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

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This report is prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). This report contains a comprehensive review of existing public literature, studies, materials, and other information and documentation (collectively the “source documentation”) available to CADTH at the time it was prepared, and it was guided by expert input and advice throughout its preparation.

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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TABLE OF CONTENTS

CLINICAL REVIEW

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

Study Design

As a follow-up to the overview of reviews conducted for Research Questions 1a and 1b in the main health technology assessment (HTA) protocol,[1] and to address gaps within the published systematic review (SR) literature, an SR of relevant published primary studies on the clinical effectiveness, comparative clinical effectiveness, and safety of interventions for the treatment of obstructive sleep apnea (OSA) in adults will be conducted. Specifically, this SR will focus on addressing Research Questions 1a and 1b, in relation to certain combinations of interventions, comparators, and outcomes that are missing in the overview of reviews, as listed in Table 1.

Literature Search

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

Published literature was identified by searching the following bibliographic databases: MEDLINE with in-process records and daily updates via Ovid; Embase via Ovid; The Cochrane Central Register of Controlled Trials via Ovid; and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were sleep apnea, sleep disordered breathing, expiratory positive airway pressure (EPAP), tongue-retaining devices, mandibular advancement devices, genial tubercle advancement, maxillomandibular advancement, positive airway pressure (PAP) devices, and lifestyle modifications.

No methodological filters were applied to limit retrieval. Retrieval was limited to documents published since January 1, 2006. The search was also limited to English- or French-language publications. Conference abstracts were excluded from the search results. See Appendix 1 for the detailed search strategy.

This search was completed in June 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.

Relevant websites from the CADTH grey literature checklist, "Grey matters: a practical tool for searching health-related grey literature" (https://www.cadth.ca/grey-matters), have previously been searched, using the methods described in the main HTA protocol.[1] An additional search of clinical trial registries will be undertaken to retrieve study data from completed trials. See Appendix 1 for more information on the grey literature search strategy.

Selection Criteria

Selection criteria are outlined in Table 1 and are mainly consistent with the selection criteria outlined within the main HTA protocol,[1] relevant to Research Questions 1a and 1b. As this review is designed to focus on identified gaps within the published SR literature, only certain combinations of interventions, comparators, and outcomes are of interest, in accordance with those gaps, as identified within Table 1.

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)

Intervention and comparator combinations:

- EPAP versus active comparators, including:
  - PAP devices (i.e., APAP, BiPAP, or CPAP)
  - Oral appliances (i.e., MAD[d] or TRD)
  - Surgery (i.e., GTA or MMA)
  - Lifestyle modifications[e] (i.e., exercise, diet, or weight loss program or positional therapy[f])
- MAD[d] versus active comparators, including:
  - Other oral appliances (i.e., TRD)
  - Lifestyle modifications[e] (i.e., exercise, diet, or weight loss program or positional therapy[f])
- TRD versus inactive and active comparators, including:
  - Inactive controls (e.g., pre-treatment, oral placebo, sham therapy, or supportive care)
  - PAP devices (i.e., APAP, BiPAP, or CPAP)
  - Surgery (i.e., GTA or MMA)
  - Lifestyle modifications[e] (i.e., exercise, diet, or weight loss program or positional therapy[f])
- GTA versus inactive and active comparators, including:
  - Inactive controls (e.g., pre-treatment, oral placebo, sham therapy, or supportive care)
  - PAP devices (i.e., APAP, BiPAP, or CPAP)
  - Oral appliances (i.e., MAD[d] or TRD)
  - Other surgery (i.e., MMA)
  - Lifestyle modifications[e] (i.e., exercise, diet, or weight loss program or positional therapy[f])
- MMA versus active comparators, including:
  - PAP devices (i.e., APAP, BiPAP, or CPAP)
  - Oral appliances (i.e., MAD[d] or TRD)
  - Lifestyle modifications[e] (i.e., exercise, diet, or weight loss program or positional therapy[f])

Intervention and comparator combinations:

- MMA versus inactive comparators, including:
  - Inactive controls (e.g., pre-treatment, oral placebo, sham therapy, or supportive care)

For the following outcomes:

- Mortality
- Change in facial aesthetics

• Positional therapy versus inactive comparators, including:
  ○ Inactive controls (e.g., pre-treatment, oral placebo, sham therapy, or supportive care)
• Combination therapy (i.e., combinations of two or more PAP, oral appliance, surgery, or lifestyle modification[e] interventions) versus:
  ○ Inactive controls (e.g., pre-treatment, oral placebo, sham therapy, or supportive care)
  ○ Active comparators (i.e., PAP devices, oral appliances, surgery, and lifestyle modifications[e])
 	
For the following 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: For intervention and comparator combinations that involve an active comparator, studies of the following designs will be considered for inclusion: • RCTs • Non-randomized controlled studies (i.e., controlled clinical trials, cohort studies, case-control studies, and controlled before-and-after studies) In addition, for intervention and comparator combinations that include an inactive comparator, studies of the following design will additionally be considered for inclusion: • Uncontrolled pre-and-post studies
Timeframe: • Publications within the last 10 years (i.e., between January 2006 and May 2016)[h]

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; GTA = genial tubercle advancement; h = hour; MAD = mandibular advancement device; MI = myocardial infarction; MMA = maxillomandibular advancement; OA = oral appliance; ODI = oxygen desaturation index; OSA = obstructive sleep apnea; PAP = positive airway pressure; PSG = polysomnography; RCT = randomized controlled trial; RDI = respiratory disturbance index; TRD = tongue-retaining device.

[a] Studies that included participants aged < 18 years old will be included if ≥ 80% were adults aged ≥ 18 years or if data for participants aged ≥ 18 years are presented separately.

[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, or if data for participants with OSA are presented separately.

[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.

[h] The date limit of 10 years was established in consultation with clinical experts based on their understanding that this limit would capture studies relevant to current clinical practice.

Exclusion Criteria

Studies will be excluded if they do not meet the selection criteria outlined in Table 1, if they are case series or case reports, or if they are duplicate publications. Multiple publications of the same study will be excluded, unless they provide additional information on the outcomes of interest. There is no restriction regarding the therapy duration or length of follow-up. Studies will be excluded if they are not published in English or French.

Screening and Selecting Studies for Inclusion

Two reviewers will independently screen titles and abstracts of all citations retrieved from the literature search, 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.[2] A list of excluded studies, with reasons for exclusion after full-text review, will be provided. A full-text screening checklist is in Appendix 2.

Data Extraction

A standardized data extraction form has been designed a priori to document and tabulate information from included studies and can be found in Appendix 3. Relevant information includes both descriptive data and results reported in all included studies; for example, participant characteristics, types of interventions and controls, therapy duration, length of follow-up, outcomes, results, and subgroup analyses.

Data from each included study will be extracted by one reviewer and checked for accuracy by a second reviewer. Disagreements will be resolved through discussion, involving a third reviewer, if necessary. Data from figures will be extracted if explicit numerical data are reported. Authors of the included studies will be contacted to provide any missing information or clarify any issues.

Risk of Bias Assessments

One reviewer will independently assess the risk of bias of the included studies, using a study design–specific risk of bias assessment tool, and another reviewer will check the assessments for accuracy. Disagreements will be resolved through discussion, involving a third reviewer, if necessary. Randomized controlled trials will be assessed using the Cochrane Risk of Bias Tool.[3] Non-randomized studies will be assessed using the Risk of Bias Assessment Tool for Non-randomized Studies.[4] Results of the risk of bias assessments will not be used to exclude studies from the review.

Summary of Evidence

Description of Study Characteristics

A summary of study characteristics, including the total number of studies by population, intervention, comparator, outcomes, and study design (PICOS) elements, years of publication, and countries of development, will be provided in the form of tables and a narrative summary.

Data Synthesis Methods

The results of the included studies will be pooled, using meta-analysis, if appropriate. If pooling is not appropriate — due to too few studies, skewed data, or significant clinical, methodological or statistical heterogeneity (see below for more information) that is unexplained or that cannot be addressed analytically — the findings for the group of studies will be synthesized narratively. As within the main HTA protocol,[1] among PAP devices, EPAP will be considered separately from the others (i.e., APAP, BiPAP, and CPAP), which will be considered as one group. The interventions under oral appliances, surgery, and lifestyle modifications will be considered separately.

Between-study heterogeneity within groups of studies being considered for pooling will be assessed, using graphical presentations (including forest plots and plots of outcomes against covariates), calculations of the I-squared (I^2) and Cochran's Q test statistics,[5] and the precision of estimates, as indicated by the summary and predictive confidence intervals. An $I^2 \geq 75\%$ will be interpreted to indicate considerable heterogeneity across studies, as suggested by the *Cochrane Handbook for Systematic Reviews of Interventions*.[5] Cochran's Q test statistics — based on chi-squared, where I^2 = (Q-degrees of freedom)/Q — will be used to test for the presence of heterogeneity, based on a level of significance of 10%. Clinical and methodological heterogeneity will be assessed in consultation with the clinical experts.

Reasons for observed heterogeneity will be explored by subgroup or multivariate regression analyses, given the availability of the data. Further detail is given of proposed patient-related subgroups below. Individual contrasts will be summarized separately, and the consistency assessed. Additional sensitivity analyses dealing with study outliers, study size, study quality,

study design, and other study- or design-related factors will also be considered to establish the robustness of findings.

If pooling of outcome data is appropriate, summary measures and confidence intervals for the reported outcomes will be reported, as described below. If pooling is not appropriate, a narrative synthesis will include the presentation of findings within summary tables, alongside study and clinical characteristics believed to contribute to heterogeneity, as determined during the exploration of the data. A narrative description will aim to synthesize the direction and size of any observed effects across studies in the absence of a meta-analysis and will include an assessment of the likelihood of clinical benefit or harm.

Meta-analyses would be carried out using the Cochrane Review Manager software, version 5.3,[6] to derive pooled estimates for each outcome of interest. In the event of unexplained heterogeneity, a random-effects model will be used; otherwise, a fixed-effects model will be used. In the event that both randomized and non-randomized studies report on the same outcome, randomized controlled trials will be considered separately from non-randomized studies. The influence of study design will be explored in sensitivity analyses.

Dichotomous outcomes (e.g., mortality or incidence of stroke) will be summarized, using relative risks and 95% confidence intervals (CIs) (or odds ratios and 95% CIs, if case-control studies are included). Continuous outcomes will be summarized, using differences in means and 95% CIs, if appropriate. If indicated (e.g., for quality of life scales), standard methods for converting between units of measurement will be used. For outcomes reported as time-to-event and given available individual patient data in the form of a survival curve or table of events or patients at risk, analyses will be performed, using Kaplan–Meier curves and Cox regression. If studies report adjusted-effects measures, the adjusted results in the primary analysis will be used, with the unadjusted result in exploratory analyses, with comments on any differences between the two. Forest plots will be shown for all individual summary estimates.

As within the main HTA protocol,[1] for each outcome of interest, analysis will be conducted for the overall study population and also for each subgroup, listed in Table 1, as the data permit. Results from the analysis of primary studies, as outlined within this protocol, will be combined with the narrative synthesis conducted as part of the overviews of reviews, as outlined in the main HTA protocol.[1]

Description of Risk of Bias Assessments

A narrative summary of the results of the risk of bias assessment for each included study will be provided. Specifically, tables will be developed to present the answers to the questions within the risk of bias tools, along with a narrative description of the strengths and limitations of the included studies within the main text of the report to provide the reader with an overview of the literature.

REFERENCES

1. Interventions for the treatment of obstructive sleep apnea in adults: a health technology assessment — project protocol [Internet]. Ottawa: CADTH; 2016 Apr. [cited 2016 May 31]. (CADTH optimal use report; vol. 6, no. 1a). Available from: https://www.cadth.ca/sites/default/files/pdf/OP0525_OSA_Protocol.pdf
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3. Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions [Internet]. Version 5.1.0. Oxford (UK): The Cochrane Collaboration; 2011 Mar. Table 8.5.a: the Cochrane Collaboration's tool for assessing risk of bias. [cited 2016 Jun 10]. Available from: http://handbook.cochrane.org/chapter_8/table_8_5_a_the_cochrane_collaborations_tool_for_assessing.htm
4. Kim SY, Park JE, Lee YJ, Seo HJ, Sheen SS, Hahn S, et al. Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. J Clin Epidemiol. 2013 Apr;66(4):408-14.
5. Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions [Internet]. Version 5.1.0. Oxford (UK): The Cochrane Collaboration; 2011 Mar. [cited 2016 Jun 10]. Available from: http://handbook.cochrane.org/
6. Review manager (RevMan) [computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2014.

APPENDIX 1: LITERATURE SEARCH STRATEGY

Supplemental Clinical Database Search for Primary Studies

OVERVIEW	
Interface:	Ovid
Databases:	Embase MEDLINE Epub Ahead of Print MEDLINE Daily and MEDLINE MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	May/June 2016
Alerts:	Monthly search updates until project completion
Study Types:	Not limited by study design
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 within a specified range (in any order)
.ti	Title
.ab	Abstract
.pt	Publication type
.kw	Author keyword (Embase)
.kf	Author keyword heading word (MEDLINE)
.yr	Year
ppez	Ovid database code; MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULIT-STRATEGY DATABASE	
#	**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	(Expiratory positive airway pressure or EPAP).ti,ab,kf.
9	(tongue adj2 (retain* or reposition* or stabiliz* or stabilis* or advancement or retention)).ti,ab,kf.
10	oral appliance*.ti,ab,kf.
11	mandibular advancement/
12	((mandibular or mandible) adj2 (advancement or advancing or protruding or reposition*)).ti,ab,kw.
13	((genial tubercle or genioglossus) adj2 advanc*).ti,ab,kf.
14	Orthognathic surgery/
15	((maxillomandibular or maxillo-mandibular or bimaxillary) adj2 advanc*).ti,ab,kf.
16	((maxillomandibular or maxillo-mandibular or bimaxillary) adj2 osteotom*).ti,ab,kf.
17	Supine position/
18	Prone position/
19	exp Posture/
20	exp Patient positioning/
21	((supine or prone or sleep* or patient*) adj2 position*).ti,ab,kf.
22	(positional therapy or posture).ti,ab,kf.
23	or/8-22
24	7 and 23
25	Continuous positive airway pressure/
26	(continuous positive airway pressure or CPAP).ti,ab,kf.
27	Airway pressure release ventilation.ti,ab,kf.
28	(nCPAP or APAP or BiPAP).ti,ab,kf.
29	((bilevel or bi-level or biphasic or bi-phasic or automatic or autotitrating or auto-titrating or autoadjusting or auto-adjusting or nasal) adj3 (positive airway pressure or CPAP or PAP)).ti,ab,kf.
30	(positive airway pressure or PAP or C-PAP).ti,ab,kf.
31	or/25-30

MULIT-STRATEGY DATABASE	
#	**Searches**
32	exp Life style/
33	exp Weight loss/
34	exp Exercise/
35	exp Diet/
36	(weight adj2 (loss or reduc* or decreas*)).ti,ab,kf.
37	(lifestyle or life style or exercise or diet).ti,ab,kf.
38	or/32-37
39	7 and 31 and 38
40	24 or 39
41	7 and ((combin* or adjunct*) adj2 (therapies or therapy)).ti,ab,kf.
42	40 or 41
43	limit 42 to english language
44	limit 42 to french
45	43 or 44
46	45 use ppez
47	exp sleep disordered breathing/
48	((sleep* or nocturnal) adj2 (apnea* or apnoea*)).ti,ab,kw.
49	(sleep* adj3 disordered adj3 breathing).ti,ab,kw.
50	((sleep* or nocturnal) adj2 (hypopnea* or hypopnoea* or hypo-apnea* or hypo-apnoea* or apneic-hypopneic or apnoeic-hypopnoeic)).ti,ab,kw.
51	((OSA or SAHS) and sleep*).ti,ab,kw.
52	OSAHS.ti,ab,kw.
53	or/47-52
54	Expiratory positive airway pressure/
55	(Expiratory positive airway pressure or EPAP).ti,ab,kw.
56	tongue retaining device/ or tongue repositioning device/ or tongue stabilizing device/ or tongue stabilising device/ or oral appliances/
57	(tongue adj2 (retain* or reposition* or stabiliz* or stabilis* or advancement or retention)).ti,ab,kw.
58	oral appliance*.ti,ab,kw.
59	mandibular reconstruction/
60	((mandibular or mandible) adj2 (advancement or advancing or protruding or reposition*)).ti,ab,kw.
61	genial tubercle advancement/ or genioglossus advancement/
62	((genial tubercle or genioglossus) adj2 advanc*).ti,ab,kw.

MULIT-STRATEGY DATABASE	
#	**Searches**
63	exp orthognathic surgery/
64	((maxillomandibular or maxillo-mandibular or bimaxillary) adj2 advanc*).ti,ab,kw.
65	((maxillomandibular or maxillo-mandibular or bimaxillary) adj2 osteotom*).ti,ab,kw.
66	maxillomandibular advancement/ or maxillo-mandibular advancement/ or bimaxillary advancement/
67	exp body position/
68	body posture/
69	supine position/
70	patient positioning/
71	((supine or prone or sleep* or patient*) adj2 position*).ti,ab,kw.
72	(positional therapy or posture).ti,ab,kw.
73	or/54-72
74	53 and 73
75	(continuous positive airway pressure or CPAP).ti,ab,kw.
76	Airway pressure release ventilation.ti,ab,kw.
77	(nCPAP or APAP or BiPAP).ti,ab,kw.
78	((bilevel or bi-level or biphasic or bi-phasic or automatic or autotitrating or auto-titrating or autoadjusting or auto-adjusting or nasal) adj3 (positive airway pressure or CPAP or PAP)).ti,ab,kw.
79	(positive airway pressure or PAP or C-PAP).ti,ab,kw.
80	or/75-79
81	lifestyle/
82	exp weight reduction/
83	exp exercise/
84	exp diet/
85	(weight adj2 (loss or reduc* or decreas*)).ti,ab,kw.
86	(lifestyle or life style or exercise or diet).ti,ab,kw.
87	or/81-86
88	53 and 80 and 87
89	74 or 88
90	53 and ((combin* or adjunct*) adj2 (therapy or therapies)).ti,ab,kw.
91	89 or 90
92	91 not conference abstract.pt.
93	limit 92 to english language
94	limit 92 to french

MULIT-STRATEGY DATABASE	
#	**Searches**
95	93 or 94
96	95 use oemezd
97	46 or 96
98	limit 97 to yr="2006 -Current"
99	remove duplicates from 98

OTHER DATABASES	
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used.
Cochrane Central Register of Controlled Trials	Searched via Ovid. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used.

Grey Literature

Dates for Search:	May/June 2016
Keywords:	Sleep apnea, obstructive sleep apnea, sleep disordered breathing
Limits:	Publication years: Clinical trials – 2006 to present

Relevant websites from the CADTH grey literature checklist, "Grey matters: a practical tool for searching health-related grey literature" (https://www.cadth.ca/grey-matters), have previously been searched, using the methods described in the main HTA protocol.[1] An additional search of clinical trial registries will be undertaken to retrieve study data from completed trials.

Clinicaltrials.gov
http://clinicaltrials.gov
Search — Studies with results | sleep apnea* OR sleep apnoea* OR sleep disordered breathing

APPENDIX 2: FULL-TEXT SCREENING CHECKLIST

Reviewer: _____ Date: _____

Ref ID: **Author:** **Publication Year:**			
Did the study include:	**Yes (Include)**	**Unclear (Include/ Exclude)[a]**	**No (Exclude)**
1) Adults (i.e., aged ≥ 18 years), diagnosed with OSA and with or without comorbidities (see Table 1 for details)	☐	☐	☐
2) The interventions and comparisons of interest (see Table 1 for details): • EPAP versus all active comparators • MAD versus TRD and lifestyle modifications • TRD versus all inactive and active comparators • GTA versus all inactive and active comparators • MMA versus all active comparators • Combination therapy versus all inactive and active comparators	☐	☐	☐
3) The outcomes of interest (see Table 1 for details): • Immediate symptoms (sleepiness, fatigue, snoring) • OSA severity • Accidents • Health-related quality of life • Mortality • Cardiovascular events • Cerebrovascular event • Blood pressure • Type 2 diabetes mellitus • Cognitive function • Psychological function • Compliance • Change in facial aesthetics (for MMA) • Adverse events	☐	☐	☐
4) The study designs of interest (see Table 1 for details): • RCTs • Non-randomized controlled studies • Uncontrolled pre-and-post studies	☐	☐	☐

Ref ID: **Author:** **Publication Year:**			
Did the study include:	**Yes (Include)**	**Unclear (Include/ Exclude)[a]**	**No (Exclude)**
Decision for including the study:[b]	**Yes** ☐		**No** ☐
Reason(s) for exclusion:	☐ Inappropriate study population ☐ No intervention of interest ☐ No/inappropriate comparator ☐ No relevant outcomes ☐ Irrelevant study design ☐ Study description only ☐ Other: _____		

EPAP = expiratory positive airway pressure; GTA = genial tubercle advancement; MAD = mandibular advancement device; MMA = maxillomandibular advancement; OSA = obstructive sleep apnea; PAP = positive airway pressure; RCT = randomized controlled trial; TRD = tongue-retaining device.

[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.

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:	□ RCT □ Non-randomized controlled study □ Uncontrolled pre-and-post study
Study participant eligibility criteria:	

PATIENT CHARACTERISTICS			
	Total	**Intervention**	**Comparator**
Sample size:			
Age:			
Sex:			
OSA severity:			
Comorbidities:			
BMI:			

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 of interest)								
Outcome	**Intervention**			**Comparator**			**Statistics**	
Dichotomous outcomes	**N**	**No. of events**	**%**	**N**	**# of events**	**%**	**RR (95% CI)**	***P* value**
Outcome 1: e.g., Mortality								
Outcome 2: e.g., Mortality subgroup analysis								
Outcome 3:								
Outcome 4:								
Continuous outcomes	**N**	**Pre**	**Post**	**N**	**Pre**	**Post**	**t-test (95% CI)**	***P* value**
Outcome 1: e.g., ESS								
Outcome 2:----------								
Outcome 3:----------								

BMI = body mass index; CI = confidence interval; ESS = Epworth Sleepiness Scale; OSA = obstructive sleep apnea; RCT = randomized controlled trial; RR = relative risk.