomia is predominantly managed by general practitioners. Comprehensive management of xerostomia includes various palliative and preventive measures, including pharmacological treatment with salivary stimulants (such as pilocarpine), artificial saliva substitutes, topical fluoride interventions, and the use of sugar-free chewing gum to relieve dry-mouth symptoms and improve the patient's quality of life (1,9).

Toothpaste is the most common way to introduce fluoride into the daily oral health regime and reduce the risk of caries, with higher concentrations of fluoride than that available over the counter available on prescription for patients who are at high risk of experiencing xerostomia induced dental caries (9,11,12). The maximum concentration of fluoride-containing toothpaste that can be purchased over-the-counter in the UK is 1,500 ppm fluoride (12).

Prescription high fluoride toothpaste can help patients effectively prevent and control caries (13–17). A Cochrane review study found that there was less new decay when toothbrushing with toothpaste containing 1,000 to 1,250 ppm or 1,450 to 1,500 ppm fluoride compared with non-fluoride toothpaste, and that toothbrushing with 1,450 to 1,500 ppm fluoride toothpaste reduced the amount of new decay more than 1,000 to 1,250 ppm toothpaste (13). This is a simple, evidenced-based means for helping patients with increased risk of developing dental caries (i.e., xerostomia patients) avoid additional caries onset or progression (12).

A cross-sectional study (n=2,147) conducted among participants of British Regional Heart Study, a prospective study in middle-aged men (n=7,735) drawn from general practices in 24 British towns,

provided novel information on the burden of oral health among older British male population (18). In relation to xerostomia, a third of participants reported (via questionnaire) that their mouth felt dry, and a third reported one or two symptoms of dry mouth. Notably, the study showed a very high prevalence (73%) of oral health problems occurring in combination, such as problems with teeth/gums along with difficulty eating and dry mouth. However, the study was limited to older white men. As xerostomia is a common condition in both genders (1) and affects quality of life of younger adults (19) as well as elderly individuals (20), it is important to understand burden of the disease in both genders and different age groups and ethnicities in the UK. Real-world evidence on the burden of dental caries in xerostomia patients would further emphasise the need for preventive strategies in the group of patients and raise awareness among physicians (1).

The rationale for the study is to provide evidence on the burden of xerostomia, patients' characteristics, comorbidities, treatments susceptible to cause xerostomia, treatment for xerostomia, and healthcare resource use that may highlight the unmet need in this patient population in the UK. Evidence from this study will be used to discuss the importance of dental caries prevention with clinicians and payers and may be used to support the development of xerostomia patient management guidelines.

Key definitions and study time period(s)

Study observation period: Study observation period starts at 1st April 2015 and ends on 31st March 2020.

Patient eligibility period: The period from 1st April 2016 to 31st March 2019 (allowing at least one year pre- and post-index time).

Index event: Patients with a first recorded diagnosis of xerostomia during the patient eligibility period.

Index date: The index date will correspond to the date of first ever diagnosis of xerostomia during study eligibility period.

Table 1. Read and SNOMED codes for xerostomia in OPCRD

Read code	Description
1927.	Xerostomia
Ryu78	Dry mouth, unspecified (old)
XE0aC	Clinical Xerostomia
X20T4	Drug-induced xerostomia
X20PI	Xerostomia-related dental caries
SNOMED code	
87715008	Xerostomia
235130007	Drug-induced xerostomia
403730001	Xerostomia caused by ionizing radiation
707297005	Xerostomia due to autoimmune disease
707296001	Xerostomia due to dehydration
95249000	Salivary dysfunction dental caries

707256003	Xerostomia due to mouth breathing
707296001	Xerostomia following radiotherapy
707256003	Xerostomia due to hyposecretion of salivary gland

Pre-index observation period (baseline): The baseline observation period for each patient will be the time prior to index date, commencing at the most recent of: date of patient's registration into the database or start of the observational period of 1st April 2015, and ending on index date.

Post-index observation period (follow-up): Time period from index date until the earliest of the following: end of the observational period on 31st March 2020, deregistration from the database (due to relocation), or death.

Figure 1 shows the key elements of the study design and time periods in Appendix 1.

Research question and objectives

This is a descriptive study and there is not a prior hypothesis to be tested. The general aim of the study is to gain a better understanding of the xerostomia patients, in terms of their characteristics, treatment patterns, and burden in primary care including primary healthcare resource use and associated costs.

The objectives of the study are:

Primary objective

- To describe patients newly diagnosed with xerostomia in terms of their socio-demographic characteristics, comorbidities, and treatments susceptible to cause xerostomia prior to index date.

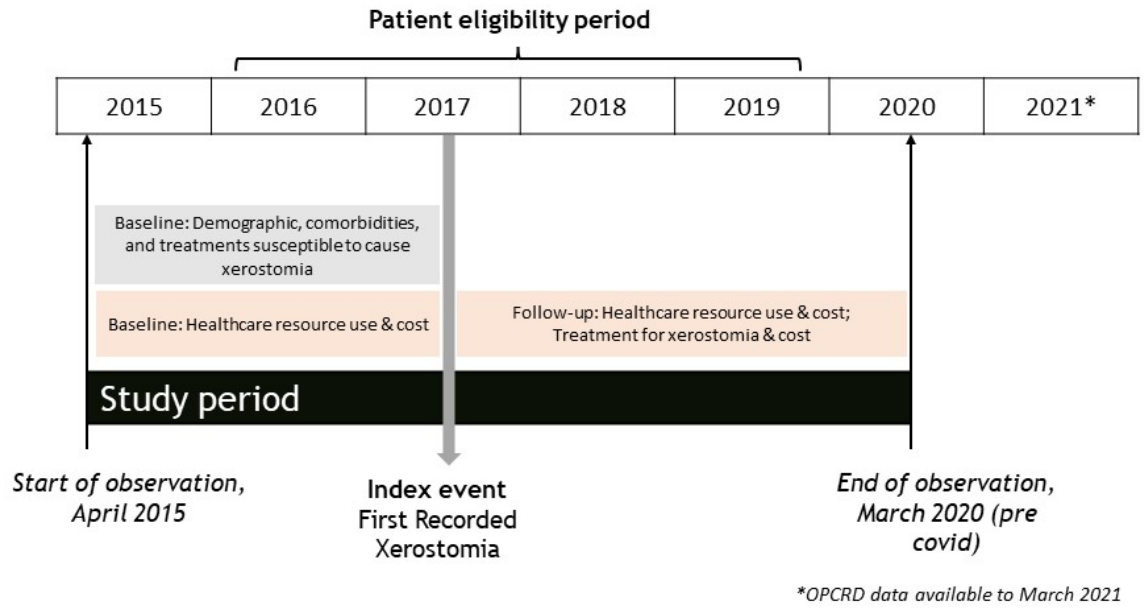
Secondary objectives

- To describe treatment for xerostomia and associated costs, post-index date.
- To describe primary healthcare resource use and associated costs, pre- and post-index date in patients with xerostomia.

Study design

This is a retrospective observational cohort study based on the Optimum Patient Care Research Database (OPCRD) and includes newly diagnosed patients with xerostomia during the study period in UK.

Figure 1. Study design and observation periods



Setting

The source population for this study is all patients registered in OPCRD during the observation period.

OPCRD is a longitudinal, real-world, research database that holds de-identified patient data from over 900 general practices. OPCRD contains de-identified primary care electronic health records (EHR) of over 14 million patients, representing approximately 20% of the UK population. The data collected includes demographic information, diagnoses, symptoms, treatments, and prescriptions issued, test results and measurements and results taken in the practice and referrals. Both clinical data and therapy data are coded using Read or SNOMED CT codes (drug codes were previously coded using British National Formulary codes).

https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/optimum-patient-care-research-database-opcrd/

Patients fulfilling the following criteria will be eligible for inclusion in the study:

Inclusion criteria

- Patients with a first record of a diagnosis of xerostomia or dry mouth during the study eligibility period (see Table 1 for code list)

Exclusion criteria

- Patients with <12 months baseline data prior to index date
- Patients with <12 months follow-up data post index date
- Patients <16 years old

Patient with at least one-year electronic medical records data available pre- and post-index date will be included. Xerostomia is not common in children and toothpastes containing higher concentrations of fluoride are not recommended for ages below 16, hence patients <16 years old are excluded from this study.

Patient selection

All eligible xerostomia patients will be included in the study.

Variables

Endpoints to address the primary and secondary objectives pre- and post- index date (see Appendix 3) include:

Primary endpoint

Patients' demographic (pre-index date):

- Age at index date
  - Further categorised into age groups 16-49, 50-59, 60-69, 70-79, ≥80 years old
- Gender
- Ethnicity
- Index of multiple deprivation
- Smoking status (most recently recorded prior to index date)
- Weight (most recently recorded prior to index date)

Patients' comorbidities (pre-index date):

- Charlson Comorbidity Index (CCI) score: The CCI will be calculated from the patient's age at the index xerostomia diagnosis by deriving it from the Metcalfe methodology (21)
- Xerostomia-related comorbidities recorded during the baseline period
  - Sjogren's syndrome
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
  - Systemic sclerosis
  - Mixed connective tissue disease
  - Primary biliary cirrhosis
  - Vasculitis
  - Chronic active hepatitis
  - Alzheimer's disease
  - Stroke
  - Anxiety or depression

- Diabetes, Type 1 or 2

- Specific dental symptoms: dental abscess, dental caries, denture unstable (if available)

Treatments susceptible to cause xerostomia prior to index-date (frequency of treatment) (if available):

- Anticholinergic agents
- Antidepressant and antipsychotic agents
  - Selective serotonin-reuptake inhibitors
  - Tricyclic antidepressant
  - Heterocyclic antidepressants
  - Monoamine oxidase inhibitors
  - Atypical antidepressants
- Diuretic agents
- Antihypertensive agents
- Sedative and anxiolytic agents
- Muscle relaxant
- Analgesic agents
  - Central nervous system/opioids
  - Nonsteroidal anti-inflammatory agents
- Antihistamines
- Antiasthma drugs
- Cardiovascular drugs
- Radiation therapy
- Chemotherapy
- Immunotherapy
- Renal dialysis

Secondary endpoints

Treatments for xerostomia and associated costs:

- Treatments prescribed in primary care for xerostomia (time on treatment, frequency of treatment) post-index date
  - Artificial saliva
  - Saliva stimulants
  - Sialagogues: pilocarpine, cevimeline
  - Oral lubricants/moisturisers
  - High fluoride toothpaste
- Cost of treatments for xerostomia post-index date

Health care resource use and associated costs:

- Visits to general practitioners, nurses, and/or healthcare allied professionals, overall and by type of practitioner pre- and post-index date
- Referral into secondary care (dental care) where xerostomia recorded, post-index date (if available)
- Cost of primary healthcare use using standard visit fees pre- and post-index date

The key data collection variables and time points required to address the study endpoints are listed in Appendix 3.

Data source

All study subjects and predictors will be identified from the Optimum Patient Care Research Database (OPCRD).

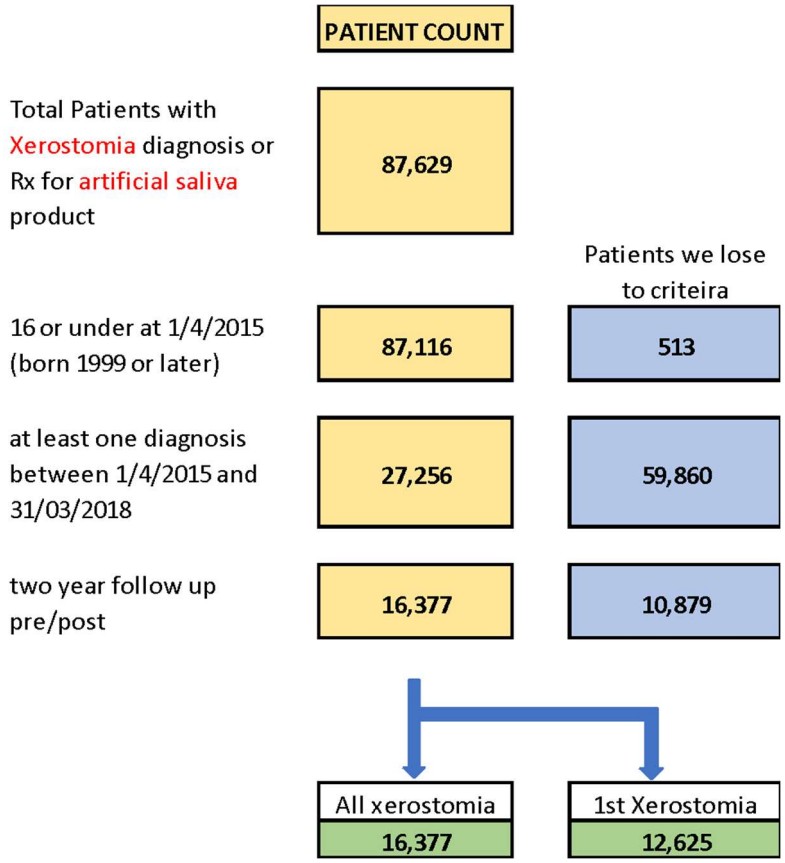
All data underwent quality control at OPCRD. The NHS Health Research Authority has approved OPCRD for clinical research purposes (Research Ethics Committee reference: 20/EM/0148) (22). https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/optimum-patient-care-research-database-opcrd/

Study size

All patients eligible to participate into the study will be included. The study is descriptive, therefore formal sample size estimates are not required. The sample size is based on data availability rather than statistical considerations.

A feasibility query conducted in OPCRD from April 2015 to March 2018 found 12,625 newly diagnosed xerostomia/dry mouth adult patient with at least two years follow-up pre/post-index date (out of 16,377 patients recorded as xerostomia/dry mouth or having prescription for artificial saliva as a proxy for xerostomia) (Figure 2, Appendix 2). A minimum of 178 newly diagnosed xerostomia patients out of 12,625 were identified with a prescription of one and/or several types of high fluoride toothpaste (Colgate Duraphat 2800: n=46, Colgate Duraphat 5000: n=115, Sodium Fluoride 0.619% dental paste: n=44).

Figure 2. Feasibility query: Number of patients with xerostomia diagnosis or Rx for artificial saliva product as a proxy for xerostomia



Data analysis

All statistical analyses will be documented in a formal statistical analysis plan (SAP) that will be finalised prior to database lock. All analyses will be descriptive. Distributions and descriptive statistics of central tendency (medians and arithmetic means) and dispersion (standard deviation, interquartile range, and range) will be presented for quantitative variables wherever possible. Categorical variables will be described with frequencies and percentages. No statistical comparisons will be performed between groups. As patients' follow-up will likely differ between patients, healthcare resource use and cost will be expressed per person-years, using all person-years at risk for each patient.

Costs for primary care activity and delivery of treatment will be derived from the BNF Drug Costs for cost treatment, and National Health Service (NHS) reference costs in Personal Social Services Research Unit (PSSRU) for activity (23–25).

Ethical and regulatory considerations

This study will comply with all applicable laws, regulations, and guidance regarding patient protection including patient privacy, and consistent with the ethical principles of the Declaration of Helsinki (26) and the requirements of the European Union General Data Protection Regulation (GDPR) (27).

This study has been designed and will be conducted according to the requirements of ENCePP (28) and International Society for Pharmacoepidemiology (ISPE) (29) guidance for Good Pharmacoepidemiology Practices, as appropriate. Permission for the current study will be requested from the Anonymous Data Ethics Protocols and Transparency committee (ADEPT). All research using OPCRD must be registered on established study databases such as the ENCePP as a requirement of ADEPT.

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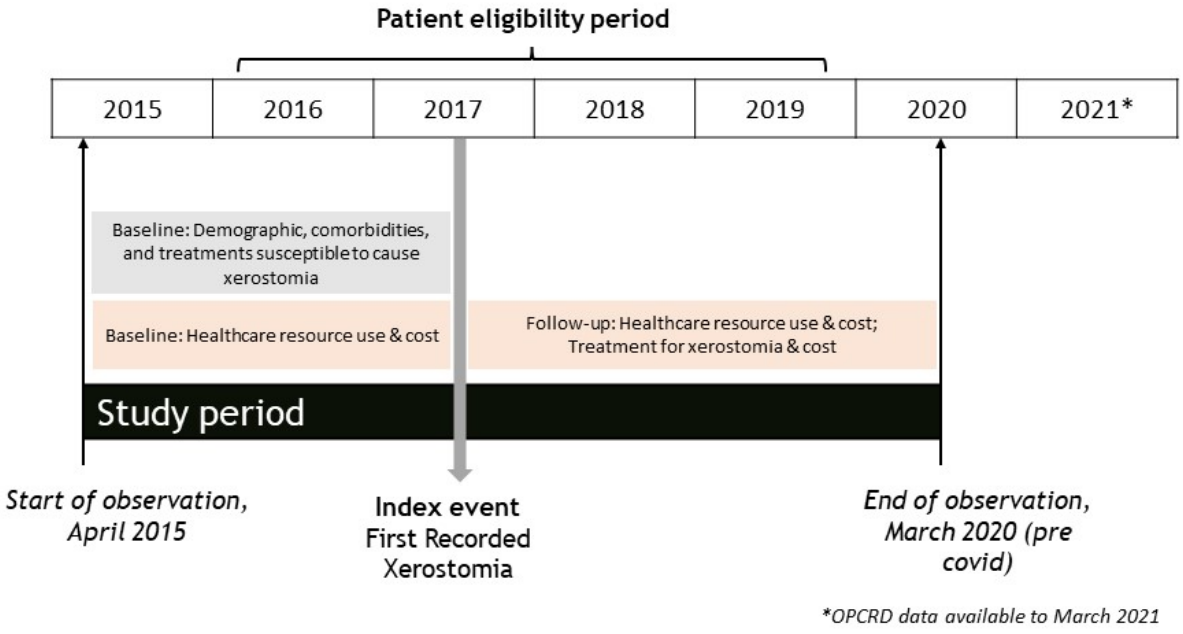
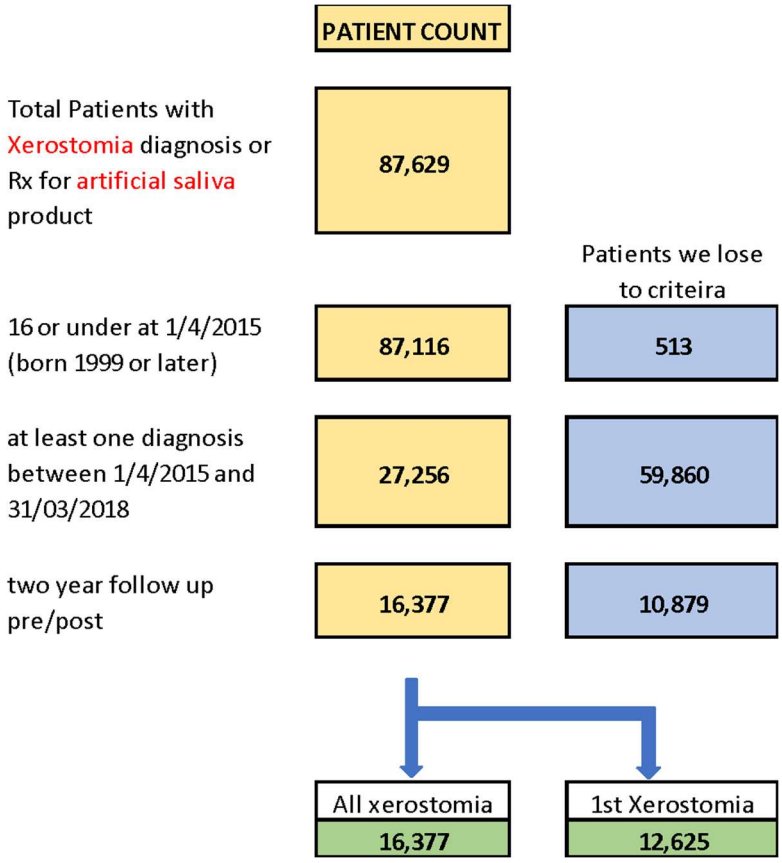
Appendix 1. Study design figure

Figure 1. Study design and observation periods



Appendix 2. Sample size calculation

Figure 2. Feasibility query: Number of patients with xerostomia diagnosis or Rx for artificial saliva product as a proxy for xerostomia



Appendix 3. Data collection variables and study time points

Table 2. Summary of data collection variables and study time points

Data collection variables	Study time points		
	Pre-index observation period	Index date	Post-index observation period Other
Age		✓	
Gender		✓	
Ethnicity		✓	
Weight	✓		
Smoking status	✓		
Index of multiple deprivation	✓		
Charlson comorbidity index	✓		
Comorbidities including Sjogren's syndrome, Rheumatoid arthritis, Systemic lupus erythematosus, Systemic sclerosis, Mixed connective tissue disease, Primary biliary cirrhosis, Vasculitis, Chronic active hepatitis, HIV/AIDS, Alzheimer's disease, Stroke, Anxiety or depression, Diabetes (Type 1 or 2)	✓		
Dental symptoms	✓		
Treatments susceptible to cause xerostomia (frequency) including ● Anticholinergic agents ● Antidepressant and antipsychotic agents ○ Selective serotonin-reuptake inhibitors ○ Tricyclic antidepressant ○ Heterocyclic antidepressants ○ Monoamine oxidase inhibitors ○ Atypical antidepressants ● Diuretic agents ● Antihypertensive agents ● Sedative and anxiolytic agents ● Muscle relaxant ● Analgesic agents ○ Central nervous system/opioids ○ Nonsteroidal anti-inflammatory agents ● Antihistamines	✓		

• Antiasthma drugs • Cardiovascular drugs • Radiation therapy • Chemotherapy • Immunotherapy • Renal dialysis			
Visits to general practitioners, nurses and/or healthcare allied professionals, overall and by type of practitioner	✔		✔
Associated costs for primary HCRU using standard visit fees	✔		✔
Treatments prescribed for xerostomia in primary care (time on treatment, frequency of treatment) grouped as: • Artificial saliva • Saliva stimulants • Sialogogues: pilocarpine, cevimeline • Oral lubricants / moisturizers • High fluoride toothpaste			✔
Referral into secondary care (dental care)			✔