CADTH Optimal Use Report

Interventions for the Treatment of Obstructive Sleep Apnea in Adults: A Health Technology Assessment – Project Protocol

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Khai Tran[1]
Joanne Kim[1]
Bernice Tsoi[1]
Tamara Rader[1]
Sarah Garland[1]
Katherine Duthie[2]
Ken Bond[1]
Kelsey Seal[1]
Dr. Fernanda Almeida[3]
Lt. Col. Glenda Ross[4]
Major Roch Messier[4]

[1] CADTH, Ottawa, Ontario
[2] Alberta Health Services, Edmonton, Alberta
[3] University of British Columbia, Vancouver, British Columbia
[4] Canadian Armed Forces

CADTH

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The information in this report is intended to help health care decision-makers, patients, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. The information in this report should not be used as a substitute for the application of clinical judgment in respect to the care of a particular patient or other professional judgment in any decision-making process, nor is it intended to replace professional medical advice. While CADTH has taken care in the preparation of this report to ensure that its contents are accurate, complete, and up-to-date, CADTH does not make any guarantee to that effect. CADTH is not responsible for any errors or omissions or injury, loss, or damage arising from or as a result of the use (or misuse) of any information contained in or implied by the information in this report.

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RATIONALE AND POLICY ISSUES

Obstructive sleep apnea (OSA) is a common disorder characterized by repetitive awakening from sleep due to obstruction of the upper airway. A 2009 Canadian survey reported that 3% of Canadian adults were diagnosed with sleep apnea, making it as common as hypertension or diabetes.[1,2] The prevalence is likely higher, with more than one in four adults presenting symptoms and factors associated with having or developing OSA.[1,3] Its major symptoms include unrefreshing sleep, excessive daytime sleepiness, lack of concentration, and decreased memory and quality of life.[3,4] Aging, the male sex, and obesity are its main risk factors.[5,6] Untreated OSA is associated with motor vehicle accidents, stroke and other cardiovascular diseases, hypertension, diabetes, cognitive dysfunction, and all-cause mortality.[1,3,7-9] Untreated OSA is also a known surgical risk and can give rise to cardiovascular and pulmonary complications.[10]

Treatment of OSA includes a wide range of options.[11] Positive airway pressure (PAP) devices and various oral appliances splint the airways open to facilitate airflow. Continuous positive airway pressure (CPAP) forces air into the upper airways to prevent soft tissues from collapsing and is considered the gold standard for the treatment of OSA.[11-13] Other PAP technologies, such as autotitrating PAP (APAP) and bilevel PAP (BiPAP), may be offered to patients with specific needs.[11,12,14] An alternative treatment for OSA other than CPAP is nasal expiratory PAP (EPAP), which is a disposable device that uses a patient's own breathing to create positive end-expiratory pressure the prevents obstructive breathing.[14] Oral appliances including mandibular advancement devices (MADs), also known as mandibular advancement splints or dental devices, and tongue-retaining devices can be offered as an alternative to CPAP.[12,15,16] For patients with mild or asymptomatic OSA, lifestyle interventions such as exercise programs, diet changes, and positional therapies may be proposed before proceeding to other interventions.[17] Surgeries may be indicated for patients with a defined anatomical obstruction or morbid obesity, or as alternatives in cases where other interventions cannot be considered or have failed.[18,19]

Therapy selection is based on an assessment of the patient by lab-based polysomnography (PSG) or home-based portable monitors.[20] The goal is to establish the Apnea–Hypopnea Index (AHI), accounting for the number of events per hour, which can be used to stratify OSA severity.[12] The AHI correlates with the risk of various cardiovascular outcomes, including hypertension, as well as all-cause mortality,[3,6,8,20,21] and can also be used to determine the effectiveness of interventions intended to treat OSA. As a general rule, the therapeutic effect size is proportional to the severity of OSA.[7,8] Other diagnostic measurements include the respiratory disturbance index (RDI) and time spent at oxygen saturation (S_{pO2}) < 90%,[5] as well as the Epworth Sleepiness Scale (ESS).[12] Despite the positive outlook of CPAP as the gold standard, between 29% and 83% of patients ultimately fail to comply to regular device use,[2,22,23] which limits its impact. In fact, low CPAP compliance is associated with significantly higher mortality.[2] Compliance of MADs is not as well documented but is regarded as being similar to CPAP.[24,25] Therefore, patient compliance may be a factor in therapy selection and effectiveness. Furthermore, while OSA interventions have shown effectiveness at reducing score on the AHI and sleepiness, no large randomized controlled trial (RCT) has yet demonstrated benefits on cardiovascular outcomes or mortality.[26]

Across jurisdictions, OSA is associated with a substantial economic and societal burden.[5,6,27] A cross-sectional study[28] in the United States (US) found that, in the year prior to the diagnosis of OSA, the mean annual medical cost per patient was $2,720 for OSA cases, versus $1,384 for age- and sex-matched controls. In the US, OSA was established as the cause of 800,000 motor

vehicle accidents in 2000, for a total of 1,400 deaths and a cost of $15.9 billion to society.[6,29] In Australia, the total impact of managing sleep disorders — including direct hospital and non-hospital costs, as well as the costs of associated conditions, such as stroke, heart diseases, depression, and accidents — was estimated at $818 million in 2010.[30] In Canada, the Assistive Devices Program within Ontario's Ministry of Health and Long-Term Care received approximately 28,000 applications for CPAP in 2008.[25] Although no trend information is available, assuming new devices are required each year, extrapolating these figures to the entire Canadian OSA population would result in roughly 72,400 new devices each year. At a cost of approximately $2,000 for CPAP or MADs,[25,31] a total of $145 million per year would be incurred as direct expenses.

Currently, public coverage for treatment of OSA varies widely across Canadian jurisdictions, which translates into differences in access. Ontario, Saskatchewan, Newfoundland and Labrador, Manitoba, Yukon, and some federal programs support CPAP therapy for OSA patients, by either leasing equipment or reimbursing part of the acquisition cost.[2] Further, criteria for patient selection and monitoring using CPAP, as well as supply agreements for lease or reimbursement, vary across these jurisdictions.[2] For dental devices, no provincial programs reimburse their cost, while some federal programs will do so for eligible patients.

Given the broad range of therapeutic approaches and the diversity of clinical presentations influenced by OSA severity, symptoms, and comorbidities, the major common issue in Canadian jurisdictions is the challenge of selecting the most appropriate therapy for OSA patients with different clinical profiles and treatment histories.

POLICY QUESTION

What is the optimal use of PAP devices, oral appliances, surgical interventions, and lifestyle for treatment of adults with OSA?

OBJECTIVES

The aim of this health technology assessment (HTA) is to assess the clinical effectiveness, cost-effectiveness, patient experiences and preferences, ethical issues, implementation issues, and environmental impacts of PAP devices, oral appliances, surgical interventions, and lifestyle for the treatment of OSA in adults.

RESEARCH QUESTIONS

The proposed HTA will address the following research questions. Details on the specific interventions and outcomes are included in Table 1.

1. What are the clinical effectiveness, comparative clinical effectiveness, and safety of PAP devices, oral appliances, surgical interventions, and lifestyle modifications for the treatment of OSA in adults?
    1a. What are the clinical effectiveness, comparative clinical effectiveness, and safety of PAP devices, oral appliances, surgical interventions, and lifestyle for the treatment of adult patients with different OSA severity (i.e., mild, moderate, severe)?

1b. What are the clinical effectiveness, comparative clinical effectiveness, and safety of interventions for the treatment of adult OSA patients with or without comorbidities (e.g., obesity, hypertension, diabetes)?

2. What is the cost-effectiveness of PAP devices, oral appliances, surgical interventions, and lifestyle for the treatment of OSA in adults?
3. What are the experiences and perspectives of adult patients, their family members, and their caregivers regarding PAP devices, oral appliances, surgical interventions, and lifestyle for the treatment of OSA?
4. What ethical issues are raised by providing PAP devices, oral appliances, surgical interventions, and lifestyle to treat OSA in adults? How should these issues be addressed?
5. What are some of the implementation issues associated with PAP devices, oral appliances, surgical interventions, and lifestyle for the treatment of OSA in adults?
6. What are some potential environmental impacts associated with PAP devices, oral appliances, surgical interventions, and lifestyle for the treatment of OSA in adults?

METHODS

Search Strategy

The literature search will be performed by an information specialist, using a peer-reviewed search strategy.

Published literature will be identified by searching the following bibliographic databases: MEDLINE, with in-process records and daily updates, via Ovid; Embase via Ovid; the Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effects (DARE) via Ovid; and PubMed. The clinical search strategy will comprise both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts will be sleep apnea and sleep disordered breathing.

For the clinical search, methodological filters will be applied to limit retrieval to HTAs, systematic reviews (SRs), meta-analyses (MAs), network meta-analyses, overviews of reviews, and guidelines. Retrieval will be limited to documents published since January 1, 2011, considering the large volume of literature currently available on clinical effectiveness. The search will also be limited to English- or French-language publications. Conference abstracts will be excluded from the search results.

Three additional searches will be performed. Economic studies will be identified by searching the following bibliographic databases: MEDLINE (1946–) and Embase (1974–) via Ovid; the NHS Economic Evaluation Database via the Centre for Reviews and Dissemination; and PubMed. Patient experiences and preferences information will be identified by searching the following databases: MEDLINE (1946–), Embase (1974–), and PsycINFO (1967–) via Ovid; Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO; and PubMed. Ethics-related information will be identified by searching the following databases: MEDLINE (1946–) via Ovid; CINAHL via EBSCO; and PubMed. None of these three searches will be limited by study design or specific technologies. Each search will employ the relevant CADTH search filter (i.e., economics, patient experiences, or ethics). These searches will be limited to the English or French language. The patient experiences search will be limited to articles published since January 1, 2006. Neither the economics nor the ethics search will be limited by

publication date. Conference abstracts will be excluded from the patient experiences and ethics search results, but will be included in the economic studies search results. It is noted that these searches will be performed only in medical databases and that no social sciences databases will be searched. Detailed strategies for all searches can be found in Appendix 1.

The initial searches were completed by March 2016. Regular alerts will be established to update the searches until the publication of the final report. Regular search updates will be performed on databases that do not provide alert services. Studies identified in the alerts and meeting the selection criteria of the review will be incorporated into the analysis if they are identified prior to the completion of the stakeholder feedback. Any studies that are identified from the external peer-reviewer phase until the publication of the report will be described briefly in the discussion, with a focus on comparing the results of these new studies to the results of the analysis conducted for this report.

Grey literature (literature that is not commercially published) will be identified by searching the *Grey Matters* checklist (https://www.cadth.ca/grey-matters), which includes the websites of HTA agencies, clinical guideline repositories, SR repositories, economics-related resources, patient-related groups, and professional associations. Google and other Internet search engines will be used to search for additional Web-based materials. These searches will be supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry.

Clinical Review

This protocol was written a priori and will be followed throughout the review process.

Study Design

An overview of SRs, MAs, and HTAs available in the literature on the clinical effectiveness, comparative clinical effectiveness, and safety of interventions for the treatment of OSA in adults will be conducted. All SRs identified that meet selection criteria will be included.

If no published SRs, MAs, or HTAs on any given intervention, comparator, or outcome of interest are identified, a SR of primary studies will be conducted. At that time, a primary review protocol will be developed accordingly and become an addendum to this protocol.

Selection Criteria

The selection criteria for Research Question 1 can be found in Table 1. For this overview of SRs, MAs, and HTAs, the selection criteria apply to the criteria used by the potentially relevant SRs in identifying primary studies to include.

TABLE 1: SELECTION CRITERIA FOR RESEARCH QUESTION 1

Population:

- Adults (i.e., aged ≥ 18 years),[a] diagnosed with any severity of OSA (either treatment-naive or previously treated), as measured objectively by PSG or portable monitoring (Type I to Type IV sleep monitors)[b]

  Subgroups:
  - With or without comorbidities, except heart failure or stroke[c]
  - OSA severity (mild, moderate, severe as measured by baseline AHI, ODI, ESS)
  - Sex (male, female)
  - Age (e.g., < 50 years, ≥ 50 years)
  - BMI (e.g., < 30 kg/m^2, ≥ 30 kg/m^2)
  - Compliance (e.g., < 4 h/night, ≥ 4 h/night for CPAP or OA)
  - Treatment duration (e.g., ≤ 12 weeks, > 12 weeks)

Interventions:

- PAP devices as follows:
  - APAP
  - BiPAP
  - CPAP
  - EPAP
- Oral appliances as follows:
  - MAD[d]
  - Tongue-retaining device
- Surgical interventions as follows:
  - Genial tubercle advancement
  - MMA
  - Nasal surgery
  - Pharyngoplasty
  - Radiofrequency ablation of tissue in soft palate
  - Uvulopalatopharyngoplasty
  - Uvulopalatoplasty (laser-assisted or not)
- Lifestyle modifications[e] as follows:
  - Exercise program
  - Diet or weight-loss program
  - Positional therapy[f]
- Combination therapy (i.e., combinations of two or more interventions in scope)

Comparators:

- Inactive controls (e.g., pre-treatment, oral placebo, sham therapy, supportive care)
- Active controls (i.e., other interventions in scope)

Outcomes:

Primary outcome

- Excessive daytime sleepiness (assessed by ESS)[g]

Secondary outcomes

- OSA severity (assessed by AHI, ODI, RDI)
- Fatigue (assessed using standardized scales)
- Snoring (assessed using standardized scales)
- Accidents (i.e., occupational or motor vehicle)
- Health-related quality of life (assessed using standardized scales)
- Mortality
- Cardiovascular events (i.e., hypertension, AF, MI)
- Cerebrovascular event (i.e., stroke)

• Blood pressure (e.g., daytime, morning, 24-hour, measured in office or home) • Type 2 diabetes mellitus (i.e., incidence or markers of diabetes in diabetic populations [e.g., A1c, insulin resistance]) • Cognitive function (e.g., memory, concentration, assessed using standardized scales) • Psychological function (i.e., depression, anxiety, assessed using standardized scales) • Compliance (i.e., proportion of patients adhering to treatment) • Change in facial aesthetics (for MMA) • Adverse events (i.e., any types, including surgical complications, harms, and treatment withdrawal due to adverse events)
Study design: • SRs, MAs, and HTAs
Timeframe: • Publications within the last 5 years (i.e., between January 2011 and March 2016)

A1c = glycated hemoglobin; AF = atrial fibrillation; AHI = Apnea–Hypopnea Index; APAP = autotitrating positive airway pressure; BiPAP = bilevel positive airway pressure; BMI = body mass index; CPAP = continuous positive airway pressure; EPAP = expiratory positive airway pressure; ESS = Epworth Sleepiness Scale; h = hours;; HTA = health technology assessment; MA = meta-analysis; MAD = mandibular advancement device; MI = myocardial infarction; MMA = maxillomandibular advancement; MSLT = multiple sleep latency test; MWT = maintenance of wakefulness test; ODI = oxygen desaturation index; OSA = obstructive sleep apnea; PAP = positive airway pressure; PSG = polysomnography; RDI = respiratory disturbance index; SR = systematic review.
[a] Studies that included participants aged < 18 years old will be included if ≥ 80% were adults aged ≥ 18 years.
[b] Studies that did not identify criteria for diagnosing OSA will still be included. Studies that included non-OSA will be included if ≥ 80% were diagnosed with any severity of OSA.
[c] Studies of patients with heart failure or stroke will be excluded because central sleep apnea may occur with those conditions.
[d] Personalized MADs only will be included, and not any over-the-counter, non-personalized devices. If it is unclear from the study report whether devices are personalized or not, the study will be included.
[e] Lifestyle interventions including clinician-directed or -prescribed programs will be considered as interventions, while advice will be considered as inactive control.
[f] Positional therapies prevent patients from sleeping in the supine position (e.g., by attaching a tennis ball onto the back of patients' pyjamas).
[g] Excessive daytime sleepiness severity is defined based on the ESS scores, as follows: normal or mild from 0 to 9; moderate from 10 to 15; and severe from 16 to 24.

There is no restriction regarding the therapy duration or length of follow-up. To be included, SRs and MAs must have the term "systematic review" or "meta-analysis" in the title or elsewhere in the text; include a detailed description of comprehensive selection criteria and search methods (i.e., as described in Assessment of Multiple Systematic Reviews [AMSTAR] checklist item #3, with at least two electronic sources having been searched, with adequate reporting of years searched and databases used, key words and/or MeSH terms and where feasible the search strategy provided); assess the quality (or risk of bias) of included studies; and synthesize the findings quantitatively and/or qualitatively.[32] For those not performing quality assessment of the included studies, the SRs will be included if they have relevant outcomes or subgroups that are not present in any of the other included SRs. In this case, quality assessment of the primary studies will be conducted de novo in duplicate. To be included, HTAs must comprise all of the aforementioned elements of SRs, with or without an economic analysis. The clinical portion only of the HTAs will be used in the clinical review.

Studies will be excluded if they do not meet the selection criteria outlined in Table 1 or if they are duplicate publications. Multiple publications of the same study will be excluded, unless they provide additional outcomes of interest. Older SRs (based on publication year) identified in the literature search results will be excluded if all the included studies in the older SRs are included in newer SRs. However, two SRs with overlapping primary studies will be included if they reported different outcomes or identical outcomes but in different subgroups of interest. The degree of overlap will be judged by building a matrix of included studies in the SRs, and reported within the results section of a final report. A list of excluded studies, with reasons for exclusion after full-text review, will be provided.

Screening and Selecting Studies for Inclusion

Two reviewers (KT and JK) will independently screen titles and abstracts of all citations retrieved from the literature search relevant to Research Question 1, followed by an independent review of the full-text articles, based on the pre-determined selection criteria outlined in Table 1. The two reviewers will then compare their included and excluded studies from their full-text review and resolve any disagreements through discussion until consensus is reached, involving a third reviewer if necessary. The study selection process will be presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart. A full-text screening checklist for Research Question 1 is reported in Appendix 2.

Data Extraction

A standardized data extraction form (Appendix 3) has been designed a priori to document and tabulate all relevant information from included SRs. Relevant information includes both descriptive data and results reported in all included SRs, such as the numbers and types of primary studies included in the SRs; age, OSA severity, and comorbidities of the study populations included in the SRs; types of interventions and controls, as well as the therapy durations and lengths of follow-up, included in the SRs; types of outcomes included in the SRs; types of subgroup analyses, meta-regression, and MAs, if conducted in the SRs; results and conclusions regarding the outcomes of interest (Table 1) and comorbidities reported in the SRs; and types of tools used and results reported regarding quality assessments, if conducted in the SRs. Two reviewers (KT and JK) will pilot the extraction form in duplicate among individual included SRs until consistency between reviewers is reached. Data from each included SR will then be extracted by one reviewer and checked for accuracy by a second reviewer (e.g., two reviewers will each independently extract from one-half of the included SRs and review the data extracted from the other half). Disagreements will be resolved through consensus, involving a third reviewer, if necessary. Data will not be extracted from figures if they do not explicitly provide numerical data. Primary studies included in the SRs will be consulted for any missing information, clarify any issues, or verify extracted data, if necessary. Authors of the included SRs will be contacted to provide any missing information or clarify any issues.

Methodological Assessments

The Risk of Bias in Systematic Reviews (ROBIS) tool,[33] designed to assess the risk of bias in SRs of RCTs and non-randomized studies, with its 21 questions across four domains, will be used as the primary instrument for assessing the included SRs. Each question will be answered as “yes,” “probably yes,” “probably no,” “no,” and “no information,” with “yes” indicating very low concerns and “no” indicating very high concerns about potential bias.

Three additional criteria (i.e., provision of a list of excluded studies, inclusion of grey literature, and declaration of conflicts of interest) from the AMSTAR checklist,[34] designed to assess the quality of SRs of RCTs, will supplement the methodological assessment of the included SRs on items that are not included in the ROBIS tool. Each question will be answered as “yes,” “no,” “unclear,” or “not applicable,” with “yes” indicating high quality and “no” indicating low quality.

Two reviewers (KT and JK) will pilot and then independently assess the methodological quality of the included SRs. Disagreements will be resolved through consensus, involving a third reviewer, if necessary. Although the results of the methodological assessments will not be used to further include or exclude the included SRs, the conclusions and discussion of the final report will focus on the findings of the SRs of higher quality.

Summary of Evidence

Description of Study Characteristics and Findings

A summary of SR characteristics, including the total number of SRs by population, intervention, comparator, outcomes, and study design (PICOS) elements, years of publication, and countries of development, and findings, will be provided. Additionally, information from SRs, including characteristics, numbers, types, and years of publication of primary studies included in the SRs, will be summarized. In the case that more than one SR is included for a given intervention, comparator, and outcome of interest, any overlap of included studies among SRs will be described and presented (e.g., by preparing a matrix of included studies in the SRs).

A narrative synthesis of the results of included SRs will be conducted. No meta-analysis or network meta-analysis will be conducted. The findings will be grouped based on interventions and comparators, and an overview of the outcomes will be synthesized narratively, highlighting any short-term versus long-term effects. Among PAP devices, EPAP will be considered separately, while APAP, BiPAP, and CPAP will be considered as one group, since evidence has shown that these devices were similar in compliance and efficacy.[3] For oral appliances, the MADs and tongue-retaining devices will be considered separately. For lifestyle modifications, depending on the inclusion criteria of the SRs, the interventions will be included either individually or in combination. No re-synthesis of the findings from primary studies will be conducted. Results will be re-presented as reported in SR study reports, including a summary estimate and confidence interval, measure of heterogeneity, and number of studies and participants contributing to each estimate, as available. Tables will be developed to present results by outcome and to accompany the narrative summary, to ensure consistency of presented information across all included SRs and to facilitate comparisons by the reader. For each outcome of interest, analysis will be conducted for the overall study population, and also for each subgroup listed in Table 1.

Description of Methodological Assessments

A narrative summary of the methodological assessment of each included SR will be provided. Specifically, tables will be developed to present the answers to the questions of the ROBIS tool, with colour codes, where green and light green indicate “yes” and “probably yes,” respectively, red and light red indicate “no” and “probably no,” respectively, and yellow indicates “no information” for each question. The tables will also present the answers to the select questions of the AMSTAR checklist, with colour codes, where green, red, and yellow indicate “yes,” “no,” and “unclear,” respectively, for each question. A narrative description of the strengths and limitations of the included SRs will also be presented in the main text of the report to provide the reader with a holistic, qualitative overview of the literature.

Economic Review

Study Design

A primary economic analysis on the cost-effectiveness of interventions for the treatment of OSA in adults will be conducted to address Research Question 2.

Primary Economic Analysis

A *de novo* decision-analytic model will be developed to assess single or combination interventions for the treatment of OSA in adults. Interventions may include PAP therapies, EPAP, dental appliances (i.e., tongue reposition and mandibular reposition), surgery, and lifestyle modifications (Table 1). A no-treatment strategy will also be considered, reflecting the natural disease progression. While the analysis will consider adults with OSA, some of the patient characteristics of interest will include OSA severity (measured by AHI), presence of symptoms (symptomatic versus asymptomatic) and comorbidities (e.g., with or without hypertension, obesity, depression, or type 2 diabetes).

Model Design

The model will be used to examine the costs and health outcomes associated with no treatment, PAP therapies, EPAP, dental appliances, surgery, and lifestyle modifications, subject to the findings from the clinical review. The model will be used to evaluate, for each identified patient subpopulation, the cost-effectiveness among a set of clinically appropriate interventions.

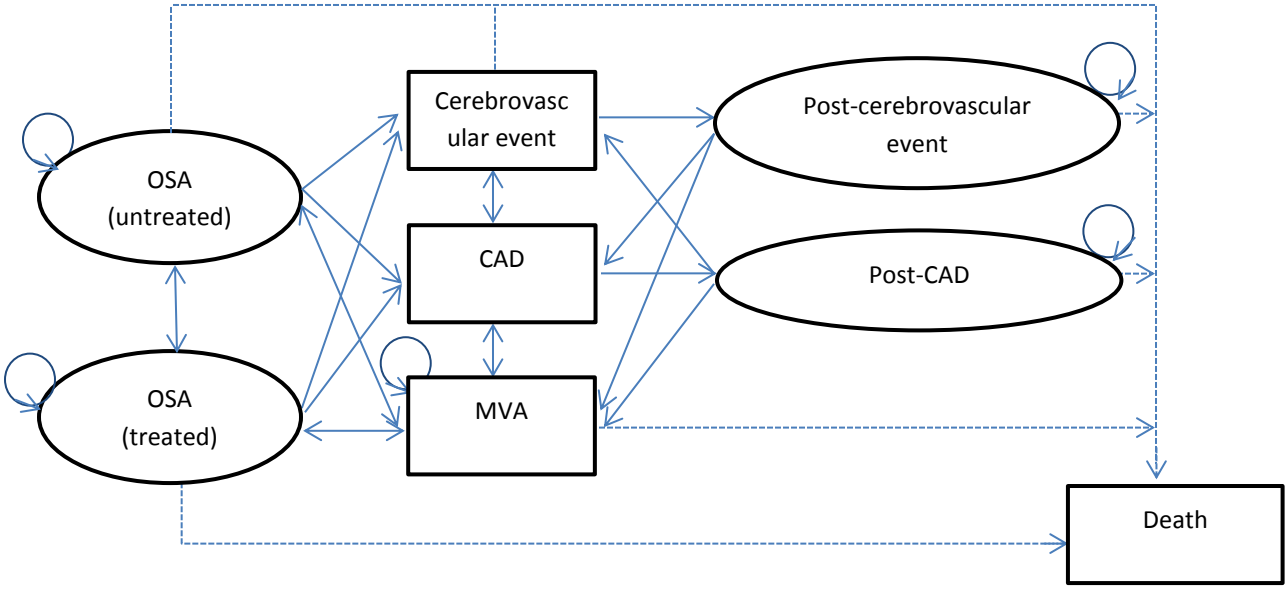
The patient cohort — described by specific risk factors and clinical characteristics that were identified from the clinical review — will begin the model as having untreated OSA. Over the course of the patients' lifetime, their OSA-related comorbidities may improve or deteriorate, depending on the effectiveness of treatment for OSA, their compliance, and the natural disease progression.

The health state of untreated OSA represents that of the patients who did not receive an intervention for OSA or who have prematurely discontinued their intervention. Patients in this health state will enter a submodel that reflects natural disease progression. If OSA is left untreated, patients will be at an increased risk for a variety of clinical consequences, including excessive daytime sleepiness and increased morbidity and mortality related to cardiovascular and cerebrovascular events.[35-38]

The health state of treated OSA describes that of the patients who have remained compliant with their OSA intervention. To capture the impact of interventions for OSA, four health states representing clinical events associated with OSA will be used: cardiovascular events (e.g., coronary artery disease [CAD]), cerebrovascular event (e.g., stroke), motor vehicle accidents, and all-cause mortality. In particular, cerebrovascular event may be defined by severity of the event, given that numerous reports suggest a difference in patient prognosis, costs, and utility based on severity.[39] Because several economic models on OSA capture different mortality risks, health utilities, and subsequent-year costs after an incident cardiovascular or cerebrovascular event, the model will further incorporate post-CAD and post-cerebrovascular event health states.[24] If the clinical data permit, compliance will be modelled by defining partial compliance and non-compliance. Partially compliant users will experience a pro-rated risk reduction for the development of clinical outcomes based on the average hours of device use. No risk reduction will be assumed in patients that are non-adherent to their device. Rather, these patients will have risks similar to those with untreated OSA.

A proposed model structure can be found in Figure 1. The details of the model will be developed based on feedback from the CADTH clinical review team and the clinical co-authors, as well as clinical experts and members of the Health Technology Expert Review Panel, to ensure that it reflects the current clinical literature and clinical practice. Both the internal and external validity of the decision-analytic model will be assessed for any logical discrepancies. The decision-analytic model will be constructed in Microsoft Excel.

FIGURE 1: PROPOSED STRUCTURE OF OBSTRUCTIVE SLEEP APNEA MODEL



CAD = coronary artery disease; MVA = motor vehicle accident; OSA = obstructive sleep apnea.
Notes: Events = rectangles; clinical conditions = oval. Compliance will affect the rate at which patients progress from the "OSA (treated)" health state to the four clinical health states events. Although not explicitly shown, patients can progress from any of the following 3 events — stroke, myocardial infarction, and MVA — to any of these events in the subsequent cycle.

Perspective

The primary perspective in the model will be that of a publicly funded health care system, focusing only on direct medical costs. Other perspectives may be considered, based on feedback from stakeholders.

Resource Use and Cost Data

The costs captured in the model will reflect the scope of the clinical review and the perspective of the economic analysis. Costs include those of the interventions and health care resources related to the occurrence of a health event, and the ongoing care following cardiovascular and cerebrovascular events. In addition, the costs associated with the treatment of hypertension will be included.

Canadian-specific costs will be used, when available. If unavailable, costs will be estimated from the medical literature and, ideally, from comparable health systems. If necessary, costs will be adjusted to 2016 Canadian dollars, using the health care component of the consumer price index.

Utilities
Utilities associated with each health state will be obtained from the literature from Canadian sources, where possible. The literature search of economics studies will provide the basis to identify suitable utility values. Utilities will be adjusted for any relevant comorbidities or patient characteristics.

Clinical Parameters
Treatment effects: Transition probabilities, describing the comparative clinical effectiveness of interventions for OSA, will be taken from the clinical review. In cases where no data are available to describe the impact of treatments to certain final clinical outcomes, attempts will be made to link and predict the development of final clinical outcomes through the use of surrogate outcomes via risk equations.

Natural history: Parameters, describing the natural history of patients with OSA and the impact of adherence to PAP devices and dental devices, surgery, and lifestyle modifications on clinical effectiveness, will be identified from peer-reviewed medical literature and medical registries.

Outcomes
The model will estimate the expected lifetime costs and quality-adjusted life years (QALYs) for each of the treatment strategies. The generic QALY outcome was selected as the measure of treatment benefit, given the broad health impacts of OSA. The primary outcome will be the incremental cost-effectiveness ratios, measured in terms of the incremental costs per QALY gained, of the treatment strategies on the efficiency frontier.

Costs, disaggregated by type, will also be reported. Additional outcomes, such as the incidence of motor vehicle accidents, may also be reported and will reflect the feedback received during patient engagement.

Time Horizon and Discounting
A lifetime horizon is proposed, given that OSA is a chronic condition and that interventions to treat OSA may have different impacts on both short- and long-term morbidity and mortality, resulting in differences in lifetime costs and benefits. Discounting will be set at 5% per year.[40]

Sensitivity Analysis
The base-case analysis will represent the probabilistic findings, capturing the extent to which parameter uncertainty may impact the incremental cost-effectiveness findings. Results of the probabilistic analysis will be presented on a cost-effectiveness acceptability curve, whereby interventions on the efficiency frontier will be highlighted across different willingness-to-pay thresholds. Uncertainty in the model will be further evaluated in a number of ways. Scenario analysis will be performed to evaluate key model assumptions, while retaining the probabilistic element of the model. Potential scenarios of interest may include:

- Lifespan of the interventions
- Device costs
- Compliance with treatment
- Discontinuation of PAP devices or oral appliances
- Recovery from surgery and surgical complications
- Long-term clinical effects of treatment, such as extrapolations of the relationship between surrogate and final clinical outcomes
- Time horizon.

Other analyses to address parameter uncertainty may include varying sets of related inputs (i.e., compliance and treatment effect) or extreme scenarios (e.g., best- and worst-case analysis, threshold scenarios). This may help identify key inputs driving the results of the cost-effectiveness analysis.

Assumptions

During the course of the model development, assumptions and limitations will be identified and acknowledged in the report. Assumptions will be tested through the conduct of sensitivity analyses, where possible.

Patient Preference and Experience

Study Design

A systematic review and thematic synthesis of the literature on the experiences and perspectives of adults with OSA, as well as their family members, partners and caregivers, regarding treatment interventions will be conducted. The primary goal of this analysis is to provide a comprehensive description of the experiences and perspectives of OSA patients and their family members, partners, and caregivers (hereafter, at times referred to as “people”) as reported in the primary literature.

Eligibility Criteria

We will include English or French reports of studies of any design that explore or assess perspectives of adults being treated for OSA with interventions, or waiting for treatment for OSA, as well as the perspectives of their partners or other family caregivers. To be eligible, studies must explore or assess the participants’ own perspectives directly. Studies that provide information collected only indirectly — e.g., clinician perspectives — will be excluded. The following types of publications will also be excluded: theses and dissertations, data presented in abstract form only, book chapters, editorials, and letters to the editor. Studies will be excluded if they are not published in English or French. Selection criteria are presented in Table 2, characterized following the PICOS elements.

Screening and Selecting Studies for Inclusion

Two reviewers (SG and TR) will independently screen the titles and abstracts of all citations retrieved from the literature search, and exclude reports that clearly do not meet the inclusion criteria. In addition, citations retrieved from the literature searches from other components of this HTA will also be screened as part of those processes and included here as appropriate. The full text of all potentially relevant reports will be ordered for detailed review. Two reviewers (SG and TR) will then independently review the full-text articles based on the detailed eligibility criteria. Any disagreements among reviewers will be resolved through discussion. During the full-text review, information on variables such as sex, OSA interventions, OSA severity, duration of treatment, prior experience with treatment, and comorbidities will be extracted into an electronic form to inform subsequent sampling decisions as described in the Article Sampling section. The study selection process will be presented in a PRISMA flow chart.

TABLE 2: SELECTION CRITERIA FOR RESEARCH QUESTION 3

Population: Adults (i.e., aged ≥ 18 years),[a] diagnosed with any severity of OSA (either treatment-naive or previously treated), as measured objectively by PSG or portable monitoring (Type I to Type IV sleep monitors)[b]	

Interventions:
• PAP devices, as follows:
  ○ APAP
  ○ BiPAP
  ○ CPAP
  ○ EPAP
• Oral appliances, as follows:
  ○ MAD[c]
  ○ Tongue-retaining device
• Surgical interventions, as follows:
  ○ Genial tubercle advancement
  ○ MMA
  ○ Nasal surgery
  ○ Pharyngoplasty
  ○ Radiofrequency ablation of tissue in soft palate
  ○ Uvulopalatopharyngoplasty
  ○ Uvulopalatoplasty (laser-assisted or not)
• Lifestyle modifications,[d] as follows:
  ○ Exercise program
  ○ Diet or weight-loss program
  ○ Positional therapy
• Combination therapy (i.e., combinations of two or more interventions in scope)
• Inactive treatments (e.g., pre-treatment, supportive care)
• Waiting list
• No treatment	

Comparators: Not applicable	
Outcomes: Perspectives and experiences regarding treatments, including such issues as preferences and beliefs about interventions; experiences waiting for treatment, with shared decision-making regarding treatment; experiences complying or not complying with treatment; reasons for complying and not complying with treatment; and other issues of importance to patients that emerge in the analysis.[e]	

Study Design:
• Descriptive studies:
  ○ Qualitative studies
  ○ Surveys
	• Mixed methods studies
	• SRs of descriptive studies

A1c = glycated hemoglobin; AF = atrial fibrillation; AHI = Apnea–Hypopnea Index; APAP = autotitrating positive airway pressure; BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; EPAP = expiratory positive airway pressure; ESS = Epworth Sleepiness Scale; HTA = health technology assessment; MA = meta-analysis; MAD = mandibular advancement device; MI = myocardial infarction; MMA = maxillomandibular advancement; MSLT = multiple sleep latency test; MWT = maintenance of wakefulness test; ODI = oxygen desaturation index; OSA = obstructive sleep apnea; PAP = positive airway pressure; PSG = polysomnography; RDI = respiratory disturbance index; SR = systematic review.

[a] Studies that included participants aged < 18 years old will be included if ≥ 80% were adults aged ≥ 18 years.

[b] Studies that did not identify criteria for diagnosing OSA will still be included. Studies that included non-OSA will be included if ≥ 80% were diagnosed with any severity of OSA.

[c] Personalized MADs only will be included, and not any over-the-counter, non-personalized devices.

[d] Lifestyle interventions including clinician-directed or -prescribed programs will be considered as interventions, while advice will be considered as inactive control.

[e] Outcomes of relevance to this research question will emerge from the data reported within included study reports. This preliminary list of outcomes is provided to outline issues that are expected to emerge; however, the final set of outcomes will emerge after iterative and careful readings of the data.

Article Sampling
As opposed to quantitative synthesis, which aims for exhaustive sampling, in qualitative and mixed methods synthesis, the principle of saturation drives sampling decisions. In this review, we will apply the concept of "conceptual saturation" to developing our sample of included studies. Conceptual saturation refers to the stage when analysis of further evidence provides little in terms of further themes, insights, perspectives, or information.[41] It may not be necessary to include every available study in the analysis, as the results the synthesis will not change whether five or 10 study reports contain the same concept.

To develop our sample of included articles for analysis, based on the list of eligible full-text articles, we will use a purposeful sampling strategy that applies the technique of maximum variation until conceptual saturation is reached. The maximum variation sampling strategy will help ensure that a range of articles representing diverse experiences with interventions for OSA are included. For example, because we are limited only by article availability, we will ensure studies are included that describe the experience of diverse patients, caregivers, or family members in varied contexts, by sampling articles based on their description of experiences by such variables as sex; age; rural, remote, or urban settings; OSA interventions; OSA severity; duration of treatment; prior experience with treatment; access to treatment; and comorbidities. Regardless of the number of eligible articles identified, conceptual saturation[41] will guide decisions regarding sample size, or the total number of eligible articles included for analysis.[41]

We will begin by sampling and analyzing SRs, moving to primary studies. Within the primary studies, qualitative studies will be sampled and analyzed first, followed by mixed methods studies and descriptive studies. Sampling of articles will cease when conceptual saturation has been reached or if there are no more relevant articles for inclusion, whichever occurs first. Upon the suspicion that saturation has been reached, relevant results from two additional articles will be reviewed to confirm saturation.

Data Extraction
From each eligible article, descriptive data will be extracted by one reviewer (either SG or TR) into an a priori developed standardized electronic form (see Appendix 4). Descriptive data include such items as first author, article title, study objectives, participant characteristics, and study design.[42] The extracted data will be subsequently verified by the other reviewer (either SG or TR). Discrepancies will be resolved through discussion, or referral to a third party if necessary.

Result statements from the eligible articles relevant to the research question will be captured for analysis using NVivo qualitative data analysis software (QSR International Pty Ltd. Version 11, 2015).[43] For further detail, refer to the Thematic Analysis section. Result statements are typically presented within the "results" section of a report, and are characterized as data-driven and integrated findings based in participant experiences. Before being coded, each result statement will be assessed to ensure it is differentiated from raw data, methods, external data, and researchers' conclusions and implications.[44] The latter will not be coded. Only results presented within the main report will be coded. Data from figures will not be used unless data points are explicitly labelled.

Methodological Assessments
One reviewer (either SG or TR) will independently assess the quality of each study using standardized criteria, depending on the study design. For example, qualitative studies will be assessed using criteria outlined in the Critical Appraisal Skills Programme (CASP) checklist.[45] Likewise, survey studies will be assessed using standardized criteria commonly applied to

assess the validity and reliability of this approach (Appendix 5).[46,47] The other reviewer (either SG or TR) will verify the assessments. Disagreements will be resolved by discussion or referral to a third party, if necessary. The results of the critical appraisal process will be reported narratively and summarized in a table to highlight the strengths and limitations of each study.

Data Analysis

Descriptive Analysis

A descriptive analysis of study characteristics will be conducted, which will involve the calculation of frequencies for relevant categories across studies. The goal is to characterize the set of included studies in terms of important study and patient characteristics (e.g., PICOS, sample size). Study and patient characteristics will be summarized in a table and accompanied by a narrative description.

Thematic Analysis

We will conduct a thematic analysis comprising three stages: coding, developing descriptive themes, and developing analytic themes. The analysis will be conducted using NVivo.[43]

Coding (Stage 1)

In the first coding stage, the results section of each full-text article will be coded line by line for meaning and content. Coding will begin with an a priori "start list" of codes developed based on the research questions, including, for example, perceived benefits and concerns, compliance, ineligibility, and access. As coding progresses, other codes not on the start list will be added inductively to capture unexpected content. When new codes emerge, all data will be re-coded to search for further instances of the meaning captured by that code. Codes will be assigned to data from all studies regardless of their design in a consistent manner of inductive and iterative coding. Quantitative data will be coded in the same manner as the qualitative data, in an approach of qualifying the quantitative data.[48]

Through a staged coding process, two researchers will initially code the first five articles from an alphabetical list of a selection of the eligible studies. They will independently assign codes to concepts, ideas, and categories to the results reported within each study report. The two researchers (SG and TR) will then compare and discuss their code assignments for the selected studies. This discussion will allow us to organize and reflect upon a wide range of interpretations across the body of research and refine the emerging coding template. Following this discussion, another set of three articles will be coded independently, with reviewers subsequently meeting to compare and discuss coding assignments, and refine the coding template accordingly. If coding is found to align at this point, coding will proceed with one researcher acting as the primary coder, and the other researcher subsequently verifying the coding. If coding does not align between reviewers at this point, another set of three articles will be coded independently and subsequently compared.

When all codes are applied to the full sample of results, they will be assessed for consistency in interpretation and application and to determine whether any additional levels of coding are needed.

Descriptive Themes (Stage 2)

In the second stage of the analysis, the codes developed in the prior stage will be organized into related areas to construct "descriptive" themes. In this process, two reviewers (SG and TR) will independently assess similarities and differences between codes. New codes might also be created during this process in order to capture the meaning of groups of initial codes. If relevant, codes may be related to one another, such as in a tree structure, or codes might not have any

relational structure.[44] When differences are identified, reviewers will assess whether these can be explained by differences in methods or sample characteristics.[49] Similarly, reviewers will assess whether emergent themes are transferable across different study contexts. If not, the question will likewise be asked as to whether the differences are a result of methods or sample characteristics. By seeking out differences in this way, the range of perspectives held by people will become apparent, and subgroups may potentially be identified for which certain results apply; for example, by OSA severity, sex, age, or access to treatment.[44] Once descriptive themes are identified, a draft summary of the results across the studies organized by each theme will be written by one reviewer (SG or TR) and subsequently reviewed by a second reviewer (SG or TR). A group discussion will be scheduled to review and discuss the emergent themes. The final version will be agreed upon by all review team members[44] and will represent a synthesis that remains fairly close to the original results of the included studies, with minimal interpretation.

Analytic Themes (Stage 3)
During the final stage, the "data-driven" descriptive themes from the prior stage will be analyzed through the theoretical structure provided by the policy question to develop "theory-driven" analytic themes in direct response to the practical needs of decision-makers. In this stage, two reviewers (SG and TR) will use the descriptive themes to independently infer an answer to the question optimal use of treatments for OSA. After each reviewer has made these inferences independently, the two reviewers will meet to review their results. A group discussion including all team members will be scheduled to likewise review and discuss the analytic themes in the context of the policy issue. It is likely that through this group discussion, more abstract or more analytical themes will emerge. If this is the case, answers to the policy question will again be examined in light of these new themes. This cyclical process of theme development will continue until a set of themes has emerged that is sufficiently abstract to include all of the initial descriptive themes and to answer the policy question.[44] As in the prior stage, throughout this process, reviewers will again ensure attention is paid to the transferability of results across different contexts as a way to determine whether some results might only apply to certain subgroups.

Throughout all stages of the analysis, regular meetings between members of the research team will take place to discuss emerging results, and preliminary analytic ideas. Further, explicit notes will be kept using the memo and annotation features in NVivo to record decisions made regarding coding and theme development, as a means to help ensure rigour in the analysis.

Ethical Issues

There are two broad ethical questions to consider regarding treatment of OSA:
1. Should we provide the complete range of technologies (CPAP, dental devices, lifestyle modification, surgery) identified in the clinical review for adult (aged ≥ 18 years) patients with OSA of varying severity (mild, moderate, severe)?
2. If all or some of these treatments should be provided, what ethical issues ought to be considered when providing these technologies?

Inquiry
The nature of bioethical analysis requires a two-step approach to identifying potential issues. In the first step, the potentially relevant issues described in the published ethics and other literature are identified. In the second step, philosophical analysis and additional searches of the literature are used to identify additional concerns and address the relative importance and strength of the identified issues.

Perspectives
The relevant perspectives that need to be considered in identifying and addressing the ethical issues associated with the various treatments for OSA include patients, family members, or informal caregivers, patient organizations, health care providers, and health care insurers.

Review of the Bioethics Literature
A review of the empirical and normative bioethics literature will be conducted to identify two types of literature relevant to the identification and analysis of the potential ethical issues with OSA treatments. The first type of literature is composed of those articles that explicitly and specifically raise ethical issues. The second type is composed of articles that are not explicitly about ethical issues — for example, an empirical investigation of patient attitudes toward CPAP — but that, when read through an ethics lens, raise or point to potential ethical issues. The relevant literature includes issues with OSA treatments specifically, and also ethical issues with similar technologies in the same population. Possible analogies will be scrutinized for relevance before being included.

The articles included in the systematic review of patient and caregiver perspectives will also be examined for relevant ethical issues.

Literature Screening and Selection
The selection of relevant literature will proceed in two stages. In the first stage, the title and abstracts of citations will be screened for relevance independently by two reviewers (KB, KD). Articles will be categorized as "retrieve" or "do not retrieve," according to the following criteria:

- Provides information (explicit) on or is relevant to identification (implicit) of an ethical issue related to OSA treatment.

Disagreements between reviewers will be resolved by discussion and consensus. In the event of persistent disagreement, a third assessor will adjudicate.

In the second stage of screening, two reviewers (KB, KD) will independently assess the relevance of the full-text reports for all citations classified as "retrieve" in the first stage of screening. The relevance of the full-text reports will be assessed according to the following criteria:

- On an OSA treatment
- Explicitly mentions ethical issues (either individual or societal).

Reports meeting these criteria will be included in the analysis. Reports that do not meet these criteria will be excluded from analysis. Disagreements between reviewers will be resolved by discussion and consensus. In the event of persistent disagreement, a third assessor will adjudicate.

Data Extraction and/or Abstraction Strategy
The bibliographic details for each report (author, publication date, journal), the potential ethical issues raised, and the report's conclusions will be captured in an Excel spreadsheet.

Analysis
Ethical issues will be identified and analyzed using the methods of clinical and health policy ethics. These methods include conceptual analysis, logical analysis, and the application of the relevant moral theory and principles. The analysis will draw most directly on two perspectives (other ethical perspectives may be used) that are well established in the health ethics literature, namely the utilitarian or consequentialist approach, and the deontological or duty-based

approach. The former focuses more directly on the overall consequences of a particular course of action and deals with questions of individual rights and duties and considerations of social justice only indirectly. In contrast, the deontological approach gives priority to considerations of individual rights and concomitant duties while treating overall utility (i.e., the greatest good for the greatest number) as of only secondary importance. From a deontological perspective, the most important consequence to consider is whether individual rights are properly honoured and accounted for, irrespective of whether some supposedly greater good might be accomplished by ignoring the rights of certain individuals. While these two theoretical approaches are often treated as contrary, there is a well-established tradition within contemporary health care ethics that treats them as complementary. The context within which a particular issue arises will determine whether consequentialist or deontological or other considerations are highlighted.

Summarizing and Presenting Results

The reporting of ethical issues will follow the key values identified or issues being explored and will be determined by the values and issues that are identified. For example, the results may be summarized according to a principalist framework (issues concerned with autonomy, beneficence, non-maleficence, and justice) or by categorizing moral concerns as micro-, meso-, and macro-level issues. Regardless of the framework selected, the implications of the choice of framework on how the findings are presented and interpreted will be described.

The ethical implications of a health technology are often determined by the nature of the local context. The implications of values of fair access and consistency of service within the population, in particular, are determined by facts about how health care services are arranged and provided. To help decision-makers better understand localized impact, a number of contextualizing questions will be developed based on the identified issues.

Implementation Issues

Study Design

A narrative review will be conducted of the literature on the implementation issues associated with different interventions for the treatment of OSA in adults.

Selection Criteria

Articles that provided insights on the implementation issues associated with interventions for the treatment of OSA, from the perspectives of Canadian patients, health care providers, and decision-makers, will be included. For example, the issues may include the following:

- Technical requirements, resource needs, logistical considerations, and operational constraints
- Staffing, training, and accreditation issues (e.g., clinical specialties)
- Referral pathways and multidisciplinary patient management schemes
- Design of public funding programs, including eligibility and prioritization criteria.

Screening and Selecting Articles for Inclusion

Citations arising from the literature searches conducted to address Research Questions 1 to 4 will be screened for information related to implementation issues, while the reviewers of the clinical, economic, patient preferences and experiences, and ethics sections of the assessment screen for their respective sections.

Data Extraction
From each relevant article, the bibliographic details (i.e., authors, year of publication, and country of origin), population and intervention information, and implementation issues identified will be captured by one reviewer in an Excel spreadsheet.

Descriptive Analysis
Information from relevant studies will be organized according to the population and intervention. This information will be summarized narratively and not systematically reviewed.

Environmental Impacts

Study Design
A narrative review of the literature on the potential environmental impacts associated with different interventions for the treatment of OSA in adults will be conducted.

Selection Criteria
Articles that provided insights on potential environmental impacts associated with interventions the treatment for OSA, in Canadian contexts, will be included. For example, the impacts may relate to resource use, waste issues, and recycling schemes associated with different interventions for the treatment of OSA in adults.

Screening and Selecting Articles for Inclusion
Citations arising from the literature searches conducted to address Research Questions 1 to 4 will be screened for information related to potential environmental impacts, while the reviewers of the clinical, economic, patient preferences and experiences, and ethics sections of the assessment screen for their respective sections

Data Extraction
From each relevant article, the bibliographic details (i.e., authors, year of publication, and country of origin), population and intervention information, and potential environmental impacts identified will be captured by one reviewer in an Excel spreadsheet.

Descriptive Analysis
Information from relevant studies will be organized according to the population and intervention. This information will be summarized narratively and not systematically reviewed.

Areas for Potential Amendments

If amendments are required at any time during the study, reasons for changes will be recorded in a study file and subsequently reported within the final study report. If necessary, a rescreening of the previous literature search or an updated literature search will be performed to capture additional data according to the amendments.

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APPENDIX 1: LITERATURE SEARCH STRATEGY

Clinical Database Search

OVERVIEW	
Interface:	Ovid
Databases:	Embase MEDLINE Daily and MEDLINE MEDLINE In-Process & Other Non-Indexed Citations Cochrane Database of Systematic Reviews (CDSR) Database of Abstracts of Reviews of Effects (DARE) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	March 2016
Alerts:	Monthly search updates until project completion
Study Types:	Health technology assessments; systematic reviews; meta-analyses; network meta-analyses; overviews of reviews; and guidelines
Limits:	Date limit: 2011-present Language limit: English- and French-language Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj	Requires words are adjacent to each other (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.kw	Author keyword (Embase); Keyword (CDSR and DARE)
.kf	Author keyword heading word (MEDLINE)
.mp	Mapped term
.yr	Year
.jw	Journal title word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily
coch	Ovid database code; Cochrane Database of Systematic Reviews
dare	Ovid database code; Database of Abstracts of Reviews of Effects

MUTLI-STRATEGY SEARCH	
#	Searches
1	exp sleep apnea syndromes/
2	((sleep* or nocturnal) adj2 (apnea* or apnoea*)).ti,ab,kf.
3	(sleep* adj3 disordered adj3 breathing).ti,ab,kf.
4	((sleep* or nocturnal) adj2 (hypopnea* or hypopnoea* or hypo-apnea* or hypo-apnoea* or apneic-hypopneic or apnoeic-hypopnoeic)).ti,ab,kf.
5	((OSA or SAHS) and sleep*).ti,ab,kf.
6	OSAHS.ti,ab,kf.
7	or/1-6
8	7 use pmez
9	exp sleep disordered breathing/
10	((sleep* or nocturnal) adj2 (apnea* or apnoea*)).ti,ab,kw.
11	(sleep* adj3 disordered adj3 breathing).ti,ab,kw.
12	((sleep* or nocturnal) adj2 (hypopnea* or hypopnoea* or hypo-apnea* or hypo-apnoea* or apneic-hypopneic or apnoeic-hypopnoeic)).ti,ab,kw.
13	((OSA or SAHS) and sleep*).ti,ab,kw.
14	OSAHS.ti,ab,kw.
15	or/9-14
16	15 use oemezd
17	16 not conference abstract.pt.
18	8 or 17
19	sleep apnea syndromes*.kw.
20	sleep apnea, obstructive*.kw.
21	((sleep* or nocturnal) adj2 (apnea* or apnoea*)).ti,ab,kw.
22	(sleep* adj3 disordered adj3 breathing).ti,ab,kw.
23	((sleep* or nocturnal) adj2 (hypopnea* or hypopnoea* or hypo-apnea* or hypo-apnoea* or apneic-hypopneic or apnoeic-hypopnoeic)).ti,ab,kw.
24	((OSA or SAHS) and sleep*).ti,ab,kw.
25	OSAHS.ti,ab,kw.
26	or/19-25
27	26 use coch,dare
28	meta-analysis.pt.
29	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/
30	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw.
31	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf,kw.
32	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf,kw.

MUTLI-STRATEGY SEARCH	
#	Searches
33	(data synthes* or data extraction* or data abstraction*).ti,ab,kf,kw.
34	(handsearch* or hand search*).ti,ab,kf,kw.
35	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf,kw.
36	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf,kw.
37	(meta regression* or metaregression*).ti,ab,kf,kw.
38	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw,kf,kw.
39	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
40	(cochrane or (health adj2 technology assessment) or evidence report).jw.
41	(comparative adj3 (efficacy or effectiveness)).ti,ab,kf,kw.
42	(outcomes research or relative effectiveness).ti,ab,kf,kw.
43	((indirect or indirect treatment or mixed treatment) adj4 comparison*).ti,ab,kf,kw.
44	(network adj3 (meta-analys* or metaanalys*)).ti,ab,kf,kw.
45	(multi* adj3 treatment adj3 comparison*).ti,ab,kf,kw.
46	((overview* or review or synthesis or summary or cochrane or analysis) and (reviews or meta-analyses or articles or umbrella)).ti,kf,kw. or umbrella review.ab. or (meta-review or metareview).ti,ab,kf,kw.
47	((overview* or reviews) and (systematic or cochrane)).ti,kf,kw.
48	(reviews adj2 meta).ab.
49	(reviews adj2 (published or quality or included or summar*)).ab.
50	cochrane reviews.ab.
51	(evidence and (reviews or meta-analyses)).ti,kf,kw.
52	or/28-51
53	18 and 52
54	27 or 53
55	(guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt.
56	(guideline* or standards or consensus* or recommendat*).ti.
57	(practice parameter* or position statement* or policy statement* or CPG or CPGs or best practice*).ti.
58	(care adj2 (path or paths or pathway or pathways or map or maps or plan or plans or standard)).ti.
59	((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti.
60	(algorithm* and (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti.
61	(algorithm* and (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti.
62	or/55-61

MUTLI-STRATEGY SEARCH	
#	Searches
63	18 and 62
64	54 or 63
65	limit 64 to english language [Limit not valid in CDSR,DARE; records were retained]
66	limit 64 to french [Limit not valid in CDSR,DARE; records were retained]
67	65 or 66
68	limit 67 to yr="2011 -Current" [Limit not valid in DARE; records were retained]
69	remove duplicates from 68

OTHER DATABASES	
PubMed	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used.

Health Economics Database Search

OVERVIEW	
Interface:	Ovid
Databases:	Embase MEDLINE Daily and MEDLINE MEDLINE In-Process & Other Non-Indexed Citations NHS Economic Evaluation Database (NHS EED) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	March 2016
Alerts:	Monthly search updates until project completion
Study Types:	Economic evaluations
Limits:	Date limit: none Language limit: English- and French-language Conference abstracts: included

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj	Requires words are adjacent to each other (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.kw	Author keyword (Embase); Keyword (CDSR and DARE)
.kf	Author keyword heading word (MEDLINE)
.mp	Mapped term
.yr	Year
.jw	Journal title word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily
cleed	Ovid database code: EBM Reviews - NHS Economic Evaluation Database
.tx	Full text field (NHS EED)

MULTI-SEARCH STRATEGY	
#	**Searches**
1	exp sleep apnea syndromes/
2	((sleep* or nocturnal) adj2 (apnea* or apnoea*)).ti,ab,kf.
3	(sleep* adj3 disordered adj3 breathing).ti,ab,kf.
4	((sleep* or nocturnal) adj2 (hypopnea* or hypopnoea* or hypo-apnea* or hypo-apnoea* or apneic-hypopneic or apnoeic-hypopnoeic)).ti,ab,kf.
5	((OSA or SAHS) and sleep*).ti,ab,kf.
6	OSAHS.ti,ab,kf.
7	or/1-6
8	7 use pmez
9	exp sleep disordered breathing/
10	((sleep* or nocturnal) adj2 (apnea* or apnoea*)).ti,ab,kw.
11	(sleep* adj3 disordered adj3 breathing).ti,ab,kw.
12	((sleep* or nocturnal) adj2 (hypopnea* or hypopnoea* or hypo-apnea* or hypo-apnoea* or apneic-hypopneic or apnoeic-hypopnoeic)).ti,ab,kw.
13	((OSA or SAHS) and sleep*).ti,ab,kw.
14	OSAHS.ti,ab,kw.
15	or/9-14
16	15 use oemezd
17	8 or 16
18	exp sleep apnea syndromes/
19	((sleep* or nocturnal) adj2 (apnea* or apnoea*)).ti,ab,tx.
20	(sleep* adj3 disordered adj3 breathing).ti,ab,tx.
21	((sleep* or nocturnal) adj2 (hypopnea* or hypopnoea* or hypo-apnea* or hypo-apnoea* or apneic-hypopneic or apnoeic-hypopnoeic)).ti,ab,tx.
22	((OSA or SAHS) and sleep*).ti,ab,tx.
23	OSAHS.ti,ab,tx.
24	or/18-23
25	24 use cleed
26	*economics/
27	exp *"costs and cost analysis"/
28	(economic adj2 model*).mp.
29	(cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s).ti,ab.
30	(cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs).ti.
31	(life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s).ab.
32	(cost or economic*).ti. and (costs or cost-effectiveness or markov).ab.
33	or/26-32
34	17 and 33
35	25 or 34
36	limit 35 to english language
37	limit 35 to french [Limit not valid in CLEED; records were retained]

MULTI-SEARCH STRATEGY	
#	**Searches**
38	36 or 37
39	remove duplicates from 38

OTHER DATABASES	
PubMed	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used.

Patient Experiences and Preferences Database Search

OVERVIEW	
Interface:	Ovid
Databases:	Embase MEDLINE Daily and MEDLINE MEDLINE In-Process & Other Non-Indexed Citations PsycINFO **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	March 2016
Alerts:	Monthly search updates until project completion
Study Types:	Patient experiences and preferences
Limits:	Date limit: 2006-present Language limit: English- and French-language Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj	Requires words are adjacent to each other (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.kw	Author keyword (Embase); Keyword (CDSR and DARE)
.kf	Author keyword heading word (MEDLINE)
.mp	Mapped term
.yr	Year
.jw	Journal title word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily
psyb	Ovid database code; PsycINFO 1967 to present
freq=2	Frequency (must appear at least two times)

MULTI-SEARCH STRATEGY	
#	**Searches**
1	exp *sleep apnea syndromes/
2	((sleep* or nocturnal) adj2 (apnea* or apnoea*)).ti,kf.
3	(sleep* adj3 disordered adj3 breathing).ti,kf.
4	((sleep* or nocturnal) adj2 (hypopnea* or hypopnoea* or hypo-apnea* or hypo-apnoea* or apneic-hypopneic or apnoeic-hypopnoeic)).ti,kf.
5	((OSA or SAHS) and sleep*).ti,kf.
6	OSAHS.ti,kf.
7	or/1-6
8	7 use pmez
9	exp *sleep disordered breathing/
10	((sleep* or nocturnal) adj2 (apnea* or apnoea*)).ti,kw.
11	(sleep* adj3 disordered adj3 breathing).ti,kw.
12	((sleep* or nocturnal) adj2 (hypopnea* or hypopnoea* or hypo-apnea* or hypo-apnoea* or apneic-hypopneic or apnoeic-hypopnoeic)).ti,kw.
13	((OSA or SAHS) and sleep*).ti,kw.
14	OSAHS.ti,kw.
15	or/9-14
16	15 use oemezd
17	*sleep apnea/
18	((sleep* or nocturnal) adj2 (apnea* or apnoea*)).ti.
19	(sleep* adj3 disordered adj3 breathing).ti.
20	((sleep* or nocturnal) adj2 (hypopnea* or hypopnoea* or hypo-apnea* or hypo-apnoea* or apneic-hypopneic or apnoeic-hypopnoeic)).ti.
21	((OSA or SAHS) and sleep*).ti.
22	OSAHS.ti.
23	or/17-22
24	23 use psyb
25	8 or 16 or 24
26	exp patient acceptance of health care/ or caregivers/
27	26 use pmez,psyb
28	exp patient attitude/ or patient preference/ or patient participation/ or patient satisfaction/ or patient decision making/ or caregiver/ or relative/ or caregiver burden/ or caregiver support/
29	28 use oemezd
30	((patient or patients or proband* or individuals or survivor* or family or families or familial or kindred* or relative or relatives or care giver* or caregiver* or carer or carers or personal or spous* or partner or partners or couples or users or participant* or people or child* or teenager* or adolescent* or youth or girls or boys or adults or elderly or females or males or women* or men or men's or mother* or father* or parents or parent or parental or maternal or paternal) and (preference* or preferred or input or experience or experiences or value or values or perspective*

MULTI-SEARCH STRATEGY	
#	**Searches**
	or perception* or perceive or perceived or expectation* or choice* or choose* or choosing or "day-to-day" or lives or participat* or acceptance or acceptability or acceptable or accept or accepted or adheren* or adhere or nonadheren* or complian* or noncomplian* or willingness or convenience or convenient or challenges or concerns or limitations or quality of life or satisfaction or satisfied or dissatisfaction or dissatisfied or burden or attitude* or knowledge or belief* or opinion* or understanding or lessons or reaction* or motivation* or motivated or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding or empower* or survey* or focus group* or interview* or questionnaire* or Likert or qualitative or theme* or thematic or barrier* or facilitator*)).ti.
31	((patient or patients or proband* or individuals or survivor* or family or families or familial or kindred* or relative or relatives or care giver* or caregiver* or carer or carers) adj2 (preference* or preferred or input or experience or experiences or value or values or perspective* or perception* or perceive or perceived or expectation* or choice* or choose* or choosing or "day-to-day" or lives or participat* or acceptance or acceptability or acceptable or accept or accepted or adheren* or adhere or nonadheren* or complian* or noncomplian* or willingness or convenience or convenient or challenges or concerns or limitations or quality of life or satisfaction or satisfied or dissatisfaction or dissatisfied or burden or attitude* or knowledge or belief* or opinion* or understanding or lessons or reaction* or motivation* or motivated or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding or empower* or survey* or focus group* or interview* or questionnaire* or Likert or qualitative or theme* or thematic or barrier* or facilitator*)).ab,kf.
32	((patient or patients or proband* or individuals or survivor* or family or families or familial or kindred* or relative or relatives or care giver* or caregiver* or carer or carers) adj7 (preference* or preferred or input or experience or experiences or value or values or perspective* or perception* or perceive or perceived or expectation* or choice* or choose* or choosing or "day-to-day" or lives or participat* or acceptance or acceptability or acceptable or accept or accepted or adheren* or adhere or nonadheren* or complian* or noncomplian* or willingness or convenience or convenient or challenges or concern or limitations or quality of life or satisfaction or satisfied or dissatisfaction or dissatisfied or burden or attitude* or knowledge or belief* or opinion* or understanding or lessons or reaction* or motivation* or motivated or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding or empower* or survey* or focus group* or interview* or questionnaire* or Likert or qualitative or theme* or thematic or barrier* or facilitator*)).ab. /freq=2
33	((personal or spous* or partner or partners or couples or users or participant* or people or child* or teenager* or adolescent* or youth or girls or boys or adults or elderly or females or males or women* or men or men's or mother* or father* or parents or parent or parental or maternal or paternal) adj2 (preference* or preferred or input or experience or experiences or value or values or perspective* or perception* or perceive or perceived or expectation* or choice* or choose* or choosing or "day-to-day" or lives or participat* or acceptance or acceptability or acceptable or accept or accepted or adheren* or adhere or nonadheren* or complian* or noncomplian* or willingness or convenience or convenient or challenges or concerns or limitations or quality of life or satisfaction or satisfied or dissatisfaction or dissatisfied or burden or attitude* or knowledge or belief* or opinion* or understanding or lessons or reaction* or motivation* or motivated or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding or empower* or survey* or focus group* or interview* or questionnaire* or Likert or qualitative or theme* or thematic or barrier* or facilitator*)).ab. /freq=2
34	(patient adj (reported or centered* or centred* or focused)).ti,ab,kf.
35	(treatment* adj2 (satisf* or refus*)).ti,ab,kf.
36	(lived experience* or shared decision making).ti,ab,kf.

MULTI-SEARCH STRATEGY	
#	**Searches**
37	or/27,29-36
38	25 and 37
39	limit 38 to yr="2006 -Current"
40	39 not conference abstract.pt.
41	limit 40 to english language
42	limit 40 to french
43	41 or 42
44	remove duplicates from 43

OTHER DATABASES	
PubMed	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used.
CINAHL	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used, including the addition of CINAHL headings.

Ethics Implications Database Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE Daily and MEDLINE MEDLINE In-Process & Other Non-Indexed Citations **Note:** Duplicates between databases were removed in Ovid.
Date of Search:	March 2016
Alerts:	Monthly search updates until project completion
Study Types:	Ethics/Legal/Social
Limits:	Date limit: none Language limit: English- and French-language

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj	Requires words are adjacent to each other (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word
.fs	Floating subheading

MULTI-STRATEGY SEARCH	
#	**Searches**
1	exp Ethics/
2	exp Privacy/
3	exp Sociology/
4	exp Jurisprudence/
5	exp Psychology, Social/
6	"Legislation & Jurisprudence".fs.
7	ethics.fs.
8	exp Geography, Medical/
9	exp Environmental Pollution/
10	Medically Underserved Area/
11	(waste* or pollution or polluting or contamination or contaminated).ti,ab,kf.
12	((Healthcare or Health Care or nonclinical or Community Based) adj (Deliver* or Distribution* or System*)).ti,ab,kf.

MULTI-STRATEGY SEARCH	
#	**Searches**
13	(geographic adj (region* or area*)).ti,ab,kf.
14	(remote or urban or rural).ti,ab,kf.
15	(ethic or ethics or ethical or moral* or bioethic*).ti,ab,hw,kf.
16	(legal* or liabilit* or litigation* or constitutional or justice or law or laws or jurisprudence or complicit*).ti,ab,hw,kf.
17	(lawsuit* or lawyer* or lawmaker*).ti,ab,kf.
18	human right*.ti,ab,kf.
19	civil right*.ti,ab,kf.
20	(prejudice* or stigma or stigmas or stigmatization or stigmatize or stigmatise or stigmatisation or inequalit* or fairness).ti,ab,kf.
21	((care or treatment) adj2 (duty or obligat*)).ti,ab,kf.
22	(social* adj (responsibl* or obligat*)).ti,ab,kf.
23	(communitarian* or beneficence or nonmaleficence or non-maleficence or accountability).ti,ab,kf.
24	harm.ti,ab,kf.
25	(privacy or private or confidential*).ti,ab,hw,kf.
26	((informed or presumed) adj2 (consent or choice or decision making)).ti,ab,kf.
27	autonomy.ti,ab,hw,kf.
28	transparency.ti,ab,kf.
29	or/1-28
30	exp *sleep apnea syndromes/
31	((sleep* or nocturnal) adj2 (apnea* or apnoea*)).ti,kf.
32	(sleep* adj3 disordered adj3 breathing).ti,kf.
33	((sleep* or nocturnal) adj2 (hypopnea* or hypopnoea* or hypo-apnea* or hypo-apnoea* or apneic-hypopneic or apnoeic-hypopnoeic)).ti,kf.
34	((OSA or SAHS) and sleep*).ti,kf.
35	OSAHS.ti,kf.
36	or/30-35
37	29 and 36
38	limit 37 to english language
39	limit 37 to french
40	38 or 39
41	remove duplicates from 40

OTHER DATABASES	
PubMed	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used.
CINAHL	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used, including the addition of CINAHL headings.

Grey Literature

Dates for Search:	March 2016
Keywords:	Sleep apnea, obstructive sleep apnea, sleep disordered breathing
Limits:	Publication years: HTA/SR/MA — 2011 to present; Economics — no date limit; Patient experiences and preferences — 2006 to present; Ethics — no date limit

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for searching health-related grey literature" (https://www.cadth.ca/grey-matters), will be searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Databases (free)
- Internet Search
- Open Access Journals.

APPENDIX 2: FULL-TEXT SCREENING CHECKLIST

Reviewer: _____ **Date:** _____

Ref ID: **Author:** **Publication Year:**			
Did the SR include:	**Yes (Include)**	**Unclear (Include or Exclude)[a]**	**No (Exclude)**
1) Adults (i.e., aged ≥ 18 years), diagnosed with OSA and with or without comorbidities (according to Table 1)	☐	☐	☐
2) The interventions of interest: • PAP devices (i.e., APAP, BiPAP, CPAP, EPAP) • Oral appliances (i.e., MAD, tongue-retaining device) • Surgical interventions (i.e., genial tubercle advancement, MMA, nasal surgery, pharyngoplasty, radiofrequency ablation of tissue in soft palate, uvulopalatopharyngoplasty, uvulopalatoplasty) • Lifestyle modifications (exercise program, diet or weight-loss program, positional therapy)	☐	☐	☐
3) The comparators of interest: • Inactive control • Active control	☐	☐	☐
4) The outcomes of interest: • Immediate symptoms (sleepiness, fatigue, snoring) • OSA severity • Accidents • Health-related quality of life • Mortality • Cardiovascular events • Type 2 diabetes mellitus • Cognitive function • Psychological function • Compliance • Change in facial aesthetics (for MMA) • Adverse events (i.e., any types, including surgical complications, harms, and treatment withdrawal due to adverse events)	☐	☐	☐

Ref ID: **Author:** **Publication Year:**			
Did the SR include:	**Yes (Include)**	**Unclear (Include or Exclude)[a]**	**No (Exclude)**
5) The study designs of interest: • SR • MA • HTA	☐	☐	☐
Decision to include the SR:[b]	**Yes** ☐		**No** ☐
Reason(s) for exclusion:	☐ Inappropriate study population ☐ No intervention of interest ☐ No or inappropriate comparator ☐ No relevant outcomes ☐ Irrelevant study design ☐ Study description only ☐ Other:----------		

APAP = autotitrating positive airway pressure; BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; EPAP = expiratory positive airway pressure; HTA = health technology assessment; MA = meta-analysis; MAD = mandibular advancement device; MMA = maxillomandibular advancement; OSA = obstructive sleep apnea; PAP = positive airway pressure; RCT = randomized controlled trial; SR = systematic review.

[a] This will be discussed with a second reviewer.

[b] If all items above are answered "yes" or "unclear," then the study will be included.

Did the SR report any data relevant to another research question (RQ)? □ Yes: RQ# _____ □ No

APPENDIX 3: DATA EXTRACTION FORM

Reviewer: _____ **Date:** _____

STUDY CHARACTERISTICS	
Ref ID:	
Author(s):	
Publication title	
Publication year:	
Country (where the study was conducted):	
Funding:	

METHODOLOGY	
Study design:	□ SR □ MA □ HTA
Number of included studies:	
Total number of participants within studies included in the review:	
Study eligibility criteria:	
Type of included studies:	
Range of publication years of included studies:	
Databases searched:	
Search period:	
Quality assessment tool:	
Subgroup analyses and/or meta-regression:	

HTA = health technology assessment; MA = meta-analysis; SR = systematic review.

COMPARISON	
Intervention:	
Comparator:	
Range of therapy duration:	

REPORTED OUTCOMES	
Primary (including definition):	
Secondary (including definition):	
Length of follow-up:	

RESULTS (TO BE COMPLETED FOR EACH COMPARISON AND OUTCOME)	
Comparison	
Intervention:	
Comparator:	
Outcome	
Study (1st author) [REF ID]	

RESULTS (TO BE COMPLETED FOR EACH COMPARISON AND OUTCOME)	
Number of included studies:	
Range of publication years of included studies:	
Study population (i.e., OSA severity and comorbidities)	
Pairwise MA	
Treatment effect (95% CI)	
***P* value for effect**	
I^2 statistics	
NMA	
Treatment effect (95% CI)	
***P* value for effect**	
Subgroups	
Subgroup 1:	
Number of included studies	
Treatment effect (95% CI)	
***P* value for effect**	
I^2 statistics	
Subgroup 2:	
Number of included studies	
Treatment effect (95% CI)	
***P* value for effect**	
I^2 statistics	
(Add subgroups as needed)	
Meta-regression	
Variables	
Variable 1:	
Variable 2:	
(Add variables as needed)	
Main conclusions:	

CI = confidence interval; MA = meta-analysis; NMA = network meta-analysis; OSA = obstructive sleep apnea.

Did the SR report any data relevant to another research question (RQ)? □ Yes: RQ# _____ □ No

APPENDIX 4: DATA EXTRACTION FORM — PATIENT PREFERENCES REVIEW

Reviewer: _____ **Date:** _____

STUDY CHARACTERISTICS	
Ref ID:	
First author:	
Publication title:	
Publication year:	
Country (where data were generated):	
Setting (where data were generated):	
Funding sources:	
Ethics approval:	□ Yes □ No Comments:
Study design:	□ Descriptive survey □ Ethnography □ Phenomenology □ Grounded theory □ Qualitative description □ Other (specify):
Study objectives:	
Eligibility criteria:	
Recruitment method:	
Sample size:	
Participant characteristics:	
Age	
Sex	
Income	
Education	
Relationship status	
Other	
Data collection methods:	□ Questionnaire □ Interview □ Focus group □ Observation □ Document review □ Other (specify):
Data analysis methods	
STUDY RESULTS	
Results statements will typically, but not always, be presented within the "results" section of a report. Results statements do not include raw data, study methods, external data, and researchers' conclusions and implications. Result statements from the eligible articles relevant to the research question will be captured for analysis using NVivo qualitative data analysis software (QSR International Pty Ltd. Version 11, 2015).[43]	

APPENDIX 5: QUALITY APPRAISAL CRITERIA — SURVEYS

Reviewer: _____ **Date:** _____

STUDY CHARACTERISTICS	
Ref ID:	
First author:	
Publication year:	
1. Was ethics approval obtained?	□ Yes □ No □ Unclear Comments:
RESEARCH QUESTION AND STUDY DESIGN	
2. Are the research questions and/or objectives clearly stated?	□ Yes □ No □ Unclear Comments:
3. Are the research questions suitable for a survey design?	□ Yes □ No □ Unclear Comments:
PARTICIPANTS AND SAMPLING	
4. Is the sampling strategy clearly described?	□ Yes □ No □ Unclear Comments:
5. Is the sampling strategy congruent with the research questions and/or objectives?	□ Yes □ No □ Unclear Comments:

PARTICIPANTS AND SAMPLING	
6. Is the sample of participants representative of the target sample or the population to which the findings will be generalized?	□ Yes □ No □ Unclear Comments:
7. Could the way the sample was obtained introduce selection bias?	□ Yes □ No □ Unclear Comments:
8. Was a sufficient sample size calculation provided?	□ Yes □ No □ Unclear Comments:
DATA COLLECTION	
9. Was a pilot test of survey methods conducted?	□ Yes □ No □ Unclear Comments:
10. Was the study questionnaire valid?	□ Yes □ No □ Unclear Comments:
11. Was the study questionnaire reliable?	□ Yes □ No □ Unclear Comments:
DATA ANALYSIS	
12. Were the data analysis strategies appropriate for the type of data collected?	□ Yes □ No □ Unclear Comments:
13. Were all analyses planned a priori?	□ Yes □ No □ Unclear Comments:

RESULTS	
14. Was a satisfactory response rate achieved?	□ Yes □ No □ Unclear Comments:
15. Were all significant and non-significant quantitative results reported?	□ Yes □ No □ Unclear Comments:
16. Were all qualitative results, resulting from open-ended questions, summarized and reported?	□ Yes □ No □ Unclear Comments:
DISCUSSION AND CONCLUSIONS	
17. Have the researchers drawn an appropriate link between the data and their conclusions?	□ Yes □ No □ Unclear Comments:
18. Have all potential biases been identified and discussed?	□ Yes □ No □ Unclear Comments: