Technology Assessment: Disposition of Comments Report

Title: Long-Term Health Outcomes in Obstructive Sleep Apnea: A Systematic Review of Comparative Studies Evaluating Positive Airway Pressure and the Validity of Breathing Measures as Surrogate Outcomes
(Title prior to review: Continuous Positive Airway Pressure Treatment for Obstructive Sleep Apnea)

Draft report available for public comment from March 30, 2021 to April 28, 2021.

Citation: Balk EM, Adam GP, Cao W, Reddy Bhuma M, Forbes S, Mehta S, Panagiotou O, D'Ambrosio C. *Long-Term Health Outcomes in Obstructive Sleep Apnea: A Systematic Review of Comparative Studies Evaluating Positive Airway Pressure and Validity of Breathing Measures as Surrogate Outcomes*. Project ID: SLPT0919. (Prepared by the Brown Evidence-based Practice Center under Contract No. 290-2015-00002-I/Task Order No. 75Q80119F32017.) Rockville, MD: Agency for Healthcare Research and Quality. December 2022.

Available at: https://www.ahrq.gov/research/findings/ta/index.html.

Comments to Draft Report

Draft reports by the Effective Health Care (EHC) Program undergo peer review and public comment. The Program encourages the public to participate in the development of its research projects. Each draft report is posted to the EHC Program Web site or AHRQ Web site for public comment for a 3-4-week period. Comments can be submitted via the Web site, mail or E-mail. At the conclusion of the public comment period, authors use the commentators' comments to revise the draft report.

Comments on draft reports and the authors' responses to the comments are posted for public viewing on the Web site approximately 3 months after the final report is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

This document includes the responses by the authors of the report to comments that were submitted for this draft report. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Summary of Peer Reviewer Comments and Author Response

This research review underwent peer review before the draft report was posted for public comment on the EHC website.

- Peer reviewers made suggestions regarding wording, such as preferred use of adherence over compliance, correct terminology for sleep testing devices, distinguishing types of positive airway pressure devices, and others.
    - We revised the full document accordingly.
- Suggestions were made to include a more thorough discussion of arousal related events in the Contextual Questions.
    - This was done.
- Comments were made regarding the study eligibility criteria and evaluated outcomes that had been finalized in the protocol, specifically related to shorter-term outcomes, blood pressure, and sleepiness.
    - Throughout and repeatedly, we made the scope of the report more explicit, included these concepts as limitations, and in the Discussion summarized existing systematic reviews regarding outcomes not covered by this report.
- It was stated that the review minimized the issue of adherence.
    - Further text and analyses were added to better describe our findings.
- It was suggested that the original (succinct) title did not capture the scope of the review.
    - We substantially revised the title.
- There were comments about potentially confusing or misleading conclusion statements.
    - We revised the conclusion statements to be more conservative and focused on the design type (e.g., RCTs do not provide evidence that…).
- One reviewer found the nomenclature for the outcomes of interest confusing.
    - We changed “clinically significant outcomes” to “long-term clinical outcomes.”
- It was noted that the draft did not have sufficient information about the individual studies’ eligibility criteria.
    - We added information, particularly related to cardiovascular risk factors and sleepiness criteria, and also about adherence.
- Suggestions were made on how to improve the Future Research section specifically regarding the difficulty conducting RCTs in patients with OSA.
    - We incorporated suggestions, including adding further discussion of appropriate analytic techniques for observational studies.
- Reviewers praised the well-written Introduction/Background, clear Methods, excellent discussions related to the Contextual Questions, an appropriate critique of the inconsistencies in definitions of sleep measures, thorough Results section, and a well-articulated, thorough Discussion.

Public Comments and Author Response

Commentator & Affiliation	Section	Comment	Response
Beaumont Hospital, Dearborn, MI	General	I have about 20 year experience working in sleep medicine. I have seen first hand how CPAP keeps patients from falling asleep at work and get better sleep at night	Thank you
Nox Health	Evidence Summary	"Missing from the summary is the fact that in most all trials with CPAP the adherence (compliance) to CPAP therapy is very poor, and the definition of ""compliance"" typically used is woefully inadequate with regards to sleep-related outcomes. Current definitions of CPAP compliance are based on Center for Medicare/Medicaid reimbursement minimums that stipulate 4 hours of nightly CPAP use over 70% of nights as meeting the definition of ""complaint"". Sleep clinicians and researchers alike know that this is a false metric and as such does not qualify as a definitive measurement to base outcome analyses upon. While we cannot re-write past CPOAP treatment trials, I suggest that the AHRQ make a statement about the inadequacy of the current CPAP clinical trials due to the definition and the questionable methodological issues with treatment adequacy with CPAP. Unlike other medication or disease-altering medical therapies, CPAP only works when it is used to restore natural sleep duration, timing and quality. CPAP itself does not provide a medical outcome; healthy sleep is what results in medical, quality of life, safety and health-related financial outcomes. While the AHRQ should not change the result of this review, it is critical to the field of sleep medicine and to the millions of Americans with sleep-disordered breathing that the conclusions of this review be contextualized to	We have added more information about adherence into the Main Points and various other parts of the results and discussion. We did not systematically assess, and therefore do not comment, on the validity of various definitions of adherence/compliance.

Commentator & Affiliation	Section	Comment	Response
		include the fact that studies are limited by limited CPAP use and even more so by the non-physiological definition of CPAP compliance adopted by clinical researchers due to economic pressures placed on the filled of sleep medicine by governmental payer organizations."	
Nox Health	Evidence Summary	"The evidence summary does not take into sufficient account the difference between, and impact of, adherent and non-adherent therapy. In an attempt to be consistent and controlled, many large scale studies skimp on methods for attaining good adherence and rely on standard categorization which is flawed. Failure to demonstrate a difference is not proof of no difference. A better conclusion might be that we lack good-quality, well-designed studies to demonstrate the clear benefits seen in any number of clinical settings."	We have revised the conclusions to be that comparative studies do not provide evidence of effects. The quality of the studies, and the resulting strength of evidence, is fully described.
NR	General	The Draft Technology Assessment on CPAP for Treatment of OSA does a valuable service in identifying the inconsistency in measurement of the apnea-hypopnea index and the lack of evidence for a reduction in cardiovascular risk with CPAP treatment. However, it is dangerously misleading to state, as the draft assessment does, that "[t]he published evidence mostly does not support that CPAP prescription affects long-term, clinically important outcomes," as the assessment has excluded from evaluation arguably the most important clinical consequence of OSA, excessive daytime sleepiness. This choice is baffling, given that excessive sleepiness is the symptom that is generally of greatest concern to patients themselves. Numerous studies have demonstrated an unequivocal reduction in	We have revised the conclusions to be that comparative studies do not provide evidence of effects. We have made it much more explicit that sleepiness (and other outcomes and other study designs) are not included.

Commentator & Affiliation	Section	Comment	Response
		sleepiness with CPAP treatment, an effect that is sufficiently clinically durable that long-term studies withholding CPAP therapy are deemed by many to be unethical. While this has led to the exclusion of excessively sleepy individuals from most long-term trials of CPAP therapy, the largest such trial does, in fact, demonstrate a sustained reduction in sleepiness: despite the exclusion of the sleepiest patients from the Sleep Apnea Cardiovascular Endpoints study, a highly significant difference in sleepiness (both statistical and clinical) between CPAP and usual care was demonstrated (McEvoy et al, reference 13 in the Draft Technology Assessment). While the Major Clinical Outcomes selected for the Technology Assessment reflect a focus on cardiovascular outcomes, this report as written concludes a lack of evidence for long-term benefit of any kind for CPAP treatment, a conclusion that is misleading with regard to the most important OSA symptom. This is an error that should be rectified prior to publication.	
Alaska Native Medical Center	Evidence Summary	"Various study findings/conclusions:CPAP treatment decreases blood pressure in OSA patients and may help prevent hypertension (Bazzano 2007)CPAP decreases occurrence of cardiac arrhythmia (Budhiraja 2010)CPAP decreases some surrogate markers of vascular disease (Drager 2007)CPAP showed significant decrease in 24-hr mean glucose for diabetic CPAP pts, with biggest drop in overnight period and lower AM fasting glucose (Mokhlesi 2016)CPAP use can improve chronic headaches (Johnson 2013)CPAP use can slow cognitive decline in dementia (Cooke 2009)"	Thank you. Our review did not address intermediate outcomes like blood pressure and glucose. We have added language to be more explicit about this and that are findings pertain to a focused review.

Commentator & Affiliation	Section	Comment	Response
Alaska Native Medical Center	Introduction	CPAP is associated with clinically significant outcomes with improvement in residual AHI and oxygen desaturation while using CPAP, with subjective improvement in daytime function and nighttime sleep, and improvement in a variety of objective measurements for clinical outcomes ranging from headache frequency and severity, memory impairment, blood pressure control, arrhythmia occurrence, vascular disease markers, and glucose control in diabetes.	Our review was restricted to specific clinical outcomes.
Alaska Native Medical Center	Methods	PubMed medical literature review	No response
Alaska Native Medical Center	Results	see evidence summary	No response
Alaska Native Medical Center	Discussion	CPAP therapy is the cornerstone for OSA treatment and there is substantial medical literature supporting associated objective improvement in clinically significant outcome markers, as well as substantial clinical experience showing associated subjective patient benefit.	We have summarized the randomized and controlled observational comparative studies, not other sources of evidence. We have stated this more explicitly in our findings.
Alaska Native Medical Center	General	"CPAP decreases respiratory events during sleep and daytime sleepiness, and increases quality of lifeCPAP improves subjective sense of well-being and ameliorates depressive symptoms - I have many patients who subjectively tell me that CPAP is life-changing and helps with their daytime sleep and subsequent daytime function."	Our review was restricted to specific clinical outcomes. We have further clarified that we do not address all outcomes of potential interest.
Baystate Medical Center	General	"On page 21, it stated that we did not find a description of the objective function the devices try to optimize, which feedback signals they use, or the integration of the feed back signals. My paper reviews how the main devices used in US (Resmed, Phillips Respironics, DeVilbiss) work and worked with engineers from each of the companies to verify accuracy of the paper. Johnson KG,	Thank you for this reference. We now state that “The algorithms that govern pressures are proprietary. To optimize respiratory pressures, devices use signals from pressure transducers, microphones, and other sensors.” We cite your work.

Commentator & Affiliation	Section	Comment	Response
		Johnson DC. Treatment of sleep-disordered breathing with positive airway pressure devices: technology update. Medical Devices: Evidence and Research 8: 425-437 (2015)."	
NR	General	"I recommend taking a more in-depth look at functional outcomes, which are very important including for healthcare utilization, and expanding the timeframe in the analysis. As a neurologist there is good evidence on CPAP usage and decreased risk of recurrent stroke/vascular events. For example in Martinez-Garcia MA et al Eur Respir J 2012, patients â‰¥ 2 months after stroke with sleep apnea with AHI >20/hr who did not use CPAP had stroke recurrence rate of 32% compared to 14% who used CPAP (P=0.021) with NNT to prevent 1 new vascular event = 4.9. This NNT is quite different than that reported in the Technology Assessment document. Ryan CM et al in Stroke 2011, which was a randomized, open label, parallel group trial with blind assessment of outcomes performed in stroke patients with OSA in a stroke rehabilitation unit, showed that treatment of OSA by CPAP in stroke patients undergoing rehabilitation improved functional and motor outcomes. In Martinez-Garcia MA et al in Chest 2005, during the 18 months of follow-up, the CPAP compliant group had a significantly lower incident of new stroke (6.7%) compared with the noncompliant group (36.1%) (P=0.03). Evidence of CPAP benefit has also been shown in other neurologic conditions including cognitive impairment and epilepsy where a 50% reduction of seizure frequency has been shown with CPAP usage."	We excluded studies of patients with a history of stroke. We have made such restricts more explicit.
Beth Israel Deaconess Medical Center	General	"Successful treatment of sleep apnea does improve clinical symptoms, the reason why the vast majority of patient present to sleep	Our review was restricted to specific clinical outcomes. We have made the focus more explicit in the findings.

Commentator & Affiliation	Section	Comment	Response
		clinic. They do not come for fear of a cardiovascular event 10 years down, and not even for hypertension. Much of medical practice is for relief of symptoms (pain, dyspnea, GERD, depression, etc.), which CPAP and other successful apnea treatment provide. However, to show benefits to cardiac/brain/metabolic outcomes, as a group effect, precision of therapy is key, the appropriate biomarkers, and of course use of therapy. Here, CPAP as the sole gold standard fails somewhat, and contributes to the heterogeneity of results, and negative results. Much has been written about the AHI and not about the impact of the AHI on sleep quality, autonomic responses, inflammation, and event-specific desaturations. Gene-environment interactions are likely important - why does the same AHI cause so much or so little biological distress in different individuals remains mostly a mystery. Not enough has been studied on the other side of breathing - stable breathing (what is good, vs. fighting over criteria of what is bad). Stable breathing is more readily recognizable and easily quantified. Sleep quality through the standard sleep stages and related measures are inadequate-alternatives which measure quality through nocturnal beat-to-beat blood pressure or heart rate kinetics, sleep stability and machine learning such as cardiopulmonary coupling, odds ratio product, EEG power analysis, and brain age index should be assessed. Some of these are already FDA approved and supported by a substantial number of publications.The biggest elephant in the room is the consideration of OSA as a monolithic isomorphic simplistic entity, completely	

Commentator & Affiliation	Section	Comment	Response
		ignoring the vast amount of data on sleep apnea endotypes/phenotypes, especially high loop gain and sleep fragmentation/low arousal threshold, which are now readily identifiable computationally. Why should we expect targeting one pathology only to provide blanket benefits to a pathophysiologically heterogenous disease? That is where the gold may be hidden.What is needed are large trials and improved compliance, yes, but not more of the same. CPAP is the sole gold standard ONLY when obstruction is the key driver pathology. Multi-modal therapy is the way forward, much like other chronic illnesses like asthma or diabetes. Upfront phenotyping, targeted therapies for high loop gain or sleep fragmentation, assessing hemodynamic/inflammatory/""deeper"" sleep biomarkers, stable breathing measures, ambulatory tracking of sleep quality during therapy with EEG wearables or ECG/oximetry-based cardiopulmonary coupling as examples, need to be integrated into clinical trials.In the meantime, we relieve symptoms."	
NR	General	It is critical to recognize that absence of proof is not proof of absence-- in my experience, CPAP has helped so many patients with OSA and it is really important to overcome the methodological issues with larger studies so we can have a definitive answer to these questions.	We agree. We have revised the findings to be that comparative studies do not provide evidence of effects of CPAP.
Redwood Pulmonary Medical Associates	Evidence Summary	"From "UpToDate, Management of Obstructive Sleep Apnea in Adults"":"" There is high quality evidence from randomized trials and meta-analyses that in most adults, including the elderly, positive airway pressure therapy reduces the frequency of respiratory events during sleep, decreases daytime	In contrast with UpToDate, we have conducted a systematic review of all eligible studies. In addition, our review is focused on specific clinical outcomes.

Commentator & Affiliation	Section	Comment	Response
		sleepiness, improves systemic blood pressure (BP), lowers the risk of crashes, improves erectile dysfunction, and improves quality of life across a range of disease severities [26,51-62]. However, no convincing effect on mortality has been demonstrated. As examples:â—□In a meta-analysis of 35 randomized trials, CPAP compared with sham resulted in a significant reduction in the apnea-hypopnea index (AHI; mean difference -33.8 events/hour) as well as improved daytime sleepiness as assessed by the Epworth Sleepiness Scale (mean difference -2 points), systolic and diastolic blood pressure, and sleep-related quality of life [26]. No appreciable effect on mortality was reported. â—□In a meta-analysis of 22 randomized trials (1160 patients) that compared nocturnal CPAP with a control (sham CPAP, placebo tablets, or conservative management), nocturnal CPAP significantly improved both subjective and objective sleepiness, quality of life, cognitive function, and depression [52].â—□In a 2019 meta-analysis of the American Academy of Sleep Medicine (AASM), compared with no therapy, CPAP had a significant impact on OSA severity (-23 events per hour; 95% CI -29 to -18 events/hour), Epworth Sleepiness Scale (ESS) score (-2.4 points; 95% CI -2.8 to -1.9 points), nighttime systolic BP (-4.2 mmHg; 95% CI -6.0 to -2.5 mmHg), diastolic BP (-2.3 mmHg; 95% CI -3.7 to -0.9), and 24 hour mean BP (-2.6 mmHg, 95% CI -3.4 to -1.4 mmHg) [7]. CPAP also positively impacted the rate of motor vehicle crashes (risk ratio 0.3; 95% CI 0.2-0.4) and quality of life. However, CPAP had no impact on cardiovascular events (eg, myocardial infarction, stroke),	

Commentator & Affiliation	Section	Comment	Response
		mortality, neurocognitive function, mood, fasting glucose or hemoglobin A1C, left ventricular ejection fraction, or risk of hospitalization. More limited data also suggest that positive airway pressure therapy can improve symptoms of gastroesophageal reflux [63], heart failure outcomes, and reduce the risk of recurrent atrial fibrillation and nocturnal arrhythmias. (See ""Obstructive sleep apnea and cardiovascular disease in adults"" and ""Sleep-disordered breathing in heart failure"", section on 'Positive airway pressure therapy'.)""" Reference: UpToDate, Management of Obstructive Sleep Apnea in Adults	
Redwood Pulmonary Medical Associates	General	"I don't understand this report at all as it is not a comprehensive review of all the literature relating to OSA and CPAP use. Any clinician who prescribes CPAP can attest to the fact that it is truly a miraculous treatment, transforming the lives of numerous patients. You can take a patient who is falling asleep repeatedly throughout the day, unable to drive and transform them into an alert and highly productive individual. Would you want your child to be driven in a bus by a bus driver with severe, untreated OSA? Would you like to drive on the highway with long-haul truckers who have untreated OSA? Would you want to be driven in a taxi, uber, or lyft by someone with untreated OSA? If you yourself had severe OSA, would you want to leave it untreated? I agree that we need better studies on CPAP that do not rely on the outdated 4 hour compliance guidelines. I have pasted the evidence section from UpToDate above, which clearly shows benefits from CPAP use.Please focus your efforts instead on eliminating the 4 hours per night, 90 day	The review is not meant to be a comprehensive review of all literature relating to OSA and CPAP use. It is focused on the posed Contextual and Key Questions, which are more focused than the important issues you raise.

Commentator & Affiliation	Section	Comment	Response
		compliance requirements from the treatment guidelines for OSA. If a patient finds a PAP machine helpful and is trying to use it that patient should be allowed to continue using it. If a patient does not find PAP helpful and is not using it at all, that patient should return their machine.Thank you for your time.	
Cleveland Clinic	General	"The resulting report is rather disturbing, and could negatively impact our ability to care for our patients going forward. The first few pages give you the idea; page 88 starts the review of the literature where many key studies are omittedAASM is drafting a formal response to address the science and literature. I have heard there is to be similar action from AAN and AARC forthcoming. we will personally advocating for the benefit of our patients by talking about this report to different people. "	Thank you
Virginia Mason Franciscan Health	General	Stop using garbage data to make harmful determinations that will negatively affect access to treatment for millions of people. Compliance is 4 hours if someone sleeps 4 hours. Otherwise it misses the most likely time that sleep apnea both occurs and is harmful. Primum non nocere.	We comprehensively review the available evidence that meets criteria.
Johns Hopkins All Children's Hospital St Petersburg, FL and NOVA School of Osteopathic Medicine	Evidence Summary	Obstructive sleep apnea is a serious and life threatening, public health condition. This disorder is grossly underdiagnosed, undertreated and underestimated as significant source of morbidity and mortality. Thus far even peer-reviewed publications to date have been of limited assistance in the evaluation of CPAP as a treatment due to limited compliance and follow through on treatment periods.	Thank you. We agree.
Johns Hopkins All Children's Hospital St	Introduction	CPAP was one of the first treatments offered for patients with sleep apnea and has drastically changed from it's introduction in the	Thank you.

Commentator & Affiliation	Section	Comment	Response
Petersburg, FL and NOVA School of Osteopathic Medicine		early 1980s. It would be unwise to base utility of CPAP on the limited data thus far. Over the last decade CPAP algorithms and interface options have improved compliance and efficacy through the use of patient engagement and understanding.	
Johns Hopkins All Children's Hospital St Petersburg, FL and NOVA School of Osteopathic Medicine	Methods	Clinical data utilizing real world patient data from SLEEPMAPPER/DREAMMAPPER, AIRVIEW and INTELLIPAP links.	Our review is focused on published, peer reviewed comparative studies that meet specific eligibility criteria.
Johns Hopkins All Children's Hospital St Petersburg, FL and NOVA School of Osteopathic Medicine	Results	Online resources from direct patient monitoring systems.	Our review is focused on published, peer reviewed comparative studies that meet specific eligibility criteria.
Johns Hopkins All Children's Hospital St Petersburg, FL and NOVA School of Osteopathic Medicine	Discussion	If we have learned nothing else from compiling years worth of older data and studies showing confounding variables in medically complex patients, particularly those published through database sources, it is not wise to publish a statement based on studies with CPAP/sham-CPAP where the treatment group could be characterized as "control/treatment." Apnea is not collect by collecting 4 hours of data in a patient that sleeps an additional 40-60% longer without CPAP and calling it "treatment failure to provide improved cardiovascular risk." Repeat real-worth studies are not being funded to produce large scale trials with actual patient data and follow through. Statements such as those presented	We aimed to primarily focus on “intention to treat” analyses that evaluate whether prescription of CPAP affects clinical outcomes. But we also discuss compliance/adherence in detail, including as-treated analyses.

Commentator & Affiliation	Section	Comment	Response
		downplay treatment of serious condition and should be avoided particularly in the face of alternatively increasing patient comorbid illness contributing to the additional health risks.	
NR	General	The report fails to consider documented benefit of CPAP therapy on patient centered outcomes such as improvement in daytime sleepiness, quality of life and functional status which has been demonstrated in multiple studies. Some examples of relevant studies that were not included follow: The report mentioned "Of interest would be whether there is a continuous (e.g., linear) association between level of compliance and outcomes or whether there is a threshold response (e.g., â‰¥4 hours per night on 70% of nights)" Yet the report does not reference an important study which answered this question [Weaver TE, Maislin G, Dinges DF, Bloxham T, George CF, Greenberg H, Kader G, Mahowald M, Younger J, Pack AI. Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning. Sleep. 2007 Jun;30(6):711-9. doi: 10.1093/sleep/30.6.711. PMID: 17580592; PMCID: PMC1978355]. This study showed that a greater percentage of patients will achieve normal functioning with longer duration of nightly use of CPAP with a linear dose response up to 7 hrs of nightly use; it also stated that there is interindividual variability in this response.	We have made it much more explicitly clear that we do not address sleepiness and other symptoms. The review does cover quality of life and functional status. Since we didn't directly address the question about type of association between adherence and outcomes, we have omitted this sentence.
NR	General	Next, the paper relies only on randomized controlled trials longer than 6 months, failing to recognize the ethical difficulties in randomizing patients with OSA to placebo or sham treatment for long periods of time. Many IRBs have refused to approve sham CPAP	We have added comments about difficulties conducting long-term trials to the Future Research section.

Commentator & Affiliation	Section	Comment	Response
		interventions for longer periods due to concerns of untreated sleepiness.	
NR	General	The CATNAP international trial randomized patients with mild to moderate OSA to CPAP or sham CPAP with a crossover after 8 weeks. The study demonstrated that CPAP improves FOSQ scores in sleepy patients with mild to moderate OSA compared to sham CPAP. However, this paper was not mentioned in the report. [Weaver TE, Mancini C, Maislin G, Cater J, Staley B, Landis JR, Ferguson KA, George CF, Schulman DA, Greenberg H, Rapoport DM, Walsleben JA, Lee-Chiong T, Gurubhagavatula I, Kuna ST. Continuous positive airway pressure treatment of sleepy patients with milder obstructive sleep apnea: results of the CPAP Apnea Trial North American Program (CATNAP) randomized clinical trial. Am J Respir Crit Care Med. 2012 Oct 1;186(7):677-83. doi: 10.1164/rccm.201202-0200OC. Epub 2012 Jul 26. PMID: 22837377; PMCID: PMC3480519.]	The 8 week study did not meet eligibility criteria.
NR	General	The report contains a section on impact of CPAP on sexual function. Yet it does not mention a multisite study that demonstrated an adverse effect of OSA on intimate and sexual relationships which is improved with CPAP therapy. [Reishtein JL, Maislin G, Weaver TE; Multisite Study group. Outcome of CPAP treatment on intimate and sexual relationships in men with obstructive sleep apnea. J Clin Sleep Med. 2010 Jun 15;6(3):221-6. PMID: 20572413; PMCID: PMC2883031.]	This study does not meet eligibility criteria. There is no comparison with another treatment and treatment is only 3 months.
NR	General	There are many other examples of omissions of clinically important studies on the impact of CPAP therapy on relevant clinical outcomes The need to perform studies that identify more	We believe we have included all studies that met eligibility criteria.

Commentator & Affiliation	Section	Comment	Response
		relevant metrics that reflect clinically important outcomes is recognized. Further, the need to determine means to identify patients who might benefit most from CPAP therapy is also recognized. However, this report does not reflect clinical experience with CPAP which recognizes benefit with regard to clinically relevant outcomes including daytime sleepiness and quality of life in many patients treated with CPAP.	
NR	Evidence Summary	Of coarse they didn't find consistent evidence. They had no idea how to conduct the study.	No response
NR	Methods	Not enough patients in the study. They state that there are not clear guidelines as to how to assess sleep apnea. There are clear guidelines stated in the AASM scoring manual which is the industry standard and what all insurances use to define OSA. Their assessment of OSA is convoluted and Does not make sense.	We discuss the lack of clarity.
NR	Results	Not reliable due to poor testing methods. Also need to assess more people. Very limited study.	This report describes our systematic review of the existing studies.
NR	General	Again, this study was poorly conducted and evaluated. There ARE very CLEAR scoring rules to evaluate AHI and the diagnosis of sleep apnea. Their opinion of there not being clear guidelines is untrue. All sleep labs and insurances go by the AASM scoring manual which states clear rules regarding the scoring of studies.	We provide a description of the wide variations in how the scoring rules are implemented by research studies.
UCHealth Pulmonology	General	I agree that there is a general lack of high quality RCT regarding OSA and CPAP but your conclusions are wholly invalid. While data on cardiac outcomes is weak, there is no question that CPAP improves quality of life, particularly in more severe patients with an excessively sleepy phenotype. I'm sure that you're not interested in case reports and	It is the case that our review is focused on comparative studies.

Commentator & Affiliation	Section	Comment	Response
		anecdotal evidence but every sleep specialist in the country (including me) could easily line up 1000 patients for you, who would swear under oath that they could not sleep, function or even still be alive without CPAP. If Medicare uses this paper as an excuse to deny care any of the 25,000,000 US residents with OSA, you will be doing an extraordinary disservice to humanity.	
Clinician	General	" There is no doubt CPAP Treatment works, however there is a problem with diagnosis and treatment. Home Sleep Testing is grossly unreliable and can is misleading. ALL patients should undergo a full PSG In an accredited Sleep Laboratory performed by a registered Sleep Technologist. This will allow for numerous sleep related parameters to be recorded, qualified, quantified, and analyzed. Home Sleep Testing is asking a patient to self administer a test, at their home, alone, with the result of this test determining diagnosis and treatment. This is Bad Medicine designed to benefit business, not the patient. Conversely, Home Sleep Testing ONLY evaluates AHI and forgoes countless measures that are ascertained from an In-Lab PSG. Home Sleep Testing was designed to increase CPAP sales, not for patient care. Moreover, CPAP Titrations should only be allowed in an accredited Sleep Laboratory and not at home via APAP. Home APAP titrations are geared for making compliance minimums thereby allowing monthly billing to continue. CPAP is a therapeutic treatment and we are asking patients to self titrate their own therapy alone at their home, this is bad medicine. "	Thank you. Our review focuses on specific Contextual and Key Questions
Clinician	Evidence Summary	20 years treating patients with CPAP Therapy	No response

Commentator & Affiliation	Section	Comment	Response
Clinician	Results	" There is no doubt CPAP Treatment works, however there is a problem with diagnosis and treatment. Home Sleep Testing is grossly unreliable and can is misleading. ALL patients should undergo a full PSG In an accredited Sleep Laboratory performed by a registered Sleep Technologist. This will allow for numerous sleep related parameters to be recorded, qualified, quantified, and analyzed. Home Sleep Testing is asking a patient to self administer a test, at their home, alone, with the result of this test determining diagnosis and treatment. This is Bad Medicine designed to benefit business, not the patient. Conversely, Home Sleep Testing ONLY evaluates AHI and forgoes countless measures that are ascertained from an In-Lab PSG. Home Sleep Testing was designed to increase CPAP sales, not for patient care. Moreover, CPAP Titrations should only be allowed in an accredited Sleep Laboratory and not at home via APAP. Home APAP titrations are geared for making compliance minimums thereby allowing monthly billing to continue. CPAP is a therapeutic treatment and we are asking patients to self titrate their own therapy alone at their home, this is bad medicine. "	Thank you. Our review focuses on specific Contextual and Key Questions
Clinician	Discussion	There is no doubt CPAP Treatment works, however there is a problem with diagnosis and treatment. Home Sleep Testing is grossly unreliable and can is misleading. ALL patients should undergo a full PSG In an accredited Sleep Laboratory performed by a registered Sleep Technologist. This will allow for numerous sleep related parameters to be recorded, qualified, quantified, and analyzed. Home Sleep Testing is asking a patient to self administer a test, at their home, alone, with	Thank you. Our review focuses on specific Contextual and Key Questions

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		the result of this test determining diagnosis and treatment. This is Bad Medicine designed to benefit business, not the patient. Conversely, Home Sleep Testing ONLY evaluates AHI and forgoes countless measures that are ascertained from an In-Lab PSG. Home Sleep Testing was designed to increase CPAP sales, not for patient care. Moreover, CPAP Titrations should only be allowed in an accredited Sleep Laboratory and not at home via APAP. Home APAP titrations are geared for making compliance minimums thereby allowing monthly billing to continue. CPAP is a therapeutic treatment and we are asking patients to self titrate their own therapy alone at their home, this is bad medicine.	
Clinician	Introduction	CPAP works	No response
Clinician	Methods	Over 7500 treated patients	No response
Wv sleep society	Evidence Summary	Our lab deals with critical apnea hypopnea index patients or AHI, ranging from mild to very severe. After the diagnostic study the patients return for a titration study which allows the physician to interpret so many variables in the patients sleep. Obstructive Sleep Apnea or OSA is revealed during the diagnostic and treated with Positive pressure. This is non invasive procedure that does not cause the patients any pain and it supports to keep positive pressure in the thoracic cavity so the heart does not have to work as hard and provides a stent into the airway so a patent airway is maintained. It is baffling to me to think that any PAP therapy does not benefit the patient as long as they use it. I would invite any colleagues that think otherwise to come in and watch a severe AHI patient get titrated in the lab, these patients	Thank you. Our review focuses on specific Contextual and Key Questions

Commentator & Affiliation	Section	Comment	Response
		are trying to breath the chest movement is there the breath is not getting through!! The oxygens levels drop the heart work harder as a polysomn tech I increase the pressure according to protocol and AASM guidelines and the breath gets through the oxygens status is maintained. I recently had a patient with an AHI of 128, severe yes so tired, works as a painter and his willing to try anything to help him feel better. During the night of this titration he had difficulties with the interfaces but we did not give up, not willing to give up on these patients they need us. So throughout the night we tried a variety of interfaces and he did go into REM several times throughout the night. Even though I did not get his AHI below to a normal range from being that severed his AHI was in the 30â€™s that morning he was so refreshed kept thanking me and when do I get the machine.....this is such a rewarding feeling to help make someone feel just a bit better, why would you even consider this therapy not to be successful. Every tech out there has a similar story to tell. The patients benefit from pap therapy to say they do not well you just have not been at our 10 bed lab with top technicians and the best physicians on the east coast providing the best care for all of our patients .	
Wv sleep society	Introduction	I have only been a sleep specialist for a short 3 years, but a seasoned respiratory therapist for 25 years. Even though I am still very young in my experience as a polysomnographer my experience with respiratory therapy and critical patient care has brought new light to my education.	No response
Wv sleep society	Methods	We use several types of PAP therapies, ranging from Cpap, bipap ASV and AVAPS.	No response

Commentator & Affiliation	Section	Comment	Response
		We have these toolls for use with a variety of patients and use them all according to the physician prescription. To help those with OSA, CSA central sleep apnea, Hypoventilation syndrome. By far the best method to treat OSA using an interface and positive pressure, nothing invasive. Only coaching and education with the patients to continue with the success of this therapy. In a society so quick to just take a pill, no medication here just interactive therapy with patient clinician and pap therapy. Sounds to good to be true actually, no drugs just compliance!!	
Wv sleep society	References	I only have my personal experiences as my references and in 3 years I have plenty and enjoy each morning well actually look forward to each morning that I have helped a patient get a restful night sleep.	No response
Wv sleep society	Results	I have stated an actual patient I had just last week, gasping trying to breath, this is very common and if we can open the airway and keep it patent with pap therapy why would you choose not to continue with this type of treatment. So I am here to advocate for all my patients having difficulties sleeping and willing to provide care to each of them for better sleep hygiene and a restful night sleep. As technicians this is all we can ask for to help provide great care and titration on polysomnographers, titration on!!	No response
Wv sleep society	General	All of our daily activities depend on sleep and if we can help relieve some patients diagnosed with OSA to sleep just a bit sounder nightly,, by initiating pap therapy the question is not if this is an affective treatment the question is question remains why would you not use pap therapy to treat OSA, the proof is in our patients. It has been a	No response

Commentator & Affiliation	Section	Comment	Response
		pleasure writing this for our WV Sleep society and I hope this may have just helped relief any doubt of PAP therapy for our patients. Our patients need us and I am here to advocate for each and every one of you.	
United States Government	Evidence Summary	I have been a CPAP user for 12 years.	No response
United States Government	Introduction	I suffered from depression. I had a great deal of trouble getting any project started. I fell asleep at the wheel and often took naps on the roadside. I would see the first half hour of a movie and the last half hour of a movie, but would sleep during the middle half hour. I got sick with whatever the children brought home and ate to stay awake. I felt that I slept well and bed mates said I did not snore. My memory and comprehension suffered greatly.	No response
United States Government	Methods	I put myself on CPAP at 10 cm/H2O. After 3.5 weeks of use, I removed the device. After 3 nights, I put it back on. I received a CPAP study two years later. My AHI was only 5.6 overall and 42 in REM.	No response
United States Government	Results	I did not notice a difference for the first week and woke 4-6 times a night for 2.5 weeks. After removing the CPAP at 3.5 weeks, I noticed significant defects in my ability to stay awake during the day and my cognition. I also suffered from headaches, even though I felt I slept well through the night. I tolerated it for three days and then put the CPAP back on.	We are pleased at your improvement with CPAP. Our review addressed specific Contextual and Key Questions.
United States Government	Discussion	CPAP has been shown to improve the outcomes of therapy on soldiers with PTSD and TBI. I am one of those affected. I have a low overall AHI with none of the major health effects of high blood pressure, diabetes, or cardiovascular issues. I also work in sleep and can see major improvements in a patient's breathing and	We are pleased at your improvement with CPAP. Our review addressed specific Contextual and Key Questions.

Commentator & Affiliation	Section	Comment	Response
		SaO2 on a nightly basis. I have tried on occasion to stop using CPAP, but never make it past two nights because every negative effect starts coming back.	
United States Government	References	12 years of using CPAP personally and 22 years as a RPSGT with a BS in Physiological Psychology.	No response
United States Government	General	You have admitted in your study of studies that each and every one uses different methods of calculating AHI. You also do not explain, and you should, that most reports are patient based. Well I hate to say it, but patients lie. Surveys are pretty useless when looking at health claims. Also the only way to do one of these studies properly is to go back in time and never give a patient CPAP after he or she has already spent a lifetime on CPAP. All of these studies are inherently flawed and so your are conclusions. There is also a problem with group size, genetics, age, weight, etc. All factors that must be taken into account when doing any of these studies, but have not been. Maybe researchers should stop counting breaths and start counting arousals? Though many times we in the sleep profession cannot agree on that either.	AHI is calculated by technicians based on readings from the polysomnography device. It does not rely on patient reporting. We did not review surveys. We have discussed the study limitations.
Kaiser TPMG	Evidence Summary	In my experience, the quality of life, the "joie de vivre," experienced on a day-to-day basis by Kaiser Members, has improved as a result of positive airway pressure (PAP) treatment for sleep dis-ordered breathing. This improvement, both objectively, and subjectively, extends to immediate family, care-givers, and particularly the spouses of the Kaiser Members whom I serve. Fifty years ago cigarette smoking -- and related health challenges -- were nearly ubiquitous as a result of paid promotion, addiction, and misguided policy. We re-thought, and health	Thank you

Commentator & Affiliation	Section	Comment	Response
		improved. It is time to re-fashion policy to promote the active restorative process we dismiss as "merely" sleep, by recognizing that "40 winks" interrupted by repetitive hypoxia and fight-or-flight reflex, i.e. tension, cannot and should not be the new "cigarette."	
Kaiser TPMG	Introduction	See above	No response
Kaiser TPMG	Methods	See above	No response
Kaiser TPMG	Results	See above	No response
Kaiser TPMG	Discussion	See above	No response
Kaiser TPMG	Appendix	See above	No response
Kaiser TPMG	References	See above	No response
Kaiser TPMG	General	See above	No response
NR	General	This report is terrible. There is no evidence PAP is ineffective. The report states, multiple times, there is not enough information to come to a correct conclusion.	Our findings are based on the reviewed studies.
Sleep Diagnostic	Evidence Summary	My personal experience as a patient and as a RPSGT. CPAP has defiantly enhanced the quality of my life by keeping my airway open so the chance of me have a stroke is decreased (I have a family history of stokes and heart conditions). Many patients in 15 years of working as a RPSGT has testified how CPAP has changed their life and they can not do without it. It would be not a good ideal to discontinue this much needed therapy.	Thank you.
Sleep Disorders Center at BayCare	Evidence Summary	Numerous patients who have suffered for years with untreated sleep apnea will tell you that CPAP has been a life saver for them. Patients with untreated sleep apnea have a poor quality of life, and when they go on PAP therapy, they will say "I see better, colors are	Thank you

Commentator & Affiliation	Section	Comment	Response
		brighter, I have seen how the field of sleep medicine has progressed over the years, the remarkable improvements in technology enable patients to get diagnosed and treated at reduced cost and better convenience. This report lacks strong evidence to support the claims and requires more concise research targeted on improving overall health in vulnerable patients. This report will negatively impact the ability of minority populations to get the treatment they deserve, especially considering that they are the population affected by co-morbid conditions that negatively impact longevity and quality of life.	
Sleep Disorders Center at BayCare	Introduction	This report does not address the fundamental issues faced by patients that suffer from untreated sleep apnea. It does not address the associated symptoms of untreated sleep apnea, drowsy driving, excessive daytime sleepiness, increased vulnerability to accidents (both industrial and personal) and the cost of untreated sleep apnea. To imply that CPAP has no long-term benefit would be disputed by most patients who have seen a significant improvement in lifestyle and health after treatment. The ethics of adopting this report should be considered as it would affect the most vulnerable populations and will eventually increase healthcare costs across the board due to increased cardiac disease, hypertension and diabetes. There is more evidence that supports the effectiveness of PAP therapy than the evidence presented in this report that disputes years of clinical research that says otherwise.	We have clarified what our review addresses, and does not address.
Sleep Disorders Center at BayCare	General	CMS must consider the positive impact that PAP therapy has on the population it serves. Patients have improved blood pressure and in some cases, normalization of blood pressure,	Thank you

Commentator & Affiliation	Section	Comment	Response
		strokes and heart disease prevention is a proven outcome from the heart-health study, and many other studies that have been conducted by the most respected clinical researchers and institutions in the country. The cost of untreated sleep apnea will far outweigh continued coverage of diagnosing and properly treating sleep apnea.	
NR	Evidence Summary	The statement in this study is very disturbing to say the least. I have witnessed patients die from sleep apnea. I have seen asystole during an episode of obstructive sleep apnea. Preventing dying is for sure a significant long term effect of CPAP Therapy. If that is not reflected in the studies reviewed then they have to look deeper or better, because the reality is otherwise. Examples are endless.	The reviewed evidence does, in fact, evaluate average effects.
NR	General	As a Registered Respiratory Therapist and Registered Polysomnographic Technologist with over 16 years of experience in the field, I'm curious how we got from PAP therapy being the "gold standard" in treatment for over 30 years to the idea that it does not have any clinical significance in the long-term. Sleep apnea effects nearly 22 million Americans. While not all patients that are prescribed treatment become or remain compliant with therapy or have the "life-changing" results that many do, I've been in the field long enough to see the many that rely on this treatment for the quality of life that it provides. It makes sense to change the narrative on something that impacts so many, because CMS can weasel out of paying for beneficial treatment which is exactly what this presentation implies. The corruption of our government and the medical field is showing, and it's embarrassing.	We hope that our review will stimulate better evidence.

Commentator & Affiliation	Section	Comment	Response
Total Sleep Management	General	"There should be a single standard - followed by Medicare and all other payors. Utilization management has led to several different pathways of care (and dead ends) after a positive OSA diagnosis is confirmed. Now we have rules for almost every payor. Symptomatic patients need help and education to get the full benefits of PAP. No matter what age or demographic there is nothing normal about a severe OSA patient struggling to breath all night. A study should be broken into the 3 tiers. Mild, Moderate, and Severe cases. This might help gauge as to possible change in criteria such as a higher minimum AHI, average oxygen levels, or a possible minimum Epworth score threshold. Also if utilization is the concern, simply state that a Medicare provider can't self refer to his/her own patient's to their own sleep lab or group owned sleep center. That would just about solve most of your problems."	Thank you.
NR	Evidence Summary	Self experience and documentation with and without CPAP use	No response
NR	Introduction	CPAP vs Non CPAP use and the affects on diabetes, hypertension, anxiety, and depression.	No response
NR	Methods	Home blood pressure testing, home blood sugar testing, home medical observation by spouse and family	No response
NR	Results	"very positive!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!! for CPAPAnxiety/Depression controlled with sleep while using CPAP not as controlled and sometimes out of control when not using CPAPhome Blood pressure checks 20 to 30 points lower while using CPAP.Blood Sugar levels 40 or more points higher with NOT using CPAP. "	No response
NR	Discussion	Spouse and family observation along with blood sugar and pressure testing.	No response

Commentator & Affiliation	Section	Comment	Response
NR	References	SELF REFERENCES	No response
NR	General	"I Have been working in sleep medicine sense the mid 1990's. I have witnessed patient after patient in public telling me how I (CPAP) Changed them and gave them back their life again. I have personally used a CPAP device for over 10 years. I have been diagnosed with hypertension, diabetes, hyperlipidemia, Neuropathy, anxiety, and depression. I am a personally testimony to CPAP treatment. I have on occasions forgotten my CPAP on a trip. I have experienced power failures that caused me to not be able to use my CPAP. I have accidentally falling asleep without my CPAP device on. On the occasional of forgotten on a trip- my fasting blood sugar was elevated by 40 points (or more). My anxiety/depression was increased, ,and my blood pressure was continuously elevated. With the way my body responds to CPAP, I would rather not even take a nap without it. I have napped before without CPAP and I wake up with a headache and a feeling that is totally opposite of the way I feel when I take a nap with CPAP. I don't have to be a scientist to understand lower anxiety/depression, lower blood sugars, and lower blood pressure, ectâ€¦ will result in a better/stronger heart, a better neurology system, better kidney functions, better focus, and on and on. I appreciate you findings, but I am very concerned with the number of cases (subjects) studies, the subjects being monitored/studied, and the way the results were achieved. I do not agree with the results because it is scientifically asinine to think that better breathing, better oxygen level, better brain wake/sleep activity, better blood pressure, better anxiety/depression levels	Thank you. Our review focused on published literature about specific clinical outcomes.

Commentator & Affiliation	Section	Comment	Response
		(personal experience), and all these thing would not have a positive affect on a human body. Thank you for listening. Questions welcomed "	
University of Cincinnati/Itamar Medical	General	"Great work with this extensive summary of the evidence. Although we agree with general statements made, we have a high level of concern that assignment ineffectiveness would be generalized to specialized populations. For instance, patients with pre-existing heart failure, atrial fibrillation, and stroke. This is a special population where much more work needs to be done. However, among patients with known atrial fibrillation a published meta-analysis [Shukla A, Chinitz L. et al Effect of Obstructive Sleep Apnea Treatment on Atrial Fibrillation Recurrence: A Meta-Analysis. JACC Clin Electrophysiol. 2015 Mar-Apr;1(1-2):41-51] of NRCT showed significant reduction in AF recurrence (relative risk: 0.58, 95% confidence interval: 0.51 to 0.67; heterogeneity chi-square p = 0.91, I2 = 0%). We agree much more work is required in this area, however the absence of addressing patients with pre-existing conditions is a risk.	We have added language to clarify the focus of the review, including which populations were excluded.
University of Cincinnati/Itamar Medical	General	Furthermore, although STOP-BANG and ESS are validated among general patients suspected of OSA they perform poorly in patients with known atrial fibrillation or congestive heart failure. In these populations the pre-test probability of OSA diagnosis is high. Use of screening tests in these populations generate false negatives, therefore should not be used."	We did not evaluate these tools
Morton Plant Mease Sleep Disorder Centers	Introduction	The data supporting the connection between cardiovascular and cerebrovascular disease and obstruction sleep apnea concerning the interrelationship between cause and effect	Thank you. We did not address these association studies.

Commentator & Affiliation	Section	Comment	Response
		along with the beneficial impact of treatment has spanned decades.	
Morton Plant Mease Sleep Disorder Centers	Results	"According to Sleep [Sleep. 1997 Dec;20(12):1077-85], a study involving 6600 men and women 40 and older as part of the Sleep Heart Health study concluded â€œThe study provides sufficient statistical power for assessing OSA and other SDB as risk factors for major cardiovascular events, including myocardial infarction and stroke.â€ This association and mechanism for the occurrence was reported in Bulletin de l'Academie Nationale de Medecine [Bull Acad Natl Med. 2005 Mar;189(3):445-59; discussion 460-4.] They concluded â€œObstructive apnea is associated with endothelial dysfunction, increased C-reactive protein and cytokine expression, elevated fibrinogen levels and decreased fibrinolytic activity. Enhanced platelet activity and aggregation, leukocyte adhesion and accumulation of endothelial cells are common in both obstructive apnea and atherosclerosis. Surges in sympathetic activity, blood pressure, ventricular wall tension and afterload adversely affect ventricular function. Many studies have shown that patients with obstructive apnea have an increased incidence of daytime hypertension, and this syndrome is recognized as an independent risk factor for hypertension. Obstructive apnea is associated with myocardial ischemia (silent or symptomatic), acute coronary events, stroke and transient ischemic attacks, cardiac arrhythmia, pulmonary hypertension and heart failure. Central sleep apnea is frequent in severe heart failure. Most heart failure patients with pulmonary congestion chronically hyperventilate because of	We have restricted our review to comparative studies of CPAP. SHHS did not evaluate the comparative effectiveness of CPAP. We evaluated only long-term clinical outcomes.

Commentator & Affiliation	Section	Comment	Response
		stimulation of vagal irritant receptors and central and peripheral chemosensitivity. When PaCO2 falls below the threshold required to stimulate breathing, the central drive to respiratory muscles and air inflow ceases and central apnea ensues. Apnea, hypoxia, CO2 retention and arousals provoke elevated sympathetic activity, increased afterload and elevated left ventricular transmural pressure, and promote the progression of heart failure. Tentative relationships have been identified between central apnea and markers of inflammation, oxidative stress and endothelial dysfunction. Recent mid-terms trials showed that nocturnal use of positive airway pressure in patients with the two types of apnea alleviates symptoms, reduces sympathetic activity, improves ventricular function and quality of life, and reduces daytime drowsiness.â€□In Circulation by the American Heart Association [https://www.ahajournals.org/doi/full/10.1161/CIRCULATIONAHA.111.070813], an extensive review of cause, effect and treatment effects was reviewed. According to this article, â€œIn the SHHS, the prevalence of nonsustained ventricular tachycardia, and ventricular bigeminy and trigeminy, was higher in subjects with OSA than in those without OSAâ€¦Cross-sectional data from the SHHS revealed a 1.58 times greater odds for stroke in the highest AHI quartile than in the lowest quartileâ€¦. Eighteen-year follow-up data from the Wisconsin Sleep Cohort showed that, in comparison with subjects without sleep apnea, the adjusted mortality risks of those with severe untreated OSA were significantly higher (3.8 times for all-cause and 5.2 times for cardiovascular	

Commentator & Affiliation	Section	Comment	Response
		mortality). Longitudinal data from the SHHS showed that men with an AHI â‰¥15 had a 1.69 times significantly greater risk of fatal cardiovascular events than those with an AHI <5â€¦.Gami and colleagues reported that, in patients with OSA, the relative risk of sudden cardiac death during the nighttime was 2.57-fold greater than the general population whose peak risk for sudden cardiac death was in the morning after awakeningâ€¦. Suppression of OSA by CPAP immediately reduces nocturnal SNA and BP. â€¦Considering only those trials in which most subjects had uncontrolled hypertension (Table 4), treatment of OSA with CPAP reduced BP during wakefulness, and was most effective in patients with increased BP and more severe OSA accompanied by hypersomnolenceâ€¦.CPAP can immediately alleviate ischemic changes in the ECG and nocturnal angina. In an observational study, patients with both CAD and OSA (AHI â‰¥15) who were treated had fewer cardiovascular events than those who were not treated. In another observational study, Cassar and colleagues reported similar findings in OSA patients (AHI â‰¥15) who underwent percutaneous coronary intervention: in comparison with untreated OSA patients, the cardiovascular death rate was reduced significantly (P=0.027) and there was less all-cause mortality (P=0.058)â€¦Several randomized controlled trials of CPAP involving HF patients with OSA have evaluated the after effects of treatment on cardiovascular variables measured during wakefulness. Kaneko and colleagues showed that, after 1 month of CPAP treatment, daytime systolic BP and HR fell, and LV	

Commentator & Affiliation	Section	Comment	Response
		ejection fraction (LVEF) increased by 9%. â€¦In another randomized trial of 3 months' duration involving patients with less severe HF and milder OSA, Mansfield et al showed that LVEF increased significantly, by 5%...Taken together, these data demonstrate consistently that treatment of OSA by CPAP in patients with systolic HF can increase LVEF and reduce SNA. Wang et al reported a trend, over a mean 2.9-year follow-up period, to a lower mortality rate in CPAP-treated patients (P=0.07), and Kasai and colleagues found CPAP-treated patients to have significantly greater hospitalization-free survival after a mean of 2.1 yearsâ€¦The recurrence rate of AF 1 year after cardioversion was found to be significantly lower in patients with CPAP-treated OSA than in those with untreated OSA (42% versus 82%)â€¦.Ryan et al, which enrolled relatively young (60 years of age) patients with OSA undergoing inpatient rehabilitation within 1 month of their index event, found a substantial benefit with respect to overall stroke recovery, functional and motor outcomes, and severity of depressionâ€¦In an observational study involving patients with ischemic cerebrovascular disease and OSA patients with an AHI â‰¥20 treated with CPAP, but who could not tolerate it, had a greater hazard ratio for mortality during 5 years of follow-up than those with an AHI <20 and those with an AHI â‰¥20 who tolerated CPAP (2.69 and 1.58, respectively). "	
Morton Plant Mease Sleep Disorder Centers	Discussion	These are just a few of the articles, which in number are vast, supporting the cardiovascular and cerebrovascular complications of obstructive sleep apnea which are positively impacted by CPAP	Thank you. Our review was restricted to long-term clinical outcomes.

Commentator & Affiliation	Section	Comment	Response
		treatment which ultimately improves outcomes and decreases health care costs including hospitalizations. I disagree with the AHRQ Report based on several decades of scientific data along with my own clinical experience of 23 years in practice as a sleep physician where I have witnessed resolution of atrial fibrillation, reduction in blood pressure medication required for management, improvement in angina symptoms along with improved quality of life and improved patient safety due to resolution of daytime somnolence with treatment with CPAP and BIPAP therapies.	
Morton Plant Mease Sleep Disorder Centers	References	"Bull Acad Natl Med. 2005 Mar;189(3):445-59; discussion 460-4.Sleep. 1997 Dec;20(12):1077-85https://www.ahajournals.org/doi/full/10.1161/CIRCULATIONAHA.111.070813"	Thank you.
NR	General	I read with interest and dismay this technology assessment report. As a nurse, sleep health professional and spouse to a CPAP user, there are important long-term benefits to CPAP. Whether or not the studies demonstrate this, it is important to note that clinical trials are not always representative of clinical practice results. If the reason that CMS commissioned this assessment is to deny reimbursement for a needed therapy, it is very short sighted and shame on them! We know that patients do demonstrate improved health and wellbeing, that individual and aggregate healthcare costs go down following diagnosis and treatment. Where we should be focused is on the patient journey from start to finish. This would include patient education and consistent mechanism for providing follow on care which should be reimbursed accordingly. It may be that the AHI is only a	Thank you for your insightful comments. We do not believe (or claim) that our review should be the sole basis for any clinical decisionmaking.

Commentator & Affiliation	Section	Comment	Response
		beginning "tool" to make the assessment and follow up similar to a diabetic educator should be employed such as the CCSH (certified in clinical sleep health). This would be a mechanism to ensure that this chronic condition receives the same consideration as that of other chronic conditions. Patients do well when adequately supported. The fact remains that sleep is an important component of health and well being, quality and quantity is disrupted by sleep disordered breathing and that is a fact that cannot be denied. I believe that this report is detrimental to patients, not only Medicare beneficiaries but for future Medicare patients as well. Adherence to drugs such as antihypertensive is sub-optimal ~50% yet providers continue to prescribe and the Rx reimbursed, the use of CPAP should not be any different. Should this report be used to limit accessibility to care, diagnosis and treatment, patients and public health will be harmed.	
Respiratory Therapy and Sleep Lab Director	Evidence Summary	It is common knowledge in the healthcare setting that CPAP works! We use it in the acute and the long term side of healthcare with great outcomes for many patients. Some patients don't have good compliance, but that has been better in the last few years with better education of why they should wear their CPAP while asleep. But in NO WAY would any healthcare professional that has knowledge of sleep disorders say that CPAP doesn't work. It has absolutely saved many of our patients life and gave them many more nights to actually sleep without having apneas, hypopneas, etc. Not to mention that it changes their day time life to a much more enjoyable experience, because they aren't tired all day long.	We reviewed only long-term clinical outcomes, not all outcomes of potential interest.

Commentator & Affiliation	Section	Comment	Response
Sleep Physician	Evidence Summary	"Thank you for the opportunity to reply to the recent AHRQ submission. I hope to provide some real-world experiences which will respond to the contention of the AHRQ publication that highlights the concern for low strength of evidence on studies involving sleep patients.I have practiced Pulmonary and Sleep Medicine for 27 years. I have practiced in both academic, private and group settings so I think that I have a breadth of experience in the many facets of clinical sleep medicine. I can say without a shred of cynicism that I remain passionate about my role particularly as a sleep physician. I always come back to the same answer as to why: the majority of my patients respond to therapy for their obstructive sleep apnea (OSA). While I see other patients with varied sleep pathology, the majority of our patients in sleep are those with OSA. What real world benefits do I see with treatment of OSA? Improved wakefulness, reduction in incidence of congestive heart failure and atrial fibrillation, reduction in stroke and improved quality of life are some of the salient features. I agree that the academic literature does not always purport to prove these benefits. I know too that the studies because of the patient population contain small numbers of participants. There is no way that a study can ethically or effectively perform a blinded CPAP study. Despite these limitations the patients tell the stories of benefits. This is not a mass delusion when millions worldwide undergoing treatment for OSA note similar benefits.I am responding to the publication not out of a sense of desperation for my job as a sleep physician, but rather out of concern that the AHRQ publication will not tell the patients' stories of	Thank you. Our review focuses only on specific long-term clinical outcomes

Commentator & Affiliation	Section	Comment	Response
		improvement. Like many clinical physicians I care about the morbidity and mortality of my patients. Reducing the importance of treatment for OSA would have dire consequences for millions. No clinician would want effective treatment removed or changed to "" see what happens.""I know that others will provide direct comments concerning the included studies. i wanted to provide my own experience as a seasoned physician treating patients in the real world. I thank you again for this opportunity."	
NR	Evidence Summary	"I read your conclusions and would like to respectfully submit my observations. I feel that you need more analysis as my experience in primary care practice has been very different from your conclusions. Based on 25 years of clinical experience as a Family Medicine physician, I have found many of my patients to have benefitted from CPAP or BiPap therapy for Obstructive Sleep Apnea and Central Sleep Apnea."	Thank you
NR	Introduction	25 years of clinical experience and observation	No response
NR	Methods	Observation	No response
NR	Results	"I have seen many patients with resistant hypertension finally come under control with the addition of CPAP therapy. The same is true for patients with Atrial fibrillation who were finally able to get a sleep consult and a sleep study who better stabilized with CPAP therapy. I have one patient in his 30's with hypogonadism whose testosterone level returned to normal with CPAP therapy. I have several patients who were found to have central sleep apnea on their sleep studies and these patients may have otherwise died in their sleep had they not had ongoing CPAP	Thank you

Commentator & Affiliation	Section	Comment	Response
		therapy. Additionally, I have had numerous patients make statements like ""I love my CPAP, I never even take a nap without it."" because they feel so much better rested which has improved their quality of life. I have also had several patients admit to falling asleep while driving who were found to have OSA and whose daytime somnolence has resolved with CPAP treatment. Finally, I have had many patients with witnessed apnea by their bed partners who have been found to have OSA and who are doing well on CPAP or BiPap therapy. Because of all of these patient experiences that I have personally witnessed over 25 years of primary care practice, I simply feel that there is more benefit to CPAP and BiPap therapy than your findings would suggest and I would recommend further investigation. "	
NR	General	I know my comments are not from an organized study but I feel that my clinical experience is valuable and I would not want to see limitations placed on my patients' ability to access evaluation or treatment.	Thank you
NR	General	"While I agree that there are a lot of poorly done studies, that only means that better studies are needed, not that the treatment is ineffective (you would need well done studies to prove that!!!!)""The published evidence mostly does not support that CPAP prescription affects long-term, clinically important outcomes,"" is a very biased statement. Since when did having refreshing sleep and avoiding motor vehicle accidents become an ""unimportant"" outcome. And what about reduction in Atrial fibrillation.	We agree that better studies are needed. The low strength of evidence of our findings speaks to the lack of definitive conclusions.
NR	General	Reference 1- Results show that patients with sleep apnea were nearly 2.5 times more likely to be the driver in a motor vehicle accident,	We were unable to locate this reference. Based on the description, it is unlikely this study would have met eligibility criteria.

Commentator & Affiliation	Section	Comment	Response
		compared with a control group of other drivers in the general population. Further risk analysis found that severe excessive daytime sleepiness, a short sleep duration of 5 hours or less, and use of sleeping pills were independent predictors of increased crash risk in patients with sleep apnea. The study also found that the incidence of motor vehicle accidents was reduced by 70 percent among sleep apnea patients who used CPAP therapy for an average of at least 4 hours per night. (Study results are published in the March issue of the journal SLEEP.)	
NR	General	What about A fib?Continuous positive airway pressure (CPAP) has been shown to reduce the rate of AF recurrence following catheter ablation in patients with sleep apnea. (Reference 2- J Atr Fibrillation. 2016 Apr-May; 8(6): 1283. Published online 2016 Apr 30. doi: 10.4022/jafib.1283)"	We did not evaluate this population
NR	Evidence Summary	I am evidence. The males in my family have died"in their sleep". I have been wearing CPAP for 19 years. I work 12hr night shifts and drive a total of 2.5hrs for work. Been doing this type of work for 31 years. I'm a registered polysomnographic sleep technologist. Every night I use CPAP on a patient I watch the respiratory, heart and saturation return to normal limits. I see bathroom visits cut in half. I see cardiac arrhythmia's decrease or stop altogether. The list goes on but to me this is ludicrous to believe there is no long term benefits. If nothing else just pick dementia as a study trial with CPAP. More and more research points to OSA as a major contributor. I believe the data collected is flawed and possibly cherry picked. If we could ask the automotive, train, pilots	No response

Commentator & Affiliation	Section	Comment	Response
		and boat captains that died from falling asleep I'm sure you'd get more accurate figures also.	
University of Pennsylvania	Results	"The results section mentions, on page 82, that ""As noted above, PREDICT did not report on compliance rates"". However, this is incorrect. The PREDICT study did report the compliance rate in one of their supplemental tables. It was only 35% at 12 months (Table S14 shows that only 36/102 met >4 hours adherence criteria at 12 months). You should be able to access the supplemental data here:https://www.clinicalkey.com/ui/service/content/url?section=static%2fimage&eid=1-s2.0-S2213260014701729&path=22132600%2FS2213260014X70232%2FS2213260014701729%2Fmmc1.pdfOr you can go to the main article and right above the ""References"" is a link to the Supplementary Material. The main article is here: http://dx.doi.org/10.1016/S2213-2600(14)70172-9Overall, this low adherence rate most likely significantly attenuated the effect size of a treatment benefit from the intervention and thus the findings from this study are likely under-representing the benefit that would have occurred if there was an acceptable adherence rate (which can be obtained if adherence support is provided. Our team has done research studies with CPAP in older adults and achieved adherence rates of 60% or more; see DOI: 10.1111/jgs.15758)."	Thank you. We have made the correction in the description of the PREDICT trial and in relevant tables.
University of Pennsylvania	Methods	"I reviewed the articles you included in your review. I would like to respectfully mention that you omitted several key articles. Please include the following articles in your review--these articles are randomized trials and merit inclusion. Several demonstrate evidence of benefit from CPAP. This list was drawn from	Most referenced studies did not meet our eligibility criteria, mostly because follow-up was short-term. We did miss Pelletier-Fleury 2004 and have added it in. Thank you.

Commentator & Affiliation	Section	Comment	Response
		the meta-analysis by Pan et al. available here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4733787/These are articles which they felt met criteria for inclusion in their meta-analysis because these studies were randomized trials and had Jadad scores of 3 or higher (i.e., indicative of high quality studies). They included the Kushida and Monasterio studies as well, which you included in your review (so I have left them out of the list below). However, the studies listed below you did not include and I would encourage you to include them: 1. Barnes M, Houston D, Worsnop CJ, Neill AM, Mykytyn IJ, Kay A, et al. A randomized controlled trial of continuous positive airway pressure in mild obstructive sleep apnea. Am J Respir Crit Care Med. 2002;165:773â€“80. [PubMed] [Google Scholar]2. Engleman HM, Martin SE, Deary IJ, Douglas NJ. Effect of CPAP therapy on daytime function in patients with mild sleep apnoea/hypopnoea syndrome. Thorax. 1997;52:114â€“9. [PMC free article] [PubMed] [Google Scholar]3. Engleman HM, Kingshott RN, Wraith PK, Mackay TW, Deary IJ, Douglas NJ. Randomized placebo-controlled crossover trial of continuous positive airway pressure for mild sleep apnea/hypopnea syndrome. Am J Respir Crit Care Med. 1999;159:461â€“7. [PubMed] [Google Scholar]4. Engleman HM, Martin SE, Deary IJ, Douglas NJ. Effect of continuous positive airway pressure treatment on daytime function in sleep apnoea/hypopnoea syndrome. Lancet. 1994;343:572â€“5. [PubMed] [Google Scholar]5. Barnes M, McEvoy RD, Banks S, Tarquinio N, Murray CG, Vowles N, et al. Efficacy of positive airway pressure and oral appliance in mild to moderate obstructive	

Commentator & Affiliation	Section	Comment	Response
		sleep apnea. Am J Respir Crit Care Med. 2004;170:656â€“64. [PubMed] [Google Scholar]6. Marshall NS, Neill AM, Campbell AJ, Sheppard DS. Randomised controlled crossover trial of humidified continuous positive airway pressure in mild obstructive sleep apnoea. Thorax. 2005;60:427â€“32. [PMC free article] [PubMed] [Google Scholar]7. Engleman HM, Martin SE, Kingshott RN, Mackay TW, Deary IJ, Douglas NJ. Randomised placebo controlled trial of daytime function after continuous positive airway pressure (CPAP) therapy for the sleep apnoea/hypopnoea syndrome. Thorax. 1998;53:341â€“5. [PMC free article] [PubMed] [Google Scholar]8. BarbÃ© F, Mayoralas LR, Duran J, Masa JF, MaimÃ³ A, Montserrat JM, et al. Treatment with continuous positive airway pressure is not effective in patients with sleep apnea but no daytime sleepiness. A randomized, controlled trial. Ann Intern Med. 2001;134:1015â€“23. [PubMed] [Google Scholar]9. Bardwell WA, Ancoli-Israel S, Berry CC, Dimsdale JE. Neuropsychological effects of one-week continuous positive airway pressure treatment in patients with obstructive sleep apnea: A placebo-controlled study. Psychosom Med. 2001;63:579â€“84. [PubMed] [Google Scholar]10. Pelletier-Fleury N, Meslier N, Gagnadoux F, Person C, Rakotonanahary D, Ouksel H, et al. Economic arguments for the immediate management of moderate-to-severe obstructive sleep apnoea syndrome. Eur Respir J. 2004;23:53â€“60. [PubMed] [Google Scholar]11. Gast H, Schwalen S, Ringendahl H, JÃ¶rg J, Hirshkowitz M. Sleep-related breathing disorders and continuous positive airway pressure-related changes in cognition. Sleep	

Commentator & Affiliation	Section	Comment	Response
		Med Clin. 2006;1:499â€“511. [Google Scholar]12. Prilipko O, Huynh N, Schwartz S, Tantrakul V, Kushida C, Paiva T, et al. The effects of CPAP treatment on task positive and default mode networks in obstructive sleep apnea patients: An fMRI study. PLoS One. 2012;7:e47433. [PMC free article] [PubMed] [Google Scholar]13. Ferini-Strambi L, Baietto C, Di Gioia MR, Castaldi P, Castronovo C, Zucconi M, et al. Cognitive dysfunction in patients with obstructive sleep apnea (OSA): Partial reversibility after continuous positive airway pressure (CPAP) Brain Res Bull. 2003;61:87â€“92. [PubMed] [Google Scholar]14. MuÃ±oz A, Mayoralas LR, BarbÃ© F, PericÃ¡s J, Agusti AG. Long-term effects of CPAP on daytime functioning in patients with sleep apnoea syndrome. Eur Respir J. 2000;15:676â€“81. [PubMed] [Google Scholar]"	
University of Pennsylvania	Methods	"I would like to draw your attention to another important article that was not included in your review:MartÃnez-GarcÃa MÃ□, Chiner E, HernÃ¡ndez L, Cortes JP, CatalÃ¡n P, Ponce S, et al. Obstructive sleep apnoea in the elderly: role of continuous positive airway pressure treatment. Eur Respir J. 2015;46: 142â€“151. doi:10.1183/09031936.00064214This article included cognitive assessments. They noted CPAP treatment led to statistically significant improvements in depression, anxiety, and sleepiness (small, moderate and large effect sizes, respectively). Statistically significant improvements for working memory (digit symbol test and Trail Making A) that were small and moderate, respectively, as well.Another important article you should include is:Dalmases M, SolÃ©-PadullÃ©s C,	None of these study met eligibility criteria due to short follow-up/treatment duration.

Commentator & Affiliation	Section	Comment	Response
		Torres M, Embid C, NuÃ±ez MD, MartÃnez-Garcia MÃ□, et al. Effect of CPAP on Cognition, Brain Function, and Structure Among Elderly Patients With OSA: A Randomized Pilot Study. Chest. 2015;148: 1214â€“1223. doi:10.1378/chest.15-0171This study found that CPAP led to statistically significant improvements in episodic, short-term memory, speed of mental processing and mental flexibility. MRI scan showed reduced cortical thinning and increased right middle frontal gyrus connectivity in the CPAP group. In addition, this randomized trial found that CPAP treatment reduced daytime sleepiness:Continuous positive airway pressure reduces subjective daytime sleepiness in patients with mild to moderate Alzheimer's disease with sleep disordered breathing, Mei S Chong 1, Liat Ayalon, Matthew Marler, Jose S Loredo, Jody Corey-Bloom, Barton W Palmer, Lianqi Liu, Sonia Ancoli-IsraelAnother key randomized study that was not included in your analysis is: Terri E Weaver 1, Cristina Mancini, Greg Maislin, Jacqueline Cater, Bethany Staley, J Richard Landis, Kathleen A Ferguson, Charles F P George, David A Schulman, Harly Greenberg, David M Rapoport, Joyce A Walsleben, Teofilo Lee-Chiong, Indira Gurubhagavatula, Samuel T KunaThis randomized study found that CPAP led to statistically significant improvements in daytime sleepiness"	
BetterNight, LLC	General	Dear Dr. Berliner,I would like to take this opportunity to strongly encourage you and the panel to re-consider the conclusions of your AHRQ on CPAP for OSA. While it may be the case that the RCTs included during the limited window of consideration have a low SoE supporting CPAP, there is a wealth of real	We have clarified the findings to be more focused on the types of evidence that were reviewed. Specifically that comparative studies do not provide evidence of effects. There are several long-term RCTs already done; however, we have added concerns

Commentator & Affiliation	Section	Comment	Response
		world evidence supporting CPAP that I do not feel was adequately considered.(1) Please consider the following:(A) It is the ultimate Catch-22 that a particular therapy is so widely recognized as the treatment of choice for OSA that the withholding of such a treatment, as would be necessary for the strongest study design, is considered unethical. Therefore, the ability to construct a true RCT is significantly compromised. (2-3) Under no circumstances would I allow one of my patients with severe OSA to participate in a long term sham study.	about difficulties conducting studies to the Future Research section.
BetterNight, LLC	General	(B) As a sleep physician with over thirty years experience treating patients with OSA it is inconceivable that an organization such as yours would leave the impression that CPAP has little value. Every day, the practice I supervise deals with countless patients whose lives have been transformed by CPAP therapy. (4-6)(C) Improvements in excessive daytime sleepiness and quality of life matter. Sleep deprivation is at epidemic levels in our society. The current pandemic has only exacerbated this fact. CPAP is the most effective tool to combat excessive sleepiness in the OSA population. The literature is replete with studies showing an increased risk for motor vehicle accidents in untreated OSA patients. Similarly, numerous studies detail clinically meaningful improvements in Epworth Sleepiness Scores following initiation of CPAP treatment. And, these results do not take six months to manifest and therefore were not adequately weighted in your analysis. (7-9)	We have clarified that we did not assess all outcomes that may be of value to patients, clinicians, and others to help with decisionmaking about CPAP. In particular, that we did not evaluate sleepiness. We have also added to the Discussion a summary of findings of these outcomes from prior systematic reviews.
BetterNight, LLC	General	(D) There is no doubt whatsoever that CPAP is the MOST effective treatment for the recurrent obstructive events that characterize OSA. These events are often accompanied by recurrent hypoxemia. We know that	We evaluated specific measures assessed in sleep studies. These included those that incorporated hypoxemia, including AHI and ODI. We did not evaluate indirect evidence

Commentator & Affiliation	Section	Comment	Response
		hypoxemia is detrimental and we know that the benefits of oxygen therapy are dose dependent. (10) The more hours an individual uses supplemental oxygen to prevent hypoxia the better the result.	(e.g., experimental data on the direct effect of hypoxemia).
BetterNight, LLC	General	Which brings me to the next point.(E) Compliance matters. A lethal flaw in the analysis is the acknowledged fact that compliance was not considered. As valuable as CPAP is, it is also a challenging treatment. Use varies widely and depending on the level of support a significant percentage of patients do not use the treatment to the extent that would be necessary to expect a measurable benefit. (11)	Adherence/compliance was considered, particularly in analyses of users and nonusers. We have added further language about adherence concerns, particularly among the RCTs.
BetterNight, LLC	General	Which leads to my final point.(F) At a time when we are making such important strides in improving CPAP compliance, the last thing we need is to sow unfounded doubt in the minds of our patients. (12)In summary, I would respectfully request that the findings in your report be used to spur the medical community to conduct the necessary additional research, but that it not be released as an indictment of a treatment that is so vital to millions of Americans.Respectfully, Dominic A. Munafo, M.D., FABSM	We are hopeful that the further clarifications about the focused scope of this review will reduce misinterpretation of our findings.
NR	General	To whom it may concern:Thank you for the opportunity respond on the AHRQ draft technology assignment titled continuous positive airway pressure treatment for obstructive sleep apnea.I and my colleagues have been treating patients with obstructive sleep apnea for many years. Many of our patients habe noted considerable improvement in both their neurocognitive symptoms as well as noted improved cardio respiratory function and overall quality of life.Thereâ€™s been several studies that	Thank you

Commentator & Affiliation	Section	Comment	Response
		show that For patients with atrial fibrillation, treatment of the stroke sleep apnea decreases the reoccurrence of atrial fabrillation. In addition multiple studies have shown improvements of markers of metabolic dysfunction including autonomic dysregulation, lipid metabolism, and insulin resistance with treatment with CPAP for obstructive sleep apnea. All of these are important pathophysiologic factors in the development of cardiovascular disease.My colleagues and I are professors of medicine in the Department of Pulmonary Medicine at The University of Texas MD Anderson Cancer Center. We have also noted with interest several studies that show that sleep apnea can lead to increasedIncidence of cancer as well as an increase in cancer mortality.We believe that CPAP is an important part of the armamentarium for the treatment of sleep apnea in order to decrease metal pole dysfunction And decrease the incidence of atrial fabulation. Studies have yet to be done to show outcomes related to treatment of sleep apnea with CPAP and cancer, however multiple centers are engaged in just that sort of research at this time.Therefore we feel it will be premature to suggest that CPAP does not have a very important role in the treatmentâ€¦ Like a sleep apnea. We ask that every consideration given to continuing to allow patients to be treated for this debilitating disease with significant mobility mortality mortalityThank you once again for allowing us to respond and for your consideration	
Council for Quality Respiratory Care	Evidence Summary	"An Executive Summary seeks to synthesize the totality of the paper, which the draft does; however, it should also provide the context in which that summary is being presented. We	As we note, the evidence base rarely addresses specific populations. We have added language to the Future Research

Commentator & Affiliation	Section	Comment	Response
		are concerned that the contextual information focuses more on the individual study results and SoE and less on the disease, disparate impact on communities of color, the difficulties with patient adherence to treatment protocols with CPAP, and the clear directional trend the studies when taken together present. We encourage these points to be included in the executive summary of the final report.	section that differences in healthcare disparity populations needs more research.
Council for Quality Respiratory Care	Evidence Summary	This CQRC is also concerned that the limitations outlined in this summary and in the paper itself focus primarily on individual studies. The Technology Assessment should include observational studies and meta-analyses to present a more holistic view of the current literature related to CPAP as a treatment option for OSA. It is inappropriate to rely upon Randomized Controlled Trial (RCT) data alone. The vast majority of medical treatments performed in the United States and worldwide are not based on RCTs, but observational studies. The traditional hierarchy of evidence is not meant to be applied dogmatically. While well-designed and conducted RCTs may be preferrable, those RCTs that are â€œsmall or inadequate should not automatically trump any conflicting observational study;â€□ further â€œ[n]ot all observational studies are misleading.â€□ It is important that all studies are considered and evaluated in an objective manner.	We have improved language, including the title, to clarify the focus of this review on only a portion of the total evidence base about PAP, namely randomized and adjusted, comparative observational studies of specific long-term clinical outcomes. The findings now are stated that comparative studies do not provide evidence of effects.
Council for Quality Respiratory Care	Evidence Summary	The statement that â€œthere is not adequate evidence to support the contention that changes in AHI or ESS translate to improvements in clinical outcomesâ€□ is not consistent with clinical practice. Because the Technology Assessment considers the SoE to be low, it is not appropriate to make a statement that there is not a benefit to CPAP	In our review we are discussing study-based evidence. There is a high bar to reach to support claims that changes in AHI or ESS are correlated with clinical outcomes.

Commentator & Affiliation	Section	Comment	Response
		because low SoE does not show a benefit. We strongly encourage AHRQ to talk directly with the American Thoracic Society, the American College of CHEST Physicians, the American Academy of Sleep Medicine (AASM), and the American Association of Respiratory Care (AARC) to identify those studies that specifically counter this statement. In addition, the limitations section does not adequately address the problem that patient adherence creates for the researchers in the studies reviewed. Adherence affects outcomes, yet few of the studies summarized in the Technology Assessment address this issue directly.	
Council for Quality Respiratory Care	Evidence Summary	It is critical to tease out the effectiveness of the CPAP treatment option from the lack of patient adherence. For example, the FDA would not change the label of a drug because follow-up studies failed to demonstrate the same or a better level of efficacy than the original clinical trials due to a lack of participant adherence in taking the medication. Similarly, AHRQ and CMS in their coverage evaluation should focus on the actual effect of CPAP on patients who adhere to the treatment requirements, not on those prescribed the treatment but who do not use it. We describe below how studies focused on adherent patients demonstrate the clear value of CPAP treatment options, while those that do not account for lack of adherence result in the more clouded view of the efficacy of CPAP. We believe it is misleading to suggest, as the Technology Assessment does, that there is â€œno difference in the effect between compliant and noncompliant CPAP users.â€ Many studies dispute this conclusion. Given these concerns, we believe	We primarily focus on intention to treat analyses, which address the question of whether prescription of CPAP is effective. This should correspond better to real-world effects of use of CPAP. This takes into account the lack of adherence. However, we also note the evidence comparing effects among compliant and noncompliant patients. We restrict ourselves, though, to eligible studies comparing PAP to no PAP (or other treatments)

Commentator & Affiliation	Section	Comment	Response
		that the certainty with which the implications and conclusions are written is not appropriate or reflective of the entire scope of clinical literature on this topic.Citations for this section:Barton, S. â€œWhich Clinical Studies Provide the Best Evidence? The Best RCT Still Trumps the Best Observational Study.â€ BMJ. 2000 Jul 29; 321(7256): 255â€“256. Chhatre S, Chang YHA, Gooneratne NS, Kuna S, Strollo P, Jayadevappa R. Association between adherence to continuous positive airway pressure treatment and cost among medicare enrollees. Sleep. 2020;43(1). doi:10.1093/sleep/zsz188; Kirsch DB, Yang H, Maslow AL, Stolzenbach M, McCall A. Association of Positive Airway Pressure Use With Acute Care Utilization and Costs. J Clin Sleep Med. 2019;15(9):1243-1250. doi:10.5664/jcsm.7912.Streatfeild J, Hillman D, Adams R, Mitchell S, Pezzullo L. Cost-effectiveness of continuous positive airway pressure therapy for obstructive sleep apnea: health care system and societal perspectives. Sleep. 2019;42(12). doi:10.1093/sleep/zsz181 (discussing that studies are limited in their scope because they do not examine, or fail to fully scrutinize, adherence to therapy). Chhatre S, Chang YHA, Gooneratne NS, Kuna S, Strollo P, Jayadevappa R. Association between adherence to continuous positive airway pressure treatment and cost among medicare enrollees. Sleep. 2020;43(1). doi:10.1093/sleep/zsz188; Kirsch DB, Yang H, Maslow AL, Stolzenbach M, McCall A. Association of Positive Airway Pressure Use With Acute Care Utilization and Costs. J Clin Sleep Med. 2019;15(9):1243-1250. doi:10.5664/jcsm.7912; Lisan Q, Van	

Commentator & Affiliation	Section	Comment	Response
		Sloten T, Marques Vidal P, Haba Rubio J, Heinzer R, Empana JP. Association of Positive Airway Pressure Prescription With Mortality in Patients With Obesity and Severe Obstructive Sleep Apnea: The Sleep Heart Health Study. JAMA Otolaryngol Head Neck Surg. 2019;145(6):509-515. doi:10.1001/jamaoto.2019.028; Gottlieb DJ, Punjabi NM. Diagnosis and Management of Obstructive Sleep Apnea: A Review. JAMA. 2020;323(14):1389-1400. doi:10.1001/jama.2020.3514; Cistulli PA, Armitstead J, Pepin J-L, et al. Short-term CPAP adherence in obstructive sleep apnea: a big data analysis using real world data. Sleep Med. 2019;59:114-116. doi:10.1016/j.sleep.2019.01.004; Malhotra A, Crocker ME, Willes L, Kelly C, Lynch S, Benjafield AV. Patient Engagement Using New Technology to Improve Adherence to Positive Airway Pressure Therapy: A Retrospective Analysis. Chest. 2018;153(4):843-850. doi:10.1016/j.chest.2017.11.005; Patil SP, Ayappa IA, Caples SM, Kimoff RJ, Patel SR, Harrod CG. Treatment of Adult Obstructive Sleep Apnea With Positive Airway Pressure: An American Academy of Sleep Medicine Systematic Review, Meta-Analysis, and GRADE Assessment. J Clin Sleep Med. 2019;15(2):301-334. doi:10.5664/jcsm.7638."	
Council for Quality Respiratory Care	Introduction	The introduction provides helpful, albeit general, background on OSA and treatment options. We suggest providing more information about the effects of OSA in communities of color, including the higher risk these Americans face with regard to comorbidities that place them at higher risk for OSA. We also suggest providing more	The Introduction (and the systematic review as a whole) is not meant to be an expansive narrative review of OSA. The studies provide almost no evidence about effects in specific populations, including communities of color. In the Discussion we have added more to our text about the need

Commentator & Affiliation	Section	Comment	Response
		information about adherence and the limitations that studies not accounting for adherence may have on the outcomes referenced in this section.	for further such research in particular subpopulations of interest. We have expanded on the issues related to poor adherence, but believe this is more salient as a finding (in the Results and Discussion) than a predefined limitation (in the Introduction).
Council for Quality Respiratory Care	Methods	"As described elsewhere in these comments, the CQRC is concerned with the reliance on only RCTs as the basis for the SoE analysis. The hierarchy of evidence should not be strictly applied, especially when there are strong and valid observational studies that counter the small and inadequate studies. For example, case-control and registry studies prove better than RCTs when trying to identify rare outcomes, especially those that require long-term follow-up. Given that the purpose of treating patients with OSA using CPAP is to reduce adverse events related to conditions with long-term outcomes, such as stroke, cardiovascular disease, and heart failure, these types of observation studies are more likely to provide the information that CMS has requested be part of the Technology Assessment. For example, medical professionals have relied on studies such as the Wisconsin Sleep Study and the Sleep Heart Health Study to validate the use of AHI through larger, observational studies that limit confounding bias by controlling for basic socio-demographic variables and other indication bias. These studies have much greater value than small, inadequate RCTs.We also note that several meta-analyses and RCTs do provide the evidence that the Technology Assessment suggests is lacking. For example, the AASM performed a meta-analysis examining the effects of CPAP	Per our protocol, we have conducted a focused review specifically of RCT and adjusted comparative studies. We do not dismiss other sources of evidence, but we do not review all possible evidence.

Commentator & Affiliation	Section	Comment	Response
		use on various outcomes including OSA severity, blood pressure, CVD events, mortality, hospitalization, and Quality of Life (QoL). The results of this analysis found highly compelling evidence of CPAP positively affecting patient outcomes. At least four RCTs have found that CPAP utilization led to significant changes in blood pressure for OSA patients. We encourage AHRQ to work with the ATS, CHEST, AASM, and AARC to identify and review all of the relevant clinical studies, including those referenced in their comment letters. The final paper should present a more holistic view of the evidence available and address directly the shortcomings of the RCTs that do not address patient adherence or other similar relevant issues.Citations for this section:Patil SP, Ayappa IA, Caples SM, Kimoff RJ, Patel SR, Harrod CG. Treatment of Adult Obstructive Sleep Apnea With Positive Airway Pressure: An American Academy of Sleep Medicine Systematic Review, Meta-Analysis, and GRADE Assessment. J Clin Sleep Med. 2019;15(2):301-334. doi:10.5664/jcsm.7638. Becker HF, Jerrentrup A, Ploch T, et al. Effect of Nasal Continuous Positive Airway Pressure Treatment on Blood Pressure in Patients With Obstructive Sleep Apnea. Circulation. 2003;107(1):68-73. doi:10.1161/01.CIR.0000042706.47107.7A; Monasterio C, Vidal S, Duran J, et al. Effectiveness of continuous positive airway pressure in mild sleep apnea-hypopnea syndrome. Am J Respir Crit Care Med. 2001;164(6):939-943. doi:10.1164/ajrccm.164.6.2008010; Lam B, Sam K, Mok WYW, et al. Randomised study of three non-surgical treatments in mild to	

Commentator & Affiliation	Section	Comment	Response
		moderate obstructive sleep apnoea. Thorax. 2007;62(4):354-359. doi:10.1136/thx.2006.063644; Nguyen PK, Katikireddy CK, McConnell MV, Kushida C, Yang PC. Nasal continuous positive airway pressure improves myocardial perfusion reserve.and endothelial-dependent vasodilation in patients with obstructive sleep apnea. J Cardiovasc Magn Reson. 2010;12(1):50. doi:10.1186/1532-429X-12-50."	
Council for Quality Respiratory Care	Results	"As a threshold matter, we ask that the Technology Assessment clearly state that it found no evidence suggesting that CPAP is not an effective treatment for OSA. The results of this study will drive the decision-making not only for the Medicare program, but also other federal health insurance programs like Medicaid, as well as commercial payers. The stakes could not be higher in terms of protecting patient access to CPAP, which is the recognized standard of care for OSA in the United States and worldwide. Thus, while we encourage AHRQ to provide not only a more holistic analysis of the available clinical literature, we also ask that it definitely state that the clinical literature does not state that CPAP is not an effective treatment option.CPAP is also an essential treatment option for Medicare if it wants to achieve its goals of getting patients the right treatment in the right setting at the right time. For example, one retrospective cohort study examining the association between CPAP use and acute care utilizations, found that CPAP use was associated with reduced inpatient and all acute care visits in a population with severe OSA at baseline. The study compared the cost of therapy for OSA and	We have revised the findings to be that comparative studies do not provide evidence that CPAP has an effect on long-term outcomes. We also have made more explicit statements about the specific focus of the review.

Commentator & Affiliation	Section	Comment	Response
		acute care utilization during an 18-month period. Participants adhering to their treatment had more than 32 percent acute care visits, compared to 47 percent for non-adherent patients. They had fewer inpatient observation visits. The mean cost of acute care visits for non-adherent patients was more than $2,000 higher than the costs of adherent patients. While more studies like this one should be done, it is clear that adhering to treatment protocols in the home setting can result in greater health care savings over time. It is important that the results outlined in the Technology Assessment recognize the trends identified in such studies and avoid creating barriers because of biases toward RCTs. The Sleep Apnea Cardiovascular Endpoints Study (SAVE) provides an example of how an RCT is not necessarily as strong as an observational study. The study was severely underpowered for the primary outcome of major cardiovascular events because there were a low number of such events coupled with the studyâ€™s short duration (3.7 years) and age of the participants (average of 61 years old). In addition, the study did not properly account for adherence, which was low and not consistent with the Medicare definition of more than four hours during 70 percent of 30 nights. More than half of the study population was not adherent to the therapy. The researchers did not account for adherence in the mortality risk. Lack of adherence likely contributed to the mostly non-significant neutral results related to the primary and secondary outcomes. Given the limitation of such a study, it and studies like it should not be relied upon to conclude that CPAP is not effective in treating OSA or	

Commentator & Affiliation	Section	Comment	Response
		improving certain outcomes.Citations for this section:Kirsch DB, Yang H, Maslow AL, Stolzenbach M, McCall A. Association of Positive Airway Pressure Use With Acute Care Utilization and Costs. J Clin Sleep Med. 2019;15(9):1243-1250. doi:10.5664/jcsm.7912. "	
Council for Quality Respiratory Care	Discussion	"Consistent with our comments on the Executive Summary and the Introduction, the CQRC is concerned that unless the Technology Assessment takes a more holistic approach to identifying and evaluating the clinical literature on the use of CPAP in patients with OSA, access to patients, particularly those within communities of color, will experience serious barriers in accessing this standard of care. While the CQRC defers to the clinical community in terms of debating the merits of the individual studies and their assessment, the principles we have articulated in earlier sections of this letter apply to the discussion section as well. Specifically, we ask that the draft report be revised to:â€¢ Recognize the importance of treating OSA in communities of color, the importance of accounting for adherence, and the clear directional trend showing the positive patient outcomes when the clinical literature is considered in total.â€¢ Include observational studies and meta-analyses to present a more holistic view of the current literature related to CPAP as a treatment option for OSA, rather than rely only on RCTs, especially when those studies are small and inadequate in their design. The hierarchy of evidence should not be strictly applied, especially when there are strong and valid observational studies that counter the small and inadequate studies.â€¢ Engage directly with ATS, CHEST, AASM,	Thank you

Commentator & Affiliation	Section	Comment	Response
		and AARC to identify those studies that specifically address the use of CPAP to treat patients with OSA. Finally, we ask that the Technology Assessment clearly state that no new evidence was identified that would call into question the current clinical criteria for Medicare coverage of CPAP."	
Council for Quality Respiratory Care	General	"The members of the Council for Quality Respiratory Care (CQRC) appreciate the opportunity to provide comments on the draft â€œContinuous Positive Airway Pressure Treatment for Obstructive Sleep Apnea Technology Assessmentâ€ (Technology Assessment). The CQRC is a coalition of the nationâ€™s six leading home oxygen and sleep therapy providers and manufacturing companies. Together we provide in-home patient services and respiratory equipment to more than 600,000 of the more than one million Medicare beneficiaries who rely upon home oxygen therapy to maintain their independence and enhance their quality of life. Similarly, we provide homecare services, equipment, and supplies to more than one million Medicare beneficiaries with Obstructive Sleep Apnea (OSA). As described below, the CQRC has concerns about the completeness of the review and the conclusions drawn based on the limited clinical studies included in the Technology Assessment. In addition, we do not believe the draft Technology Assessment supports changes to the current coverage requirements for CPAP when prescribed to patients with OSA. We ask that the Technology Assessment clearly state that no new evidence was found calling into question the current clinical criteria for Medicare coverage of CPAP.OSA, a sleep disorder hallmarked by repeated episodes of	We have revised our findings to better clarify the focused scope of our review. The SoE refers to the evidence base assessed. We have no recommendation about or assessment of the Medicare CPAP coverage criteria, including whether our findings warrant changes. The included evidence did not address differences across populations, including racial disparities. We have added this lack in the Future Research section of the Discussion.

Commentator & Affiliation	Section	Comment	Response
		upper airway closure, affects 9 percent to 26 percent of the U.S. adult population. Patients with certain comorbidities are more at-risk for OSA. These comorbidities include: cardiovascular disease, hypertension, heart failure, stroke, arrythmias, coronary artery disease, and type-2 diabetes. The Centers for Medicare & Medicaid Services (CMS) 2018 Chronic Disease Data highlight the disproportional impact these diseases have on Blacks, Hispanics, and Native Americans/Pacific Islanders in the United States, which then places them at greater risk for OSA. Recent clinical literature identifies the racial disparities in the prevalence, risk factors, presentation, diagnosis, and treatment of OSA. For example, â€œ[a]mong African Americans, Native Americans, and Hispanics, OSA prevalence is increased, likely due in part to obesity. Burden of symptoms, particularly excessive daytime sleepiness, is higher among African Americans, though Hispanics more often report snoring. Limited data suggest African Americans may be more susceptible to hypertension in the setting of OSA.â€ According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2021 Report on Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease, â€œIn patients with both COPD and obstructive sleep apnea there are clear benefits associated with the use of continuous positive airway pressure (CPAP) to improve both survival and the risk of hospital admissions.â€ The American Association of Respiratory Care, the professional society of respiratory therapists, describes CPAP as	

Commentator & Affiliation	Section	Comment	Response
		â€œthe current standard [of care] for the majority of patients because of its demonstrated efficacy in reducing apneas and hypopneas.â€ President Biden and Vice President Harris have renewed the commitment to the American people to protect and expand Americansâ€™ access to quality, affordable health care. This includes reducing health care disparities. Given the growing prevalence of OSA in communities of color and the disproportionally poorer outcomes experienced by Blacks, Hispanics, and Native Americans/Pacific Islanders when diagnosed with OSA, any proposal or assessment suggesting a change to the current standard of care in a manner that could further disenfranchise communities of color should be undertaken only with the utmost caution.The CQRC seeks to protect access to CPAP treatments for patients diagnosed with OSA whose physicians prescribe this respiratory therapy for them. Our members do not prescribe CPAP therapy, but like pharmacists, fill prescriptions written by patientsâ€™ physicians. We support ongoing efforts to consider the most recent studies in evaluating coverage determination, but are concerned that the strength of evidence (SoE) review presented on a study-by-study basis misses the clear benefit the totality of clinical literature shows when taken as a whole. While we agree that more studies could be undertaken to address the current gaps in the literature, the practical reality is that the studies that exist today when taken together demonstrate that adherence to a CPAP treatment protocol in patients with OSA reduces morbidity and mortality related to cardiovascular diseases, obesity, type II diabetes, stroke/transient	

Commentator & Affiliation	Section	Comment	Response
		ischemic attack, atrial fibrillation, hypertension, and coronary artery disease. Our recommendation to AHRQ is to acknowledge the weight and consistency of the evidence across the entire body of research, as well as to address the studies referenced by other commenters including the professional societies in a revised Technology Assessment. Presenting a more complete analysis, similar to the assessment in 2011, would demonstrate the continued importance of CPAP to patients who require it, especially in communities of color. Even without these additional studies, the Technology Assessment does not support changing the coverage criteria for CPAP. We encourage AHRQ and its sister agencies within the Department of Health and Human Services to find ways to help patients resolve the socio-economic and socio-demographic factors that can reduce adherence. Citations for this section:Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993; 328(17): 1230-5. American Association for Respiratory Care (AARC). â€œClinicians Guide to PAP Adherence.â€ 1-3 (2009) available at: https://www.aarc.org/wp-content/uploads/2014/04/pap_adherence.pdf. Katherine A. Dudley and Sanjay R. Patel. â€œDisparities and Genetic Risk Factors in Obstructive Sleep Apnea.â€ Sleep Med. 2016; 18: 96â€“102.Global Initiative for Chronic Obstructive Lung Disease (GOLD). â€œ2021 Report on Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease.â€ 62 (2021), citing Marin JM, Soriano JB,	

Commentator & Affiliation	Section	Comment	Response
		Carrizo SJ, Boldova A, Celli BR. Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome. Am J Respir Crit Care Med 2010; 182(3): 325-31. "	
Frederick Health Sleep Medicine	Evidence Summary	I have reviewed the AHRQ report and have several observations and concerns based on 29 years of clinical experience in the field of sleep medicine. As Medical Director for the Sleep Medicine practice and laboratory at our local hospital*, I speak for myself, and not for the organization, but I speak with experience of involvement in the care of thousands of sleep apnea patients.First and foremost, sleep apnea is a condition which results in profound sleepiness in many patients, impacting their ability to work, think and drive safely. CPAP undeniably and unequivocally treats the drowsiness caused by repeated interruptions in continuous sleep due to airway obstruction. This point seems to be buried in this report.	Thank you. We have made it more explicit that we do not cover all outcomes, including sleepiness. We have added information about effects on sleepiness from other reviews to the Discussion.
Frederick Health Sleep Medicine	Evidence Summary	While it is important to recognize that AHI as a surrogate measure of clinical outcomes may be imperfect and incomplete, and that AHI itself has been variably defined, it is also important to recognize that in practice, clinical management of patients and the ability to provide covered services to them has been locked to AHI, using 4% desaturation rather than AASMâ€™s guidelines for definition of AHI. In order for future research to be optimally useful in clinical practice, there must simultaneously be flexibility in allowing clinical judgment of what surrogate markers we use clinically, and agreement in refining a global assessment and standardization of surrogate measures for research purposes.	We fully agree that AHI is an imperfect measure and describe and discuss this at length.

Commentator & Affiliation	Section	Comment	Response
Frederick Health Sleep Medicine	Evidence Summary	Next, I would like to comment on the conundrum of reliance on RCTs for assessing a modality (CPAP) which is impossible to blind, and is unethical to withhold. To conclude that data to support CPAP use are not sufficiently robust because of lack of RCTs is circular logic. Additionally, blinding often de facto makes it impossible to support CPAP use in the same way we do in clinical practice, with frequent pressure, mask, technique and comfort adjustments over a period of time which involves establishment of strong connections between clinical staff and patient. One cannot work sincerely with a patient to optimize pressure, eg as weight or medical conditions change over time, when the patient has been randomized to sham CPAP..	We have better clarified the limited scope of this review and that it does not cover all evidence or all outcomes of potential interest.
Frederick Health Sleep Medicine	Evidence Summary	Finally, it is critical to consider the classic CPAP study conundrum in which a CPAP intervention is prescribed, but compliance is not optimized, the attempt at blinding is ineffective, and then a conclusion is drawn on intent to treat basis. This is generally followed by a dismissal of any post hoc analysis of compliant v. noncompliant patients. While it is reasonable to assume that patients who are compliant may have unmeasured factors that differ markedly from noncompliant patients, it is my clinical experience over thousands of patients over almost 3 decades of experience in the field (including ABSM and ABIM Board certifications in Pulmonary and Sleep Medicine) that there is a linear relationship between hours of use as well as percentage of total sleep time protected by CPAP use and alertness, cognitive clarity, and cardiovascular health. This is the study design that needs to be done on a large scale to determine what	We do not believe we are being dismissive about post hoc analyses, but we include the information to increase transparency. There are higher risks of bias in reported post hoc analyses, which should not be dismissed. We also hope this report will spur better future studies.

Commentator & Affiliation	Section	Comment	Response
		CPAP can do: Control for AHI and oxygen desaturation, start PAP therapy using intensive best practices, and follow outcomes that track hours and percentage of usage to assess correlation with outcomes.It is my hope that this report will spur more dedicated attention to optimizing study of this gold standard treatment for a condition that is highly prevalent and associated with high morbidity	
Frederick Health Sleep Medicine	General	"As an addendum, I include my letter to the editor at the Washington Post from several years ago:Wake up, people â€" for this cure to work, you have to use it I have been a sleep specialist for about a quarter-century and have taken care of thousands of patients with sleep apnea. The Aug. 29 news article â€œNew study questions the effectiveness of CPAP in some sleep apnea casesâ€ noted that in that study continuous positive airway pressure, or CPAP, â€œusersâ€ averaged only 3.3â€‰hours of use per night (which arguably falls short of even the minimal Center for Medicare and Medicaid Services requirements for â€œuseâ€). The real point may be that CPAP doesnâ€™t work if you donâ€™t use it.No one would argue that a well-insulated coat doesnâ€™t keep you warm, but if you are in the freezing cold for seven hours, and you wear the coat for less than half that time, you are likely to freeze. My patients hear from me that the goal of therapy is to use their CPAP device whenever they sleep, and my job is to help optimize their comfort with their device. While I am delighted to find sleep news in The Post, Iâ€™m concerned that the message was blurred.Katherine S. Maul Buki, FrederickThe	Thank you

Commentator & Affiliation	Section	Comment	Response
		writer is on the board of directors of the Maryland Sleep Society."	
St. Elizabeth Healthcare Sleep Disorders Center	Evidence Summary	"Position Statement in Response to AHRQ Medicare RequestWe have a number of objections to the AHRQâ€™s draft Technology Assessment report titled â€œContinuous Airway Pressure Treatment for Obstructive Sleep Apnea.â€ The AHRQ states inadequate testing, study power, and or inconsistent terminology makes drawing reliable conclusions difficult. Subsequently, the AHRQ states â€œAdditional evidence would most likely support our current findings but significant doubt remains.â€ Such statements conclude that no reliable conclusions can be drawn from the AHRQ report.	We found the evidence to, at best, support only low strength of evidence.
St. Elizabeth Healthcare Sleep Disorders Center	Evidence Summary	In addition to this less than convincing summary of data, we have multiple issues with the summary, however we will address the more important ones to keep comments to the CMS/ARHQ short and concise.1. AHRQ states â€œ CPAP does not yield clinically significant changes in anxiety, depression, cognitive function or QOLâ€.Numerous studies dispute these claims, as well as numerous patients in our practice describe CPAP as â€œgame changerâ€ and have stated that they â€œfeel like I have my life back.â€ Thousands of patients in my career would dispute this AHRQ claim. Too many studies exist to cite them all, however one strong study counters the AHRQ claim is by demonstrating : that outcomes after 6 months of CPAP therapy proves significant improvements in QOL, daytimes sleepiness, and other serious symptoms (Avlonitou).	Our conclusions are based on the eligible studies, specifically comparative studies (vs. no CPAP) with long-term followup. The referenced studies do not meet these criteria.
St. Elizabeth Healthcare	Evidence Summary	2. AHRQ states that CPAP had no Effect on CV outcomes when compared to no CPAC	The RCTs compared prescription of CPAP to no CPAP. Our primary question did not relate

Commentator & Affiliation	Section	Comment	Response
Sleep Disorders Center		use.These studies cited to make this claim were not properly operated and conclusions can only be drawn from the literature that less than 4 hours of daily CPAP usage does not reduce cardiovascular outcomes. This is not a clinically useful or meaningful length of time as less than 4 hours usage per day is considered non-compliant on the patientâ€™s part. Further properly operated studies with better definitions, compliance, and longer follow up would be needed to draw any conclusions of CV outcomes and risk of death. In addition, a study followed 1,651 patients over 10 years and demonstrated that untreated severe OSA patients had increased fatal cardiovascular events as compared with treated with CPAP, mild to moderate untreated patients and healthy controls (Marin).	to the efficacy of CPAP (use vs. no use), but we did fully describe such analyses, as reported. We have added further description and discussion about adherence and the comparison between ITT and as-treated analyses (which interestingly, and maybe counterintuitively) did not find significant differences in results between analyses). The reference did not meet eligibility criteria since they did not directly compare CPAP versus nonCPAP (but only indirectly compared through healthy controls)..
St. Elizabeth Healthcare Sleep Disorders Center	Evidence Summary	3. AHRQ states CPAP has not been proven to reduce Accidents.We do not agree with this statement. All the patients we see that have fallen asleep at the wheel have been corrected to become safe drivers with CPAP. This is further support by studies. (Karimi).	We included only evaluations of CPAP, not observational studies of OSA.
St. Elizabeth Healthcare Sleep Disorders Center	Evidence Summary	4. AHRQ reports CPAP and A-PAP have â€œNo significant difference in functional status score and or limited data. Noted other long term clinical data have not been studied or reported.â€□We disagree with this statement based on actual patient care, lack of data, and the fact that many patients should not be prescribed A-PAP in our practice. We see a significant amount of heart failure, COPD, respiratory failure patients as well as patients subject to significant mask leak and movement disorder with frequent position changes/morbidly obese at risk for hypoventilation. These patients are	We focus on comparative studies. We do not claim to cover all types of evidence, including actual patient care, etc. We have made the focus of the report and findings clearer.

Commentator & Affiliation	Section	Comment	Response
		specifically at risk for treatment and compliance failures, risk of central events, and or hypoxia and may require O2 titration as well. In addition to these patients who require fixed PAP device management, there are numerous patients that simply do not fare well on auto CPAP. I would caution AHRQ suggesting there may be no difference in functional scores and suspect the patients that did poorly on auto PAP were not well represented in the studies and or exclusion criteria. In addition, craniofacial, palate deformities, and pediatric patients typically do not fare well on auto devices for a host of reasons including excessive mask leak and frequent body position changes. They may not be well managed on the auto devices proprietary mechanisms which are subject to failure with mask leakage.	
St. Elizabeth Healthcare Sleep Disorders Center	Evidence Summary	In addition to our responses to specific claims in the assessment draft report, there were also two areas of omission that were of concern to us:1. AHRQ fails to mention one of the strongest and most meaningful benefits of CPAP as it pertains to CMS goals and outcomes. CPAP has been proven to reduce readmission rate of cardiac patients with co-morbid conditions such as arrhythmias, myocardial infarction, and CHF. (Kausta). In addition, untreated OSA is an independent risk factor for 30 day re-admissions (Scalzitti).	These were outcomes of interest, but eligible studies did not report them. The Kauta and Scalzitti studies did not meet eligibility criteria.
St. Elizabeth Healthcare Sleep Disorders Center	Evidence Summary	2. AHRQ fails to mention any of the numerous important studies on blood pressure and response to CPAP. We feel this should have been included and or mentioned in the CV data reports in their summary. It has been proven that CPAP lowers blood pressure in both the literature and in actual patients interactions at our institution as noted by	It is correct that we did not review intermediate outcomes, including BP.

Commentator & Affiliation	Section	Comment	Response
		Sleep, Nephrology and Cardiology Practitioners. A 2014 Meta-analysis with 30 randomized trials over 1900 CPAP patients demonstrated significant reductions in blood pressure. Furthermore a 1-2 mmg Hg reduction in blood pressure confers a reduction in major cardiac events such as CVA/CHF and is statistically significant. Lancet 2003 Nov 362 (9395)Thank you for your consideration of our comments and concerns.Sincerely,W. Clay Willmott, MD Director Saint Elizabeth Sleep Disorders CenterRalph F. Huller MDPatricia Miles MDNeal J. Moser MD	
St. Elizabeth Healthcare Sleep Disorders Center	General	Thank you for the opportunity to comment on this Technology Assessment (TA) Report that may have a significant impact on sleep patients and treatment for sleep apnea.	No response
ASI Neurology and Sleep Medicine	Evidence Summary	My evidence is based on 20+ years in sleep medicine. I am not sure how anyone can dispute the use of PAP to maintain a patent airway in patient's with diagnosed sleep apnea. We all understand that non-compliance is an issue and of coarse these folks would not benefit from PAP therapy. I think that if you interview folks who have benefited immensely from the the treatment of their Sleep Apnea.	Thank you.
ASI Neurology and Sleep Medicine	Introduction	Bradley Weaver, RCP, RPSGT... My career has been in Respiratory and Sleep Medicine for 32 years. I have had the privilege of working in IDTF's, physician office, educational facility and Department of Veteran Affairs.	No response
ASI Neurology and Sleep Medicine	Methods	Direct Contact with OSA population with multiple comorbidities, PTDS, No other health issues and children.	No response

Commentator & Affiliation	Section	Comment	Response
ASI Neurology and Sleep Medicine	General	I think this research may need some additional investigation, patient selection. I can not imagine that we can say with all the research confirming that PAP is the gold standard treatment for Obstructive Sleep Apnea.....	We systematically reviewed specific evidence.
VGM & Associates	Evidence Summary	Subject: Comments on the draft Continuous Positive Airway Pressure Treatment for Obstructive Sleep Apnea Technology Assessment.â€	No response
VGM & Associates	Introduction	"Subject: Comments on the draft Continuous Positive Airway Pressure Treatment for Obstructive Sleep Apnea Technology Assessment.â€VGM & Associates (VGM), founded in 1986, is the nationâ€™s largest and most comprehensive member service organization for post-acute healthcare including DME/HME, Respiratory, Sleep, Wound Care, Complex Rehab, Womenâ€™s Health, Home Modifications, and Orthotics & Prosthetics suppliers. Over 2,500 durable medical equipment suppliers, with nearly 7,000 locations rely on VGM to connect them to valuable resources every day. VGM was founded on the premise that personal connections create growth and opportunity. Today, our relationships and entrepreneurial spirit continue to allow us to add services, resources, and programs that suppliers will not get anywhere else to help their business and ultimately, their patients. We also collaborate and have strong strategic partnerships with vendors and manufacturers throughout the supply chain to help create programs and solutions that allow HME suppliers to operate as efficiently and effectively as possible. We are writing to you on behalf of our 2,500+ home medical equipment suppliers that serve a variety of	No response

Commentator & Affiliation	Section	Comment	Response
		patient types from working adults, pediatrics, disabled and elderly population in the country. While the HME community is proud to serve this group, the HME industry plays an integral role in the lives of millions of Americans.Obstructive Sleep Apnea (OSA) has been known to affect an estimated one billion people worldwide and leads to many co-morbidities as well as mortality. The high costs associated with co-morbidities of OSA patients in addition to insurance payers benefit from policies that keep these same patients performing standard daily living activities in their homes. On behalf of VGM and its supplier community across the country, we seek to protect access for patients in medical need of CPAP therapy prescribed by a physician. Without this form of therapy, healthcare costs will not be affordable instead it will become unmanageable in addition to the access to proper care and treatment for these functioning patients will be either very limited or unavailable."	
VGM & Associates	Discussion	"Comments1. No Evidence to Support a Change in the Current Policy: The AHRQ draft report reviews a small volume of studies that lacks sufficient evidence substantiating changes to current Medicare coverage criteria. To validate evidence guiding any changes to a Medicare national coverage determination medical policy, there needs to be a larger collection of studies that gathers sufficient information that would recommend any changes.	Thank you. We agree.
VGM & Associates	Discussion	2. Support of Clinical Groupsâ€™ Comments: VGM fully supports comments submitted by organizations involved within the clinical community ensuring proper and effective	Thank you

Commentator & Affiliation	Section	Comment	Response
		treatment for patients with OSA that also ensures access to care. These organizations are American Academy of Sleep Medicine (AASM), American Association for Respiratory Care (AARC), and CHEST. In addition, VGM supports comments submitted by the manufacturers of the CPAP therapy devices that included Phillips Respironics, ResMed, and Fisher & Paykel Healthcare. In addition, we support comments submitted by the Council for Quality Respiratory Care (CQRC).	
VGM & Associates	Discussion	3. Support of Comments by Industry Stakeholders: VGM fully supports comments submitted by American Association of Homecare (AAHomecare), a nationally recognized organization in the DME/HME industry."	Thank you
VGM & Associates	General	"ConclusionCPAP therapy has been a proven method of treatment for patients diagnosed with OSA based on the volume of clinical data. On behalf of VGM and its membership of 2,500+ home medical equipment suppliers and millions of beneficiaries they serve, we greatly appreciate the opportunity to provide comments on the draft Technology Assessment report. We welcome any further discussions with your group regarding this topic.	No response
WVU Sleep Medicine Center, WV Sleep Society Board Member	General	"We know that untreated sleep apnea leads to increased risk for hypertension, heart disease and stroke. CPAP efficacy studies are riddled with issues, mostly duration of CPAP use. More studies are needed if you are to say that CPAP is ineffective, particularly when we have little other treatment options to offer. Please tell 80% of my patients that I follow for sleep apnea that their CPAP is not beneficial when I hear repeatedly. ""This machine save my life."" ""I am not falling asleep while	Thank you. The authors of the review are independent of any decisionmaking organization. We do not make recommendations.

Commentator & Affiliation	Section	Comment	Response
		driving."" ""I can function and take care of my children."" ""I am not falling asleep at work."" ""I can't sleep without this machine."" ""I finally have my life back."" ""I feel like a different person."" ""My mood is better."" ""My blood sugars are better."" "" I don't have high blood pressure in the am.""I hope you as a governing body can live with yourself knowing that you are considering not covering a treatment for such a known risk factor for cardiovascular disease (due to poorly performed studies funded by industry that is scrambling to make money on other treatments...that currently do not exist). "	
Philips Healthcare	General	"Philips has received the report â€œContinuous Positive Airway Pressure Treatment for Obstructive Sleep Apneaâ€ prepared by Agency for Healthcare Research and Quality (AHRQ) on behalf of the Centers for Medicare and Medicaid Services (CMS). (1) Obstructive sleep apnea (OSA) is a significant health issue in the United States. Evidence indicates that OSA can lead to a number of adverse cardiovascular consequences, including high blood pressure, heart failure, arrhythmias and stroke, increased risk of motor vehicular accidents, greater healthcare costs, and a negative impact on sleep, daytime performance, mood, safety and quality of life.(2,3,4,5,6) Philips is committed to the creation of technology and services that are effective and safe for individuals with OSA. We also recognize that there are important disparities in the delivery of sleep care that emphasize the need to promote greater access to, equity in and quality of health services that are responsive to patient needs and preferences. (7)Philips understands our shared role within the	Thank you. We fully agree that “there are other sources of evidence that are not captured by the AHRQ report”. We have revised our findings to better focus on the studies included and have added statements throughout about the focused scope of the review. We have reviewed the noted references for potential eligibility.

Commentator & Affiliation	Section	Comment	Response
		healthcare community to promote evidence-based care that captures improved medical outcomes, improved patient experience, and lower cost to the healthcare system. We believe that there have been many important developments for patients with OSA and reconfirm our commitment toward improving patient lives with CPAP along with patient engagement technologies and services that will improve long term adherence and health outcomes. We also continue to hear first-hand testimonials from our patients that these therapies support their quality of life and help them to feel well rested; an important consideration in the efficacy of the solutions we provide.We acknowledge and applaud the work that our industry partners and professional organizations have put in to review and analyze AHRQâ€™s recent report. As this dialogue continues, Philips reaffirms our commitment to working closely with to these groups to address our shared concerns regarding possible unintended negative consequences on patient lives if the AHRQ report is in any way misinterpreted. Philips will continue to work closely with our customers, patients, healthcare providers, and medical insurers to better understand the studyâ€™s conclusions and recommendations, as well as its methodology, search results, and interpretation of studies. It is important to note that there are other sources of evidence that are not captured by the AHRQ report, such as CMSâ€™ own data describing (a) increased health care utilization and costs across all points of service among Medicare beneficiaries with untreated OSA compared to matched controls [2006-2013 Claims data](8), (b) underdiagnosis and	

Commentator & Affiliation	Section	Comment	Response
		undertreatment of comorbid sleep apnea in Medicare beneficiaries with heart failure, and significant improvement in two-year survival in patients whose sleep apnea was diagnosed and treated compared to those who were not [2003 to 2005 Medicare Standard Analytical Files](9), and (c) reduction in hospitalization for chronic obstructive pulmonary disease (COPD)-related conditions when positive airway pressure therapy is given to elderly patients with COPD and coexisting OSA.(10) More importantly, CPAP adherence among older adult Medicare beneficiaries with OSA was associated with greatly reduced risk for cardiovascular events(11) and stroke(12) [2009-2013 Medicare data]. Furthermore, several studies have demonstrated the cost-effectiveness of CPAP compared to no treatment among middle-aged adults with OSA(13), as well as in patients with comorbid cardiovascular disease(14) or type 2 diabetes mellitus.(15)The AHRQ report points out important research metric limitations such as reliance on the Apnea Hypopnea Index (AHI) and at Philips we have long supported the scientific communitiesâ€™ efforts to improve the science in this area.	
Philips Healthcare	General	It is also important to recognize additional research limitations in the field of obstructive sleep apnea including the challenge of conducting blinded, placebo interventions when using CPAP as well as the ethical concern of conducting longer (> 6 months) studies that require control groups to suffer many of the symptoms of OSA that show short term resolution with treatment. Philips looks forward to working with AHRQ, CMS, patients, and the healthcare community to advance the field of sleep medicine in a	We agree fully. We have revamped our future research needs section to focus more on the need for multiple, large, well-analyzed observational studies. We have added to our descriptions about the challenges of conducting RCTs and other experimental studies. We have also added a description of some of the advantages of “real world” (observational) studies, related to applicability.

Commentator & Affiliation	Section	Comment	Response
		direction that emphasizes innovative approaches to coordinated clinical management, addresses shortcomings in research, and empowers patients and clinicians. . "	
American Association for Homecare	Introduction	"The American Association for Homecare (AAHomecare) is pleased to submit comments to the Agency for Healthcare Research and Quality (AHRQ) on its draft report Technology Assessment: Continuous Positive Airway Pressure Treatment for Sleep Apnea. AAHomecare is the national association representing durable medical equipment, prosthetics, orthotics, and supplies (DMEPOS) suppliers, manufacturers, and other stakeholders in the homecare community. Our members are proud to be a part of the continuum of care that assures Medicare beneficiaries receive cost effective, safe, and reliable home care products and services. Many of our members provide a comprehensive range of respiratory therapy items and services to Medicare beneficiaries in their homes, including continuous positive airway pressure (CPAP) therapy and related items and services. Obstructive sleep apnea (OSA) impacts almost one billion people worldwide and leads to higher morbidity and mortality in other high-cost chronic conditions including obesity, type II diabetes, stroke/transient ischemic attack, atrial fibrillation, hypertension, and coronary artery disease.* With the prevalence of OSA and the costs associated with the chronic co-morbidities, patients and payers benefit from policies that keep patients well and functioning in their homes and out of more costly health care sites. An efficient health care system should include and foster	Thank you

Commentator & Affiliation	Section	Comment	Response
		coverage policies that provide improved outcomes, optimize quality of care, and support patient access to home-based therapies. * Oâ€™Keefe T and Patterson EJ. Obes Surg. 2004, Bitter T, Langer C, et al. Dtsch ArztebIInt. 2009, Einhorn D et al. Endocr Pract 2007, Johnson KG, Johnson DC J Clin Cleep Med. 2010; Oldenburg O et al. Eur J Heart Fail 2007; Sapina-Beltran et al. Annals of Am. Thoracic Society. 2019; and A. Benjafield, K. et al. Lancet Respir Med 2019."	
American Association for Homecare	General	"Comments1. Support clinical groupsâ€™ comments. AAHomecare fully supports the comments submitted by the 19 organizations representing the clinical community involved with the care and treatment of patients with OSA lead by the American Academy of Sleep Medicine (AASM). In addition, we support the comments of manufacturers of CPAP devices, including ResMed.	Thank you
American Association for Homecare	General	2. AAHomecare is particularly concerned by the overall message conveyed by the draft report. As the clinical organizationsâ€™ comments explain in detail, the concern is that the draft reportâ€™s message that there are no significant benefits, short or long-term, from CPAP treatment is simply not reflected by the available evidence. We are concerned that the draft report, if finalized, will be misconstrued and will have detrimental repercussions for the care of millions of Americans receiving benefit from CPAP therapy now and in the future.	We have better focused the findings on the assessed study designs, namely that comparative studies do not provide evidence that CPAP affects outcomes. We have added language that other sources of evidence are important to consider.
American Association for Homecare	General	3. AAHomecare asks that the Technology Assessment clearly state that it found no evidence suggesting that CPAP is not an effective treatment for OSA. The results of this study will drive the decision making not only for the Medicare program but also other	We have better focused the findings on the assessed study designs, namely that comparative studies do not provide evidence that CPAP affects outcomes.

Commentator & Affiliation	Section	Comment	Response
		federal health insurance programs like Medicaid as well as commercial payers. This is critically important in terms of protecting patient access to CPAP, which is the recognized gold standard of care for OSA in the United States and worldwide.	
American Association for Homecare	General	4. The important role of home respiratory suppliers. Every day our members are providing CPAP items and services to patient in their homes across the country. AAHomecare members work hand in hand with the clinicians that prescribe CPAP therapy; they provide ongoing monitoring of these patients to ensure the patients are compliant and benefiting from the therapy. These respiratory suppliers play a critical role by first delivering the CPAP machine and supplies and providing important education to the patient and his/her caregiver to ensure appropriate use of the device and better ensure compliance. Home respiratory suppliers provide ongoing monitoring of the patient, respond to patient questions/issues, and report back to the prescriber and/or respiratory therapist any issues the patient may be experiencing. Respiratory suppliers are often the critical communication link between the patient and their clinicians, contributing to better patient compliance and better outcomes.	No response
American Association for Homecare	General	ConclusionAs the clinical groups noted above have explained more fully in their comments, the draft AHRQ Technology Assessment report concludes that CPAP treatment for OSA does not appear to do any harm and, indeed, does have some overall mortality benefit in the elderly Medicare population. The report should refrain from clinical care commentary, as is less appropriately stated,	We have better focused our findings and conclusions to be based on the specific scope of the review (related to study design and long-term outcomes). We do not provide recommendations related to clinical care or decisionmaking.

Commentator & Affiliation	Section	Comment	Response
		â€œpublished evidence mostly does not support that CPAP prescription affects long-term, clinically important outcomes.â€ We recommend that the clinical benefit of CPAP therapy, especially from a more patient-centric standpoint, be more fairly acknowledged for the Medicare beneficiaries currently and in the future using CPAP successfully.We appreciate the opportunity to provide comments on the draft Technology Assessment report. Please contact me at tomr@aahomecare.org with any questions or if you would like additional information."	
ResMed	Evidence Summary	"ResMed welcomes the opportunity to provide comments on the draft technology assessment and appreciates the Agencyâ€™s undertaking of this research. However, we believe that it is important to recognize that RCTs are not the only form of research to provide a high level of evidence. Although the RCT design has obvious strengths, it is not always the best design to answer all research questions, such as circumstances in which randomizing patients into sub-standard treatment would be considered unethical (as would be the case in withholding CPAP treatment, as CPAP is considered standard of care for OSA) or when assessing the effect CPAP has on healthcare resource utilization (HRU). High-quality, well-designed studies that utilize Real World Evidence (RWE) offer a high level of evidence to answer many of the key questions raised in the context of this technology assessment. Determining the strength of evidence (SoE) contributed by a study should not be based solely on whether the design is an RCT, but instead on a more nuanced and thoughtful approach. The methodology must be closely	We were charged with (in part) a focus question about the effect of CPAP in RCTs. During protocol development, we expanded to include adjusted, comparative observational studies. We have made more clear that this review addresses a focused set of questions and does not summarize all evidence that may be needed for decisionmaking. We also have added stronger language supporting future well-conducted observational studies.

Commentator & Affiliation	Section	Comment	Response
		reviewed to determine if it is well-designed and whether it is the most appropriate approach to answer the research question. While RCTs can show intervention impact in a controlled and ideal environment, more pragmatic designs allow for the assessment of outcomes that more closely mirror how everyday patients use CPAP. This approach results in the ability to generalize findings to broader clinical populations while identifying factors that may impact adherence and outcomes in real world settings. We strongly recommend RWE, including retrospective data analyses, to be included in this approach as these designs can offer important information for healthcare decision makers, payers, regulators and policy makers. The need for additional research on long-term clinical outcomes is also highlighted in the implications and conclusions section of this technical assessment. Prospective cohort studies and retrospective observational studies are complementary designs to RCTs to assess long-term outcomes. In fact, recently published RWE studies have demonstrated improvement of long-term clinical outcomes, with increased CPAP adherence. , For example, one study found decreased incidence of Type 2 diabetes mellitus, ischemic heart disease, and myocardial infarction among CPAP users over an average of 15 years2, while another demonstrated that CPAP adherence was associated with a reduced risk of new CVD events over 25 months.1 Additionally, PAP has been the standard treatment for OSA for decades so further RCTs analyzing safety and efficacy are no longer needed and ethically difficult to randomize a patient with OSA to not	

Commentator & Affiliation	Section	Comment	Response
		receive treatment long-term, but further RWE studies can continue to answer research questions about the effectiveness of CPAP in various populations (for example, focusing on rural and small communities where implementing a full RCT would be impractical) and with treatment modifications (for example, telemonitoring or patient engagement). RWE studies need to be considered as providing a high level of evidence and be included in this type of assessment.	
ResMed	Evidence Summary	The importance of compliance with CPAP use is identified in the assessment as an issue that could not be adequately examined. This lack of research addressing compliance is a particularly relevant gap in evidence given that CPAP therapy is the exposure of interest and adherence to the therapy notably impacts its ability to affect health outcomes. RWE studies, particularly those including implementation outcomes paired with clinical outcomes, would allow for examination of this important issue. RWE studies can examine how patients actually use CPAP and measure the effect that different levels of compliance have on clinical outcomes (dose response), especially over longer periods of time. There is growing acknowledgment of the limitations of RCTs3 and the methodology of this review should reflect this by including high-quality RWE studies. RCTs and RWE studies can complement one another to provide a more comprehensive picture of a research topic."	We agree. However, we did not specifically address how to impact compliance or other issues related to compliance.
ResMed	Introduction	The introduction to this assessment questions the validity of AHI as a surrogate outcome based on the lack of association between AHI and CVD, kidney, or weight outcomes in the Sleep Apnea cardioVascular Endpoints (SAVE) trial. However, the average patient in	The inclusion of SAVE in the Introduction was provided as background for the concerns that lead to request for the current review. Of note, in our analysis of SAVE, we describe how within SAVE the analysis of compliers vs.

Commentator & Affiliation	Section	Comment	Response
		this study was not adherent to CPAP therapy, with an average usage of 3.3 hours/night compared to 4 hours/night required for compliance by Medicare. The efficacy of a treatment cannot be accurately assessed without a patient population that is using the therapy in the prescribed way. The lack of a significant association between AHI and clinical outcomes could simply be due to the fact that not enough patients met the exposure threshold to receive clinical benefits.	noncompliers also failed to support a difference.
ResMed	Methods	"AHI severity and the risk of hypoxia are the main indicators of OSA severity. Together, with signs and symptoms and with comorbidities, these indicators are immensely valuable to help clinicians properly diagnose OSA. Key question 2 looks to address whether AHI is a valid surrogate outcome. We believe that the literature search methodology to address this question biased the results towards a finding of insufficient evidence to support AHI as a surrogate measure.	It is the case that we used strict criteria to support the hypothesis about the association between *change* in AHI (etc.) and clinical outcomes.
ResMed	Methods	It is concerning that the AHRQ protocol excluded blood pressure as an outcome, because four of the RCTs that found a significant decrease in AHI with CPAP use also found a significant change in blood pressure.4â€“7 These findings indicate that CPAP may have an impact on blood pressure, potentially through its effect on AHI, which would support AHI being a valid surrogate measure. It is unclear why blood pressure was used as part of the exclusion criteria, but the effect of this decision leads to bias in the results by excluding valid evidence supportive of AHI as a surrogate outcome.	It is the case that our protocol focused on clinical, not intermediate outcomes. We do not claim that BP is unimportant, but it was not within our scope. We have added language to state this more clearly.
ResMed	Methods	Additionally, only RCTs were considered to provide a high level of evidence. AHI as a surrogate outcome is prognostic, so according	This statement is not quite accurate. Well-conducted nonrandomized studies could also

Commentator & Affiliation	Section	Comment	Response
		to the evidence-based medicine paradigm, any prospective study, observational study or RCT, would be considered high level evidence. Therefore, RCTs should not be given preferential treatment, or weighting over prospective cohort studies in the evidence synthesis8 Additionally, retrospective studies would be considered moderate evidence and should not be completely excluded from consideration.8 The unwarranted weight that RCTs are given over all other study designs leads to the exclusion of many prospective RWE studies that can provide evidence relevant to the key question. Failure to include studies simply because they are not RCTs is an inappropriate methodological choice that may bias against studies that are equally or better able to address the question. High quality prospective RWE studies may: a) represent patients with a wider range of AHI, b) follow patients longer, c) have a larger sample size and therefore have more power, and/or d) be more representative of the general population of CPAP users, all of which can be invaluable in addressing whether AHI serves as a surrogate for clinical outcomes. Based on the current paradigm of evidence-based medicine, these studies need to be considered and included."	provide a high level of evidence. Adjusted observational studies were included. We did not grade the level of evidence for Key Question 2 (correlation of *change* in AHI (etc.) and clinical outcomes.
ResMed	Results	As stated in our response to the Evidence Summary section, RWE studies can complement and enhance the results of RCTs examining the effect of CPAP on various outcomes. We believe that RWE studies should be considered when reporting on the effect of multiple outcomes including atrial fibrillation, accidents, incident hypertension, quality of life (QoL), and adverse events. Here we provide specific examples of potentially	Although we separated out conclusions, we did evaluate and summarize adjusted comparative observational studies. We incorporated these into our strength of evidence evaluations. We did however, require that the same eligibility criteria apply as for RCTs and that adjustments for possible confounders were made.

Commentator & Affiliation	Section	Comment	Response
		relevant RWE demonstrating the benefits of CPAP therapy. Although no significant effect of CPAP was found on incidence of atrial fibrillation, a meta-analysis by Shukla et al. found a decrease in atrial fibrillation recurrence with CPAP use.9 When looking at the rate of driving accidents, the PREDICT trial found no change in rate of accidents with one year of CPAP use, but this study had a small sample size, a low number of events, and looked at a relatively short follow-up period. The Swedish Traffic Accident Registry (STRADA) found that CPAP adherence (â‰¥ 4 h/night) was associated with a reduction in MVA incidence.10 BarbÃ© et al. suggested that incident hypertension or cardiovascular event may be reduced in patients with compliant CPAP usage (â‰¥ 4 h/night).11	It is correct that PREDICT reported on accidents, but (as we summarized) the analyses were imprecise (and inconclusive). STRADA did not present an adjusted analysis of the risk of accidents. Barbé was included for the specific outcomes addressed by our review.
ResMed	Results	The AHRQ authors reported that there was no significant difference in incident hypertension between CPAP and non-CPAP users, yet failed to mention that results become significant when accounting for adherence.	Only Barbé reported on incident hypertension (specifically). We included both the overall ITT and the secondary as-treated analyses. Both results were similar and nonsignificant. Given the sparseness of evidence, we make no summary conclusions about the effect of CPAP on incident hypertension.
ResMed	Results	Improved QoL was found in the SAVE Study, an important patient-centered outcome.12	From SAVE, we report SF-36 mental and physical component scores (MCS and PCS) and EuroQoL (EQ-5D).
ResMed	Results	CPAP adherence has been associated with greatly reduced risk of CVD events in older adult Medicare beneficiaries with OSA, consistent across race, sex, and socioeconomic subgroups.1	We did not evaluate CPAP adherence, per se. Such an analysis would have covered a very different evidence base (mostly single group studies of CPAP users analyzing the association between adherence and outcomes).
ResMed	Results	In addition, long-term PAP therapy use has been associated with lower mortality,2,13,14 lower incidence of Type 2 diabetes mellitus2,	There are other sources of evidence, but we have restricted our review to eligible studies within scope. We have added language to the

Commentator & Affiliation	Section	Comment	Response
		and shortened hospital stays after treatment initiation.13	Discussion, including based on prior systematic reviews, about other outcomes.
ResMed	Results	Finally, although CPAP is regarded as safe, there are some known side effects which are considered minor and can be corrected with simple interventions such as proper mask fitting and humidification. This is the reason that the majority of studies do not aim to collect safety data, because the safety profile of this technology is well known. The safety of CPAP is endorsed by the American Academy of Sleep Medicine (AASM) task force, which concluded that â€œthe potential benefits of CPAP outweighed the harms in those patients with excessive daytime sleepiness, other symptoms impairing sleep-related QoL, or with hypertension.â€□15	We did not evaluate minor side effects.
ResMed	Results	The addition of RWE studies is appropriate and should be considered as high level evidence to complement RCTs in presenting a more complete view of the effects of CPAP. "	Eligible observational studies were included.
ResMed	Discussion	"An overarching conclusion of this assessment is that there is sparse evidence regarding the effectiveness of CPAP devices and that much of the evidence offers a low level SoE. However, we believe that the method of weighting studies prevented adequate evaluation of the effectiveness of CPAP. As noted in our comments regarding the Evidence Summary, the decision to not consider anything other than an RCT as offering a high level of evidence is not appropriate, as RWE studies are often the best study design to address questions of effectiveness. For example, because CPAP is considered the standard of care, randomizing a patient to withhold therapy would be unethical. A high level of evidence can be achieved if the study design is the most	We included non-RCT evidence.

Commentator & Affiliation	Section	Comment	Response
		appropriate design to answer the research question, given the body of evidence and standards of care in place. As CPAP is a well-accepted standard of care, RWE studies will continue to grow in terms of their use for monitoring the effectiveness of CPAP and should be considered as providing a high level of evidence. Additionally, RWE designs can provide a picture of outcomes associated with actual clinical practice, patient behaviors, and diagnosis. As noted in the assessment, a limitation of the literature is that there is no clear and consistent definition of OSA diagnosis (including both signs and symptoms or AHI and hypoxic episodes) or of how to identify severity (comorbidities, signs and symptoms, or AHI). Therefore, including additional RWE studies would help identify trends in diagnosis as well as what measures are most common and useful in clinical practice. The picture of the clinical landscape offered by RWE and the inclusion of a wider variety of patients means that results can apply to a much broader patient population, making the results of RWE studies more applicable to actual clinical outcomes than many RCTs. RWE studies often have much larger sample sizes, allowing these studies to be adequately powered to find statistical differences. While results in RCTs have not reached statistical significance, RWE studies have shown significant improvements in QoL and chronic conditions such as cardiovascular disease and diabetes with CPAP use.1,2 Reconsidering what constitutes a high level of evidence, thereby allowing additional RWE studies to be considered, will improve the level of confidence in the results and help draw more conclusive results from this	

Commentator & Affiliation	Section	Comment	Response
		assessment. Future RWE studies will be invaluable to help answer questions about CPAP usage that RCTs are insufficient to answer.The need to consider RWE can also be seen in the conclusions regarding AHI. While the results of this assessment downplay the clinical importance of AHI, it is important to note that AHI has been an important marker to help diagnose incidence and severity of OSA, along with signs and symptoms, hypoxic events, and comorbidities. This assessment found that there was insufficient evidence to support AHI as a surrogate outcome; however, the Wisconsin Sleep Cohort Study showed a dose-response effect between AHI and cardiovascular disease or heart failure after adjusting for traditional confounders.16 Dose-response effects are Prenticeâ€™s third criteria for a surrogate measure17, and support the validity of AHI influencing outcomes. RWE produced by high quality study designs can provide extra credibility and confidence to support the use of AHI as a surrogate outcome."	
ResMed	Appendix	The MERGE study was excluded for the reason that it was only an abstract; however, this study was published in the peer-reviewed journal Lancet Respiratory Medicine in 2020.18 Results of the study show that 3 months of CPAP use improved QoL for patients with mild OSA and indicate that providers should consider treatment for patients with mild OSA. While the MERGE study should be excluded based on the protocol design, the reason would be for the length of follow-up <6 months, not lack of results, and the table should be updated to reflect this. The fact that this RCT was able to show significant improvements in QoL but is	The citation listed in the appendix is the conference abstract. The full study was found in the updated literature search but was excluded at the abstract screening phase for the reason the reviewer cites, that it was of 3 month duration, less than 6 months. The list of rejected studies includes only those screened in full text, which Wimms 2020 was not. This review was not interested in short term outcomes, only long-term. The effect of CPAP on short-term outcomes is a different topic. Furthermore, a systematic review should never include a study only because it showed a significant improvement. This would lead to highly biased results.

Commentator & Affiliation	Section	Comment	Response
		excluded due to the length of follow-up indicates a limitation of the protocol, as studies examining short-term benefits are excluded.	
ResMed	General	"Although RCTs are often considered the highest level of evidence, not all RCTs are free of bias and methodological problems, which may limit the generalizability of the findings. The dependence on RCTs in this assessment may explain much of the neutral or negative results seen throughout. Additionally, CPAP treatment is considered standard of care for OSA patients, so randomization to a control group or sham CPAP would be considered unethical, especially for patients who present severe daytime symptoms such as daytime sleepiness, given the danger sleepy patients could present to themselves and others. This lack of ability to randomize severe patients means that they would be underrepresented in long-term randomized studies. For example, the SAVE trial excluded symptomatic patients, so the results cannot be generalized to OSA patients who experience severe daytime sleepiness. Yet, evidence shows that only excessively sleepy patients have increased cardiovascular risk.19,20 To validly assess the effects of CPAP on cardiovascular risk, patients with excessive sleepiness need to be included. This can only happen through RWE studies. In a special article published by Pack et al., the authors, considered experts in the field, conclude that â€œit is premature to conclude that CPAP treatment does not reduce cardiovascular events.â€□3 Additional RWE studies can provide the evidence needed to determine if CPAP treatment is associated	We agree and included non-RCTs.

Commentator & Affiliation	Section	Comment	Response
		with reduced cardiovascular events.Another problem with many RCTs intended to study the effects of CPAP is low adherence to therapy. In clinical practice, healthcare providers use several tools to support patients who need to get acclimated to the therapy. RCTs showed that telemonitoring increases compliance.21â€“23 In addition, recent RWE studies showed improved adherence among patients who used telemonitoring24,25 and/or engagement tools25,26 in comparison to usual care. RWE studies are a stronger study design to show barriers to therapy adherence and the effects of patient compliance and behaviors on clinical outcomes.Given the biases described here and, in the assessment, we believe that alternative methods for estimating treatment effects, such as used in RWE studies, should complement the results seen in RCTs to provide better insight into how CPAP devices are used in daily practice and the actual effects these devices have on patientsâ€™ lives. The conclusions made in this assessment should be revised to include RWE. Even if there is a desire not to change the inclusion criteria to include RWE, the lack of high-level evidence in support of CPAP does not prove that CPAP is not effective, but that additional evidence is needed. Any conclusions to the contrary are premature and the regulatory decisions that may result from this conclusion could have negative impacts on millions of patients.RWE is also uniquely able to examine effects on healthcare costs, which has shown CPAP usage to be cost-saving, as Medicare beneficiaries with untreated OSA had increased healthcare utilization costs across all points of service compared to matched	

Commentator & Affiliation	Section	Comment	Response
		controls.27 PAP usage has been linearly associated with reduced impatient and acute care visits, as well as reduced likelihood of positive costs from these visits. Adherent patients had fewer emergency department visits and inpatient stays than non-adherent patients.28 This decrease in healthcare resource utilization is higher in patients who are adherent.29 Patients with OSA have high healthcare costs, especially if they are not effectively treated, so evidence suggesting a decrease in healthcare resource utilization through CPAP use is an important area of interest to payers as they try to decrease healthcare spending.Support for the use of RWE to answer effectiveness research questions is growing. The FDA is embracing the benefits of RWE studies in regulatory decisions for both pharmaceutical products and medical devices. â€œRWE is the clinical evidence regarding the usage, and benefits and risks, of a medical product derived from the analysis of RWD. The real-life clinical performance of a medical product might be more clearly demonstrated through RWD/RWE because a controlled clinical trial often cannot evaluate all applications of a product in clinical practice across the full range of potential users.â€30 The strengths of RWE and RCTs are synergistic and together provide a more holistic look at a research question, allowing for better-informed decisions. Without the inclusion of all applicable high-level evidence, incorrect conclusions may be drawn that can negatively impact large numbers of people. RWE is needed to fully understand the impact of CPAP on patients with OSA and should be	

Commentator & Affiliation	Section	Comment	Response
		more fully considered in this tech assessment."	
Sleep 360 Sleep Diagnostic center, Texas A&M University	General	"As a practicing sleep physician for nearly 25 years, I have seen the field of sleep medicine evolve clinically and technologically. It is a good thing scientifically the field is evolving, which means we are doing clinically relevant studies which has impact on patient outcomes. This is a field of science and it will keep evolving. We need to remember that when we are reading scientific literature. The document has raised some important points on standardizing the criteria for measurements which are already known to sleep medicine community and we are implementing those changes. We do take patient's clinical presentation in perspective and consider the data sleep study report as one aspect of making a clinical decision. We do have to remember that we are not treating numbers but a patient on whom the treatment has to be beneficial with positive outcomes on health. We have seen that clinical improvement in patient's health time and again with PAP therapy and with alternate treatments. We have seen improvements in their daytime functioning, daytime sleepiness, tiredness, fatigue, memory, hypertension, recurrence of atrial fibrillation, arrhythmias, better control of their diabetes. Some of the things the that were mentioned in the draft are not accurate. Many of these patients are diagnosed and treated for sleep apnea much later in their life after the damage has been already done by untreated sleep apnea for several years. We have to consider hypertension, atrial fibrillation, weight gain, obesity, memory problems, mood problems are consequences of untreated sleep apnea	Thank you

Commentator & Affiliation	Section	Comment	Response
		by several years. When we are addressing treating sleep apnea and treating it so late in their disease process, the results are that much slim.If we really have to make an impact on patients health outcomes, start screening and treating sleep apnea prior to them getting diagnosed with hypertension, atrial fibrillation, arrhythmias, diabetes, obesity, memory problems etc; not after the damage is already done to their health because of long standing untreated sleep apnea.It is no secret that hypoxia damages every cell in the body. Imagine effects of prolonged hypoxia night after night on our cellular function. It is definitely going to have an effect on every organ system in the body. If we want to make a real impact on patient's health, I would recommend to start screening every adult for sleep apnea and treat it before the onset of other chronic conditions. Include that as part of an annual screening program. Every health care provider has to include inquiring about a patient's sleep health in their review of systems so we can address their sleep health. Good sleep is of paramount importance similar to nutrition, exercise and stress reduction."	
National Sleep Foundation	General	"April 23, 2021 Elise Berliner, PhD Task Order Officer Center for Evidence and Practice Improvement Agency for Healthcare Research and Quality 5600 Fishers Lane Rockville, MD 20857 Re: Draft Technology Assessment Continuous Positive Airway Pressure Treatment for Obstructive Sleep Apneaâ€ Dr. Berliner: The National Sleep Foundation (NSF) appreciates the opportunity to comment on the draft technology assessment entitled, â€œContinuous Positive Airway Pressure (CPAP) Treatment for	Thank you. We have added language to clarify the focused scope of our review and findings.

Commentator & Affiliation	Section	Comment	Response
		Obstructive Sleep Apnea (OSA),â€ prepared for the EPC program at AHRQ at the request of the Centers for Medicare & Medicaid Services (CMS). As the preeminent organization dedicated to improving health and well-being through sleep education and advocacy, NSF commends CMS for requesting, and AHRQ for initiating, this evidence review. While these reviews are an essential component to the enhanced delivery of patient care, they may not always present a complete picture and may suggest bias. Without clarification, can have unintended consequences that might incorrectly inform policy decisions to the detriment of the public. Given the policy impact this report will likely have on OSA patients, and based on our organizational focus to advance sleep health, we are asking the AHRQ to consider revising and clarifying some aspects of the report. Fundamentally, NSF has a public health mission, serving as the global voice of sleep health for more than 30 years. Related to members of the public who are or who may become people diagnosed with OSA, we are very concerned that this draft assessment may unintentionally serve as a source of confusion or misinformation, and ultimately affect acceptance of or access to the current standard of care.	
National Sleep Foundation	General	We are particularly concerned about any negative effects the report may have on special and vulnerable populations who can benefit from CPAP, including the elderly and other communities where we continue to see disparities in sleep health.	We have added language about the need for Future Research for healthcare disparity populations.
National Sleep Foundation	General	Furthermore, to the extent the AHRQ conclusions can inform US policy decisions, we are concerned about any US policy	We have improved the title and summaries of our conclusions to clarify that we have evaluated only a focused set of research

Commentator & Affiliation	Section	Comment	Response
		changes that might limit the publicâ€™s access to CPAP.For this report, the evidence-based review that was conducted focused specifically on â€œlong-term outcomeâ€ with the conclusion that CPAP has no impact on â€œlong-term, clinically important outcomes.â€ We request that the AHRQ technology assessment should include the evidence for all outcomes that patients and clinicians are likely to consider important. The consequences of OSA and its treatment with CPAP have been recurring topics of public interest and education by NSF over several years. Based on our history of public advocacy and research, including our Sleep in AmericaÂ® Poll, NSF asserts that many of the outcomes that were dismissed or downplayed in the draft report, such as sleepiness, are in fact meaningful to the public and are critical aspects of patient care that can be confirmed by clinicians and the representative professional societies who specialize in sleep disorders medicine. NSF supports the intent of the AHRQ report to improve patient care but is concerned that the report does not adequately acknowledge that CPAP is an effective treatment for OSA. Limiting the studies of CPAP treatment to long-term studies does not recognize the clear benefits experienced by CPAP-treated patients. Sleepiness is the OSA symptom for which most patients seek treatment and often determines patientsâ€™ adherence to long-term therapy. A cursory reading of the draft report may suggest to the public that there are no significant benefits from CPAP treatment. While we acknowledge the need to improve education and support for CPAP adherence and recognize the limitations to the available	questions, and not all outcomes that patients and clinicians are likely to consider important. Our exclusion of these outcomes should not be interpreted to mean that we have dismissed or downplayed their importance.

Commentator & Affiliation	Section	Comment	Response
		evidence, the report conclusion does not completely reflect patient experiences which, as written, could negatively impact patients currently benefiting from CPAP treatment and create barriers for future patients. From a perspective of public health and safety, NSF also has consistently highlighted the risks and negative impacts of drowsy driving, including as part of our annual Drowsy Driving Awareness WeekÂ® campaign and in our published consensus statement on the subject. Treatment with CPAP has been shown to significantly reduce drowsy driving incidents, among patients who self-report adherence to CPAP treatment. Additionally, the AHRQ report should acknowledge that there is evidence supporting a CPAP effect on reducing motor vehicle accidents. We agree with the reportâ€™s recommendation for better designed future studies, but it should include shorter-term studies that report benefits from the use of CPAP and those long-term studies that do include outcomes, such as sleepiness, that are meaningful to patients. Ultimately, the report language seems to present its conclusions in a way that could lead people to believe that there is no benefit to CPAP treatment, from which many Americans already benefit. , It is our hope that the final AHRQ report will reference all important outcomes and will not jeopardize public access to CPAP, which has been established as a standard of care for the treatment of OSA. Thank you for your consideration of these comments. As appropriate, we welcome the opportunity to discuss our concerns in the interest of sleep health and public safety.	

Commentator & Affiliation	Section	Comment	Response
University of Pennsylvania	Evidence Summary	"I am writing to express concern that the approach taken in this review does not appropriately fit the nature of the condition. Specifically, the The Centre for Evidence-Based Medicine ""Levels of Evidence"" table includes a category referred to as 1c for All or None conditions. This level of evidence is met when ""Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it."" https://www.ebmconsult.com/articles/levels-of-evidence-and-recommendationsThis applies in the case of sleep apnea and CPAP. Prior to the development of CPAP, patients with significant sleep apnea would have prolonged episodes of anoxia (due to the obstructive apneas) which leads to death. This is similar to the situation for diabetic hyperglycemia, for example, and insulin therapy. The nature of sleep apnea is such that, in this ""All or None"" context, doing a randomized trial is no longer feasible. There are multiple reasons why a traditional, double-blind, long-term randomized trail is not feasible and thus is not an appropriate standard to use in this context:1. The All or None nature of sleep apnea makes it unethical to withhold therapy for prolonged periods, especially for severe cases	We have documented several recent RCTs that have been conducted, despite the important concerns raised here. We have refocused the Future Research section to better emphasize well-conducted observational studies.
University of Pennsylvania	Evidence Summary	2. Randomized trials that exclude severe cases suffer from ceiling effects -- since the severe, life-threatening cases have been removed, only the mild cases remain and the treatment benefit experienced by mild cases is much smaller, thus leading to a smaller effect size and an underpowered or negative study	We have added to our discussion of applicability issues, including about study eligibility restrictions.

Commentator & Affiliation	Section	Comment	Response
University of Pennsylvania	Evidence Summary	3. Sham CPAP is easy to distinguish from active CPAP, thus it is difficult to double-blind the study. Furthermore, there is a high attrition rate in the sham arm. In our own research, we found that patients in the sham arm would drop out at higher rates. Other types of control arms, such as a placebo pill, are obviously different from the CPAP arm and blinding is again lost.	We make no claim that sham CPAP is an ideal placebo, but we do consider it to be more blinded than no device at all. The included studies did not report differential dropout between CPAP and sham CPAP.
University of Pennsylvania	Evidence Summary	4. CPAP is readily available either by insurance companies or for self-purchase. In this case, it is very difficult to recruit a subject to a study which involves withholding a therapy to which they could easily get access through their insurance. 5. Healthcare providers are reluctant to refer patients to long-term studies of sleep apnea that involve withholding treatment. We conducted a survey of the primary care providers at our institution, and over 85% would not want their sleep apnea patients to participate in a randomized trial which included a placebo treatment arm.Given these realities, it is difficult to do even short-term studies and essentially impossible to do a long-term study.For all of these reasons, I encourage the authors of this review to consider that evaluating the efficacy of a CPAP intervention is wholly different than trying to compare two different classes of medication to see if one has more evidence support, for example. The all or none nature of the condition, especially in severe cases, justifies the Level 1c evidence rating. Consistent with this, from my own clinical experience, I have seen hundreds of patients substantially benefit from CPAP therapy.	We have added this as an applicability issue, namely that patients enrolling in CPAP studies are fundamentally different than average patients.
Alliance of Sleep Apnea Partners	General	The Alliance of Sleep Apnea Partners (ASAP), a 501c3 organization founded by Sleep Apnea patients and patient caregivers,	Thank you. We have made improvement to make clearer the focused nature of this review and that it does not address all issues (or

Commentator & Affiliation	Section	Comment	Response
		offers the following in support of much-needed research leading to therapeutic benefit for patients. ASAP appreciates the resources and time the AHRQ has invested in reviewing evidence from research studying the impact of Positive Air Pressure (PAP), the most common Sleep Apnea treatment. A large part of the U.S. population suffers from Sleep Apnea, with a majority undiagnosed and untreated. Recent research has determined that Sleep Apnea is as much as five times more prevalent in the minority population than it is in the general population. Sleep Apnea patients often present with major co-morbidities (e.g., CVD, DM2, HBP, AFIB, stroke, CHF, etc.). Those who also contract COVID have negative outcomes estimated to be 70% higher than that of the general population, with underserved groups showing the worst outcomes. While we appreciate that the meta study performed by the AHRQ is constrained by rigorous scientific methodology and procedures and must be conducted with great attention to study assessment protocols, we are concerned that the AHRQ conclusions to the effect that there is weak support in the studies for the effectiveness of PAP, could be easily misinterpreted to mean that you have concluded that PAP is ineffective. Sentences such as, “RCTs provide low strength of evidence (SoE) that CPAP does not affect the risk of all-cause mortality…” (incorporating as it does, an implied double negative) seem particularly likely to cause confusion outside the ranks of medical research professionals. Those of us who have used PAP all night, every night, for many years know the benefits	evidence) that may be important for many patients and clinicians.

Commentator & Affiliation	Section	Comment	Response
		of PAP therapy. PAP has enabled us (and many family members) to keep our jobs, careers and marriages. PAP helps us to stay alive and out of the dementia wards of nursing homes. PAP has reduced or eliminated our severe O2 desaturations, stopped the TIAs and absence seizures, the premature bigeminy, PVCs and AFIB, raised HDL significantly, stopped the gout. In many cases, PAP has helped us lose the weight which Sleep Apnea made us gain. PAP has stopped our zombie-like fatigue. For some of us, unable to sustain REM sleep since childhood, PAP has restored our dreams-- in every sense. We hasten to note that those of us experiencing the greatest improvements in health from PAP treatment continue to be excluded from studies for ethical reasons (O2 desat too great, AHI too high, etc.) We, the sickest patients and the most likely to show benefit, are never represented in the studies. This exclusion badly undermines the statistical significance of the evidence that can be ethically gathered in the studies. For many of us, PAP treatment ended decades of expensive (in terms of both financial costs and adverse health consequences) misdiagnoses and mistreatments by numerous specialists, all to try to determine what was wrong with us, before we were ever successfully diagnosed and treated. A Sleep Apnea patient, once correctly diagnosed and appropriately treated, costs the health care system far less. Unfortunately, for both the individual and the	

Commentator & Affiliation	Section	Comment	Response
		system, that often doesn't happen until we are in our 50's, 60's or later. Recently there has been a trend in the direction of tightening the criteria for various Sleep Apnea related treatment and support. While the AHRQ report has focused on specific criteria for hypopnea scoring and definitions of the AHI, the findings of the study suggest that there is not a direct association between AHI (regardless of scoring criteria) and several health outcomes. We do not feel this diminishes the importance of treating patients who have symptoms -including snoring and apneas at night, disrupted sleep, and daytime fatigue and sleepiness, and poor quality of life. We urge that the report does not use the review of AHI values to restrict treatment, but rather balances the importance of symptoms and quality of life to patients rather than a single number from a single study on a night that may or may not be representative of their typical sleep. ASAP is most concerned that the AHRQ report, as currently worded, could easily be misunderstood by payers (CMS and insurers), further eroding the already limited and much needed treatment and support options available to Sleep Apnea patients, especially in underserved minority populations. We understand that weak evidence of benefit is not evidence of weak benefit; and that ineffective studies of PAP are not probative evidence that PAP is ineffective. But we hasten to ask:	

Commentator & Affiliation	Section	Comment	Response
		Will all those reading this review of studies appreciate and understand those logical and scientific points? Will the press understand it? Will patients, especially those struggling with adherence, reading a journalist's synopsis which references the AHRQ report, understand that?	
Alliance of Sleep Apnea Partners	General	ASAP trusts that it is part of your Agency mission and responsibility to assure that your findings are stated in the way least likely to be misunderstood, misinterpreted or misapplied. Accordingly, please consider prominently and expressly advising at appropriate points, (possibly the Conclusion, Abstract and/or Main Points?) that: "The findings reviewed are inconclusive for use in evaluating therapeutic benefit of PAP." And perhaps that: "The lack of strong evidence underscores the need for more inclusive additional research". We hope that the result of the publication of this study will be a renewed impetus supporting better, more conclusive research relative to Sleep Apnea, and NOT the further erosion of treatment and support for Sleep Apnea patients.	We have revised the findings to more explicitly refer to the focused scope of the review, namely that comparative studies do not provide evidence that CPAP affects outcomes. We state that most findings are of low strength of evidence, with an interpretation of this conclusion. The final paragraph of the abstract calls for "Additional well-conducted comparative studies".
Clinician	General	I am a life long researcher on sleep-disordered breathing and CVD. CV attached, along with 2 relevant publications. I thank you for what you have done to advance the field. However, the story is much more complex and the discussion needs to emphasize the pitfalls of the RCTs which we have published on extensively, both in US and Eur high impact Journals, the European Respir J, The American J of Respir Crit Care and CHEST.	Thank you. We have added further descriptions about limitations to generalizability of the RCTs.

Commentator & Affiliation	Section	Comment	Response
		The bottom lines are : the patients recruited in these trials are not our patients!!. the trials are not powered, and multiple composite end points may have resulted in negative outcomes, as the adverse effects of OSA on cerebrocardiovascular outcomes are quite different as explained in the commentaries. Adherence has been uniformly poor. In the paper in the Am J, when we compared CPAP users vs control, cerebrovascular disease , and cardiac outcomes were different. Consistent with physiology of OSA on brain vs heart and also epidemiological studies showing stroke is the worst downstream outcome of OSA Please read carefully and let me know, if you would like to talk to me ,I will be glad. Once more I thank you for this timely report to advance the field of sleep apnea. Please confirm the receipt.	
AASM, CHEST, AAN, ATS, SRS, representing others	General	The undersigned organizations wish to comment on the draft technology assessment entitled, “Continuous Positive Airway Pressure (CPAP) Treatment for Obstructive Sleep Apnea (OSA),” prepared for the Evidenced-based Practice Center (EPC) program at AHRQ at the request of the Centers for Medicare & Medicaid Services (CMS). We commend CMS for requesting, and AHRQ for initiating, this evidence review. Periodic evidenced-based reviews of technology are essential to inform clinical practice, enhance delivery of patient care, and focus research priorities. However, evidence-based reviews have limitations in informing policy decisions, often based on their scope, requiring the need	Thank you. We have made it clearer that we have conducted a focused review and that we do not imply that other outcomes or evidence are unimportant or not of interest.

Commentator & Affiliation	Section	Comment	Response
		to look at additional evidence for a more complete picture and inform policy recommendations. As discussed in this response, we believe that most patients and clinicians would place a high value on some outcomes, excessive sleepiness in particular, that this draft report appears to indicate are not clinically important. We request that if AHRQ wishes to draw conclusions about clinically important outcomes, the technology assessment should assess the evidence for all outcomes that patients and clinicians are likely to consider important. The AHRQ draft report performed a comprehensive review to primarily address two key areas: 1) the effectiveness of CPAP therapy to improve clinically significant long-term outcomes in patients with OSA and 2) the evidence that measures of sleep-disordered breathing are valid surrogate or intermediate measures for clinically significant outcomes. Overall, the evidence-based review focused specifically on “long-term outcomes” and conveys the general state of knowledge regarding the effects of CPAP treatment on some clinically significant outcomes (e.g., mortality and cardiovascular events) for people with OSA, describes the limitations of the current literature, and provides recommendations for future studies that the sleep research community should consider. However, the overall message conveyed by the draft report is that there are no significant benefits, short- or long-term, from CPAP treatment, when this conclusion does not reflect the totality of available evidence. We are concerned that the draft, as written, has a high likelihood of being misconstrued	

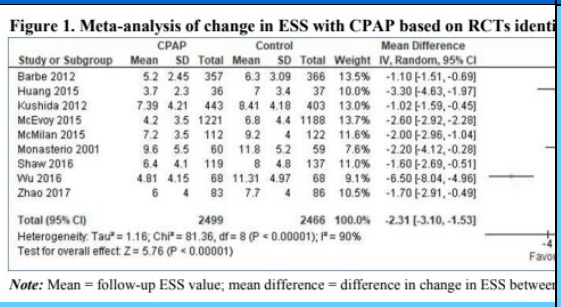
Commentator & Affiliation	Section	Comment	Response
		and will have detrimental repercussions for the care of millions of Americans with OSA receiving benefit from CPAP therapy now and in the future.	
AASM, CHEST, AAN, ATS, SRS, representing others	General	Our specific concerns include: • Excessive sleepiness was not considered a clinically important, patient-centered, long-term outcome: Sleepiness was relegated to a surrogate or intermediate outcome rather than a meaningful, clinically significant outcome of great importance to patients. The consequence of this decision is the absence of analyses that demonstrate the effectiveness of CPAP in improving sleepiness over a period of 6 months or more.	We have clarified that the focused scope does not include sleepiness. In the Discussion, we add a summary of the effect of CPAP on sleepiness from prior reviews, including from the 2019 AASM review.
AASM, CHEST, AAN, ATS, SRS, representing others	General	• Important data on motor vehicle crashes was not considered: Limiting analyses to only include recent randomized controlled trial (RCT) data assessing the impact of OSA treatment on motor vehicle crashes is worrisome given the major personal and public health implications of this outcome.	The review was not restricted to recent RCTs.
AASM, CHEST, AAN, ATS, SRS, representing others	General	• Improvement in blood pressure was not considered a clinically relevant outcome: The draft report focused only on the prevention of incident hypertension and normalization of blood pressure but failed to consider blood pressure reduction as a long-term, clinically important outcome.	Per our protocol, we did not include intermediate outcomes. We briefly discuss these in the Discussion, based on prior reviews.
AASM, CHEST, AAN, ATS, SRS, representing others	General	• Analyses of AHI as an intermediate outcome had potential limitations: A suboptimal methodologic approach was used to determine the validity of the apnea-hypopnea index (AHI) as an intermediate or surrogate outcome by examining correlational changes in the AHI with CPAP therapy and changes in clinical outcomes.	Our Key Question pertained to *change* in AHI (etc.). We did not evaluate AHI as a predictor of outcomes.

Commentator & Affiliation	Section	Comment	Response
AASM, CHEST, AAN, ATS, SRS, representing others	General	• The future research section did not adequately consider the barriers to conducting RCTs: Complementary, alternative study designs should be considered for future trials of OSA on long-term outcomes, including in targeted patient groups.	We have revised the Future Research section to better acknowledge these issues and to raise the importance of well-conducted observational studies.
AASM, CHEST, AAN, ATS, SRS, representing others	General	• The summary statements were unclear: The language used to summarize the strength of evidence and directionality of effects was difficult to interpret. This creates a strong potential for misinterpretation by non-expert readers.	We have revised the findings to statements that comparative studies do not provide evidence that CPAP affects outcomes (low SoE).
AASM, CHEST, AAN, ATS, SRS, representing others	General	Given the tremendous policy impact that the final AHRQ report will likely have in the care of patients with OSA, we are asking the AHRQ to carefully consider our detailed comments and consider revising the draft report prior to final publication to avoid misinterpretations or the appearance of bias.	Thank you
AASM, CHEST, AAN, ATS, SRS, representing others	General	Excessive sleepiness was not considered a clinically important, patient-centered, long-term outcome.	We have clarified that the focused scope does not include sleepiness. In the Discussion, we add a summary of the effect of CPAP on sleepiness from prior reviews, including from the 2019 AASM review.
AASM, CHEST, AAN, ATS, SRS, representing others	General	A critical concern is that the AHRQ report does not acknowledge that CPAP is an effective treatment for OSA-related symptoms, in particular, excessive daytime sleepiness (referred to as excessive sleepiness in this response). Rather, the statement made repeatedly throughout the draft is that CPAP has no impact on "long-term, clinically important outcomes." Although the AHRQ report ultimately acknowledges the strong evidence for the impact of CPAP on excessive sleepiness, it was only recognized at the end of the report (see page 118 of the draft report) with the following statement: "The generally low SoE regarding	We have revised the findings to statements that comparative studies do not provide evidence that CPAP affects outcomes (low SoE). We have clarified that the focused scope does not include sleepiness, other symptoms, or intermediate outcomes. In the Discussion, we add a summary of the effect of CPAP on sleepiness from prior reviews, including from the 2019 AASM review.

Commentator & Affiliation	Section	Comment	Response
		the use of CPAP to prevent long-term clinical outcomes (for most outcomes) is in contrast with high SoE of the effect of CPAP to improve AHI and other sleep and symptom measures, as evaluated by ESS," and cited two reviews, one of which was authored by the AHRQ.1, 2	
AASM, CHEST, AAN, ATS, SRS, representing others	General	Fundamental limitations of the current draft are: 1) the failure to consider excessive sleepiness as an important, long-term clinical outcome, 2) not acknowledging the clear symptom benefits, particularly excessive sleepiness, derived with CPAP treatment from the outset in the draft report, and 3) minimizing the importance of shorter-term studies as discussed further below. By not acknowledging or presenting this information, AHRQ gives the non-expert reader the impression that CPAP has no important, long-term, clinically important benefits.	We have revised to clarify our focus on specific long-term clinical outcomes, excluding symptoms.
AASM, CHEST, AAN, ATS, SRS, representing others	General	Another major limitation of the draft is that excessive daytime sleepiness (measured by the Epworth Sleepiness Scale, ESS) is exclusively viewed as an intermediate or surrogate outcome, that "...may be effective to improve symptoms (as measured by the ESS) but these effects do not impact clinical outcomes" (see page 114 of the draft report). Although the presence of excessive sleepiness may contribute to changes in mood, cognition, and quality of life in OSA patients, excessive sleepiness is a key clinically important, patient-centered outcome for people with OSA, just as relief of arthritic pain is considered a clinically important outcome and a target for treatment of arthritis. Excessive sleepiness is by far the most common daytime, OSA-related symptom for	We have revised our wording to better clarify what was meant by clinical outcomes. We did not mean to imply that sleepiness is not important, and state this explicitly.

Commentator & Affiliation	Section	Comment	Response
		which patients seek treatment and is the strongest clinical indication for prescription of CPAP by clinicians. Furthermore, daytime sleepiness is a major determinant of patients' acceptance of, and adherence to, CPAP over the long-term.3, 4	
AASM, CHEST, AAN, ATS, SRS, representing others	General	A premise of the draft is that evidence from short-term studies is not relevant for long-term benefits with CPAP treatment, which is another limitation of the report. The AHRQ report relegates the relief of OSA symptoms, such as excessive sleepiness, as a "short-term benefit" of OSA therapy. However, this patient-centric benefit is a long-term, clinically important effect, which is dependent upon continued adherence to CPAP therapy. Excessive sleepiness predictably recurs upon interruption of CPAP in the clinical setting and has been demonstrated in studies implementing 1-2 weeks of CPAP withdrawal in participants on chronic CPAP therapy.5, 6 We believe that a more accurate characterization of the evidence is that CPAP improves excessive sleepiness when used, and patients must continue CPAP long-term to continue to derive this benefit. Short and long-term studies have clearly demonstrated the benefits of CPAP in improving excessive sleepiness. In a recent systematic review and meta-analysis of the effects of CPAP in people with OSA conducted by an American Academy of Sleep Medicine (AASM) Task Force,7, 8 a meta-analysis of 33 RCTs of at least 4 weeks' duration confined to participants with excessive sleepiness yielded a mean improvement of -2.7 (95% CI: -3.2 to -2.15) points in the ESS with CPAP compared to a control condition (Figure S3 in online supplement).8 The minimal clinically important	Per protocol, we evaluated direct evidence of the effect on long-term clinical outcomes, but not sleepiness. We are silent about (and make no presumptions about) whether short-term outcomes may predict long-term outcomes.

Commentator & Affiliation	Section	Comment	Response
		difference (MCID) reported for the ESS is considered to be 2.0 (Table 3 in the online supplement).7 The strength of this evidence led to the recommendation that: “We recommend that clinicians use positive airway pressure, compared to no therapy, to treat OSA in adults with excessive sleepiness. (STRONG).”7 The AASM systematic review included trials of less than 6 months duration; however, 10 of the 12 RCTs included in the AHRQ report provide data on the improvement in ESS with CPAP versus a control condition, in studies of at least six months duration. As shown in Figure 1 below, we performed a meta-analysis of nine of the studies in the report (Note: Craig et al 20129 did not provide data in a suitable format for analysis but did report a mean treatment effect on ESS of -2.0 (95% CI: -2.6 to -1.4, p <0.001)). Several of these studies excluded participants with at least mild10 or moderate-severe11-14 excessive sleepiness based on ESS, including two with the longest follow-up.11, 12 Despite this, the estimated mean effect of CPAP treatment on ESS was a reduction of -2.31 (95% CI: -3.10 to -1.53) for the nine studies (see Figure 1 of this response). Therefore, studies identified by the draft report provide support for the long-term benefit of CPAP therapy on ESS in patients with OSA, a critical, patient-centered outcome. Figure 1. Meta-analysis of change in ESS with CPAP based on RCTs identified by the AHRQ report	

Commentator & Affiliation	Section	Comment	Response
		 Note: Mean = follow-up ESS value; mean difference = difference in change in ESS between CPAP and control groups	
AASM, CHEST, AAN, ATS, SRS, representing others	General	RECOMMENDATION: To avoid misinterpretation of the AHRQ report, we strongly encourage revisions that acknowledge that excessive sleepiness is a clinically important outcome for patients with OSA. Specifically, we recommend that this be stated at key points within the report, including the abstract, the executive summary, the report findings, discussion, implications, and conclusions. Furthermore, we recommend that a meta-analysis of excessive sleepiness in the included studies be performed with the findings then added to the report. We have no doubt that AHRQ recognizes the value that patients place on the long-term control of symptoms and believe addressing these concerns will minimize misinterpretation that could lead to detrimental policy decisions for patients with OSA.	We did not review sleepiness; therefore, we cannot make key point conclusions about the outcome. We did however summarize prior reviews in the Discussion, including from AASM, regarding sleepiness. We are unable to change the protocol at this stage.
AASM, CHEST, AAN, ATS, SRS, representing others	General	Important data on motor vehicle crashes (MVCs) was not considered. Another impactful long-term clinical outcome, which has received inadequate consideration in this report, is motor vehicle crashes. There is abundant evidence that untreated OSA is associated with an increased rate of car	We did not evaluate OSA as a risk factor (or predictor) of clinical outcomes.

Commentator & Affiliation	Section	Comment	Response
		crashes.15 There are, however, important limitations to relying on RCT data to demonstrate reduction in crashes with CPAP. Specifically, the strong evidence for the effect of CPAP on excessive sleepiness has made it unethical to randomize study participants with severe sleepiness to ineffective treatment for extended periods of time, i.e., 6 months or longer, particularly when the outcome being assessed is potentially fatal. Moreover, as discussed in more detail below, another limitation of the OSA literature is that treatment studies have often not targeted participants with baseline impairment in the outcome of interest who are most likely to benefit from treatment. For MVCs, excessive sleepiness is clearly the greatest predisposing factor such that exclusion of markedly sleepy patients inevitably attenuates any treatment effect.	
AASM, CHEST, AAN, ATS, SRS, representing others	General	These limitations are evident in the RCT data on MVCs presented (see pages 64-65 of the draft report) from the SAVE12 and PREDICT16 studies. The analysis identified no significant reduction with CPAP in either study, although there was a trend to reduction of the annual rate of crashes causing injury in SAVE (RR 0.84 (95% CI: 0.70 to 1.00). Of note, however, neither study was powered for this secondary outcome, and more importantly SAVE excluded patients with moderate-severe sleepiness (ESS >15), and while PREDICT included patients with ESS >9, patients with a history of sleepiness while driving were specifically excluded. As stated elsewhere in this response, the absence of a high strength of evidence (SoE) in favor of an OSA treatment is not equivalent	Almost all outcomes under review were not powered with the RCTs and were secondary outcomes. For each outcome, including accidents, we note whether studies were powered for the outcome. We have added the useful information about the sleepiness-related eligibility criteria for SAVE and PREDICT. It is correct that this review did not evaluate all types of evidence. We did not include pre-post studies, including for motor vehicle accidents. We have made this criterion more explicit.

Commentator & Affiliation	Section	Comment	Response
		to evidence against such an effect. Indeed, for a matter of such great patient and public safety concern, alternate study designs are clearly required, but in the interim, consideration needs to be given to “lower levels” of evidence where available. Two recent meta-analyses8, 17 have examined data from non-randomized comparative studies (NRCS) on the effect of CPAP treatment of OSA on motor vehicle crashes and yielded very similar findings. The results of the most recent meta-analysis8 are summarized in the Forest plot below. Th 10 studies included consisted mostly of pre- to post-CPAP comparisons for single groups of patients conducted prior to 2010 (and thus did not meet eligibility criteria for the NRCS analyses (see Appendix of draft report, page A8)). However, follow-up in these studies ranged from 2 years before to 0.5 – 6.0 years after enrollment, thus evaluating the long-term impact of OSA treatment. The rate of MVCs was strikingly reduced following CPAP treatment, with an overall risk ratio of 0.28 (95% CI: 0.18 to 0.43).8 The AASM Task Force established a risk ratio MCID of 0.9 a priori for this outcome, thus this finding was deemed highly clinically significant.8 The methodologically strongest of these studies18 compared crash rates for 210 patients with OSA before and after CPAP treatment to population control rates during the same time period, with adjustment for annual distance driven and verification of crashes from transport authority records. These authors reported a risk ratio of 0.43 (95% CI: 0.30 to 0.63) for MVCs following CPAP therapy, similar to the overall point estimate. These	

Commentator & Affiliation	Section	Comment	Response
		data have been considered to be sufficiently compelling to inform recommendations and policies by scientific societies and government transportation agencies for both non-commercial and commercial drivers.19, 20 Furthermore, this evidence has been translated into a policy change for OSA screening and treatment by commercial trucking agencies, and subsequently has been shown to reduce MVCs among CPAP adherent drivers.21, 22 Figure 2. Meta-analysis of PAP pre-treatment vs. PAP post-treatment (MVC Risk Ratio) from NRCS (Figure S51 from the AASM Systematic Review on Treatment of Adult OSA with PAP)8 **Figure 2. Meta-analysis of PAP pre-treatment vs. PAP post-** **(Figure S51 from the AASM Systematic Review on Treatmer** PAP post-treatment / PAP pre-treatment / Risk Ratio Study or Subgroup: Events, Total, Events, Total, Weight, M-H, Random, 95% C Barbe 2007: 10, 76, 24, 76, 14.5%, 0.42 [0.21, 0.81 Cassel 1996: 3, 59, 14, 59, 8.3%, 0.21 [0.06, 0.71 Engleman 1996: 4, 147, 34, 147, 10.1%, 0.12 [0.04, 0.32 Findley 2000: 0, 36, 5, 36, 2.1%, 0.09 [0.01, 1.59 George 2001: 31, 210, 72, 210, 18.7%, 0.43 [0.30, 0.63 Horstmann 2000: 1, 73, 11, 71, 3.9%, 0.09 [0.01, 0.67 Karimi 2015: 3, 263, 10, 263, 7.6%, 0.30 [0.08, 1.08 Komada 2009: 9, 291, 49, 291, 14.1%, 0.18 [0.09, 0.37 Krieger 1997: 36, 547, 60, 547, 18.4%, 0.60 [0.40, 0.89 Yamamoto 2000: 0, 39, 13, 39, 2.2%, 0.04 [0.00, 0.60 Total (95% CI): 1741, 1739, 100.0%, 0.28 [0.18, 0.43 Total events: 97, 292 Heterogeneity: Tau² = 0.23; Chi² = 22.95, df = 9 (P = 0.006); I² = 61% Test for overall effect: Z = 5.67 (P < 0.00001)	
AASM, CHEST, AAN, ATS, SRS, representing others	General	While this body of data may not have met the eligibility criteria for NRCS inclusion set by the report authors, in view of the methodologic considerations discussed above and the patient benefit and public safety implications of these studies: RECOMMENDATION: We strongly recommend that the search and inclusion criteria for the outcome of motor vehicle crashes in this report be modified to include	At this stage, it is not feasible to alter the study eligibility criteria. We have added important caveats and clarifications about the reviewed evidence base to cover the important issues raised here, particularly related to the focused scope of the review in terms of included study designs and outcomes.

Commentator & Affiliation	Section	Comment	Response
		non-randomized cohort and control studies both prior to and since 2010 for the evaluation of evidence regarding the effect of CPAP on reducing motor vehicle crashes. In addition, the limitations of this analysis, which included the review of studies that excluded sleepy patients and did not consider alternative study designs, should be discussed in the final AHRQ report.	
AASM, CHEST, AAN, ATS, SRS, representing others	General	Improvement in blood pressure was not considered a clinically relevant outcome. We are also concerned about the AHRQ report's approach in evaluating hypertension as a long-term clinical outcome. The draft narrowly focused on the development or resolution of hypertension, which led to the identification of only one RCT for each outcome. This was surprising as we were able to identify one additional study that should have met the report's inclusion criteria (i.e., a NRCS, which uses modelling or other analytical methods to minimize confounding).23 The study by Marin et al was a prospective cohort study of almost 1900 participants without hypertension, and with and without OSA, followed for a median of 12.2 years for the development of incident hypertension. The study found a reduced risk of incident hypertension (HR 0.71; 95% CI: 0.53 – 0.94) in participants with OSA treated with CPAP compared to those without OSA. In contrast, participants who were ineligible for CPAP, declined CPAP, or were non-adherent to CPAP had a higher risk of incident hypertension. Although the AHRQ report did identify this study, it was excluded in the context of key clinical question 2 (KCQ2) but does not appear to have been evaluated for KCQ1 (see Appendix	As per the protocol, we did not include intermediate or surrogate outcomes, including BP. The Marin study used people without OSA as their control group. We could not parse comparisons of OSA vs. no OSA from the adjusted analyses. Per protocol, we did not evaluate the crude comparisons. There was a series of typos in the appendix related to changes in the protocol (the order of the Key Questions was swapped). Thus, where it had referred to KQ 2, it should have been KQ 1 (regarding effect of CPAP treatment). This has been corrected.

Commentator & Affiliation	Section	Comment	Response
		of draft report, page B-6). RECOMMENDATION: We recommend that the authors of the draft report re-evaluate this study for inclusion.	
AASM, CHEST, AAN, ATS, SRS, representing others	General	The report concludes that, due to the limited number of studies, there is “insufficient evidence to determine the effect of CPAP on risk of incident HTN or reversion to normotension.” By limiting the focus to the development or resolution of hypertension, the AHRQ report ignores the salient outcome of the magnitude of blood pressure (BP) reduction, which can have important patient-level benefits (e.g., reduction in the number of BP medications) and population-level benefits (e.g., reduction in mortality and cardiovascular outcomes).24 In focusing on the development or resolution of hypertension, the AHRQ report fails to acknowledge that hypertension is multi-factorial in etiology with only some intermediate pathways potentially affected by CPAP treatment. While a single anti-hypertensive drug may be expected to lower BP to normal levels in some patients with mild hypertension, it would not be expected to either resolve or prevent new hypertension in all patients. Thus, the effect of CPAP in mitigating OSA and improving hypertension is expected to vary considerably between individuals with studies demonstrating that hypertension phenotype (e.g., uncontrolled, resistant, or refractory hypertension; see Appendix, Table 1), younger age, the presence of excessive sleepiness, greater severity of OSA, and higher adherence to CPAP are important factors in predicting CPAP-induced lowering of BP.25-28	While we acknowledge the importance of reducing BP, per our protocol, this was not an outcome addressed by this review. We have added language to clarify that we have evaluated a focused set of outcomes. The caveats about the focus have also been added as limitations to the report.

Commentator & Affiliation	Section	Comment	Response
		The Eighth Joint National Committee's ("JNC 8") 2014 Evidenced-Based Guideline for the Management of High Blood Pressure in Adults29 stated that the "main goal of hypertension treatment is to attain and maintain goal blood pressure." An important observation by the report is that one treatment is often inadequate to maintain full control, and the treatment regimen must be adjusted as needed. In clinical practice, hypertension is managed by a combined approach involving weight loss, exercise, reducing salt intake, drug therapy and other interventions, including CPAP in patients with hypertension and OSA. A multi-modality approach is necessary as the anti-hypertensive effect of any single, isolated intervention is modest, variable, and unpredictable. Indeed, even with a multi-modal approach, less than half (43.5%) of patients have adequately controlled hypertension.7, 8, 30 Thus, there has been no BP threshold ever established, to our knowledge, that is required to approve effective anti-hypertensive therapy. By limiting evaluation of the benefit of CPAP in patients with OSA to the prevention or resolution of hypertension, the AHRQ report effectively holds CPAP to a different standard than anti-hypertensive pharmacotherapy. With this standard, there would be no approved treatments for hypertension. Therefore, what is critical is to demonstrate an independent blood pressure lowering effect attributable to a single specific therapy, in the context of RCTs, as has been demonstrated in patients with hypertension and OSA treated with CPAP.7, 8, 30 Two recent meta-analyses with similar inclusion criteria have evaluated the effects of CPAP compared to	

Commentator & Affiliation	Section	Comment	Response
		control on blood pressure.7, 8, 30 Both systematic reviews found clinically significant reductions in blood pressure with CPAP. One review30 reported a mean reduction of -2.6 (95% CI: -3.6 to -1.6) mm Hg for systolic BP and -2.1 (95% CI: -2.8 to -1.4) for diastolic BP from 33 studies ranging in duration from 4 – 52 weeks (with the exception of Huang et al11 which had an even longer follow-up). OSA has also been established to impair nocturnal BP dipping,31 the absence of which in cardiovascular studies has been associated with end-organ damage and cardiovascular and cerebrovascular events.32-35 In the AASM systematic review, the impact of CPAP on nocturnal BP was evaluated in 14 studies. Treatment with CPAP resulted in a mean decrease of -4.2 (95% CI: -6.0 to -2.5) mm Hg for systolic BP and -2.3 (95% CI: -2.7 to -0.9) for diastolic BP (see supplemental figures S10-S11 in the AASM systematic review8). As shown in Appendix, Table 1 of this response, reductions in BP were more pronounced when only patients with hypertension and OSA were randomized. The evidence for clinically significant reduction in BP with CPAP treatment in OSA led to the AASM Clinical Practice Guideline recommendation: “We suggest that clinicians use positive airway pressure, compared to no therapy, to treat OSA in adults with comorbid hypertension. (CONDITIONAL).”7 While many of the studies highlighted in this response are shorter than the minimum 1-year duration required by the AHRQ draft report, there is evidence that the BP-lowering effect of CPAP is maintained long-term. For example, 2 weeks of CPAP withdrawal in patients with	

Commentator & Affiliation	Section	Comment	Response
		OSA on long-term CPAP therapy resulted in significant increases in blood pressure.5 In addition, a large body of cardiovascular literature has demonstrated that sustained reductions in BP by 1-4 mm Hg with anti-hypertensive therapy translates into meaningful long-term cardiovascular risk reduction.24, 36-38 We recognize that very large, multi-center studies, with follow-up over several years will ultimately be required to demonstrate the direct impact of BP lowering by CPAP on clinically important cardiovascular outcomes. However, there is every reason to anticipate that BP reduction effects reported with CPAP will be significant based on the above discussion. In the interim, the AHRQ draft report should not misconstrue the absence of evidence for the long-term benefit of CPAP as evidence of absence of a benefit. Furthermore, we view the short-term effect of BP lowering as being highly relevant for long-term clinically relevant outcomes in OSA. RECOMMENDATION: We, therefore, strongly recommend that the AHRQ report be revised to include analyses of long-term data from RCTs and NRCS on changes in blood pressure with CPAP treatment for patients with OSA.	
AASM, CHEST, AAN, ATS, SRS, representing others	General	Analyses of AHI as an intermediate outcome had potential limitations. Two of the stated key clinical questions (KCQs) addressed by the draft report ere whether: 1) currently utilized measures of sleep-disordered breathing (e.g., the apnea-hypopnea index; AHI) are valid surrogate or intermediate measures for clinically significant outcomes (KCQ2) and 2) there is within-study	We have further clarified that the potential surrogate or intermediate measure we assessed was *change* in measure over a longitudinal timeframe. We have stated more explicitly that “We did not assess the validity of single measurements of breathing or sleepiness measures (e.g., measured pretreatment) as predictors of outcomes or treatment effect.”

Commentator & Affiliation	Section	Comment	Response
		concordance between the AHI and sleepiness (using the ESS) and clinically significant outcomes. After conducting analyses, the AHRQ report concluded that the "evidence base neither supports nor refutes whether commonly used measures (AHI, oxygen desaturation index [ODI], ESS) are valid intermediate or surrogate measures for long-term clinical outcomes" (see page 126 of the draft report), therefore, conclusions could not be drawn regarding these questions.	
AASM, CHEST, AAN, ATS, SRS, representing others	General	We concur with the AHRQ report that there were limited data in the available literature to address the goal of the KCQ. However, we respectfully disagree with some aspects of the framework established to address this specific KCQ, and strongly encourage that revisions to the report consider proposed alternative approaches and/or incorporate elements of the below comments in the section titled "Ideal Study Design to Establish Validity of Mediator (Intermediate) and Surrogate Measures" (see page 107 of the draft report). To address these questions, the methods employed were to determine if a change in the AHI in response to CPAP correlated with a change in clinical outcome. We would argue that this approach is flawed and does not provide needed information regarding a potential dose-response effect between reductions in AHI and improvements in clinical outcome since CPAP adherence was not accounted for. CPAP is prescribed to patients with OSA to essentially minimize the AHI and improve clinical outcomes. CPAP is effective for the goal of minimizing the AHI,8 particularly if utilized for the entire period of sleep. Thus, reductions in AHI with CPAP	We have addressed the Key Questions as written in the final protocol. They cannot be changed at this stage. Regarding the "Ideal Study Design to Establish the Validity of Mediator (Intermediate) and Surrogate Endpoints", the section, as written is an accurate description of pertinent aspects of mediation theory. The goal of mediation analysis is to estimate the fraction of the total effect of CPAP on the clinical outcome that passes through a change in AHI, accounting for covariates. Mediation analysis is a causally explicit analysis: To distinguish correlation from causation, the designs described in the section should be used. The comment proposed two approaches. The first is to "examine the extent to which CPAP alleviates the AHI, accounting for the duration of CPAP use as a proportion of total sleep time […]. At least two measures have been described, the mean disease alleviation index and determination of an effective AHI both of which account for average CPAP use relative to total sleep duration. Correlation of either of these metrics with changes in clinical

Commentator & Affiliation	Section	Comment	Response
		treatment are likely to be a function of the baseline severity but should not be used in determining whether the AHI is an appropriate intermediate or surrogate outcome for clinical outcomes. The approach used in the report primarily reflects the baseline severity of OSA, but does not take into account adherence to, or the "dose" of CPAP, that could influence the particular clinical outcome analyzed. CPAP is an imperfect therapy, and like most treatments, adherence is variable. We propose at least two more appropriate approaches for examining a dose-response relationship between changes in AHI and any clinical outcome be considered. First, one could examine the extent to which CPAP alleviates the AHI, accounting for the duration of CPAP use as a proportion of total sleep time. At least two measures have been described, the mean disease alleviation index39 and determination of an effective AHI,40, 41 both of which account for average CPAP use relative to total sleep duration. Correlation of either of these metrics with changes in clinical outcomes would more directly assess potential dose-response relationships between changes in AHI and clinical outcomes. A second approach is to examine the relationship between hours of CPAP use and improvements in clinical outcomes. This approach has been used in at least two previously published studies.42, 43 In both studies, a dose-response relationship was found between hours of CPAP use and reductions in subjective sleepiness. In one of the studies,43 a dose-response relationship was found between hours of CPAP use and	outcomes would more directly assess potential dose-response relationships between changes in AHI and clinical outcomes." Note that (i) a *disease alleviation index* and an *effective AHI* (as defined in the comment) are different intermediate outcomes than AHI (they have a different mathematical definition). The same designs discussed for AHI can be used for these outcomes as well. (ii) in a mediation analysis for a mediator M, say, AHI, or *disease alleviation index,* one can/should adjust for appropriate covariates when estimating the effects of CPAP on the mediator; the effects of the mediator on the outcome; and the effects of CPAP on the outcome, as described in the text. (iii) Note that the estimation of the mediation effects is not the same as assessing a correlation, as the comment implies. The second approach is to "examine the relationship between hours of CPAP use and improvements in clinical outcomes." This is a very reasonable analysis, but it is not directly relevant to the section at hand, which focuses on intermediate and surrogate outcomes.

Commentator & Affiliation	Section	Comment	Response
		measures of objective and subjective sleepiness, as well as functional status, with a greater proportion of patients achieving normal functioning with longer nightly CPAP use. However, these studies would not have been included in the draft report as the studies were of 3 months duration, rather than the minimum of 6 months that the draft report required.	
AASM, CHEST, AAN, ATS, SRS, representing others	General	Finally, we are concerned that the primary analysis performed to determine whether the AHI is a valid mediator of clinical outcomes is flawed because of the singular focus on long-term studies of 6 months or more. Short-term studies can provide valuable information as to whether a measure such as AHI is a valid intermediate outcome for some longer-term clinical outcomes. Short-term studies are more likely to be studies of efficacy as participants are more likely to maintain adherence over shorter periods. In contrast, longer-term studies are more likely to be studies of effectiveness, reflecting more "real world" conditions, with variable use of a particular therapy. As an example, in the largest RCT included in the AHRQ report, the SAVE trial, mean CPAP adherence was 4.4 □ 2.2 h/night at the first month and fell to 3.3 □ 2.3h after a mean follow-up of 3.7 years.	In order to evaluate the validity in relation to long-term clinical outcomes, a given study must measure the long-term outcomes. Thus, despite the limitations of long-term studies, they are the only ones that can be considered.
AASM, CHEST, AAN, ATS, SRS, representing others	General	The AHRQ draft report provides an excellent description of ideal study designs to establish the validity of mediator and surrogate measures and provides specific examples for researchers in this field to consider. However, as described in this section, we believe that the approach used would not have allowed the AHRQ to appropriately answer the question posed. We recognize that these analyses have not been widely implemented	The section "Ideal Study Design to Establish Validity of Mediator (Intermediate) and Surrogate Measures" describes how, according to well established causally explicit statistical theory, one can assess whether a candidate measure (e.g., AHI, RDI, effective AHI etc) is a mediator of the treatment effect, that is whether a portion of the treatment effect on the outcome is conferred from a change in the candidate intermediate

Commentator & Affiliation	Section	Comment	Response
		to date; however, there is a need to encourage appropriate study designs. RECOMMENDATION: Therefore, we strongly recommend that the draft report be revised to acknowledge the limitations of the analyses performed using change in AHI as an intermediate measure, acknowledge the importance of CPAP adherence in examining dose-response relationship with short- and long-term outcomes, and incorporate the alternative approaches described in the section titled "Ideal Study Design to Establish Validity of Mediator (Intermediate) and Surrogate Measures" (see page 107 of the draft report).	outcome. Correlational analyses are insufficient for this purpose. Please see response in the comment above. Briefly, the first proposed approach proposes different candidate intermediate measures, namely, a *disease alleviation index* and an *effective AHI.* The study designs in section "Ideal Study Design to Establish Validity of Mediator (Intermediate) and Surrogate Measures" would apply to these metrics as well. The second proposed approach (evaluate CPAP use as a modifier of the effectiveness of CPAP) is not directly relevant to the section on ideal study designs for mediation analysis.
AASM, CHEST, AAN, ATS, SRS, representing others	General	The future research section did not adequately consider the barriers to conducting RCTs. The AHRQ draft report provides a strong rationale and useful suggestions for future studies evaluating the long-term benefit of CPAP therapy. However, we believe that the recommendations put forth for specific future studies are incomplete. The draft report does not fully recognize the challenges in this area and the needs to move research on OSA forward. The challenges are related to the heterogeneity of the disorder and the reluctance of patients and physicians to risk randomization into no treatment, given the known symptomatic benefits of CPAP including reductions in excessive sleepiness. There is an outstanding opportunity for the AHRQ report to have a positive, major impact for the research community by providing a more complete roadmap for research into OSA treatment.	We have made revisions to the future research section to include a better acknowledgement of the barriers to conducting experimental studies, including RCTs. We have added further text about alternative study designs or analytic approaches. We have also expanded on the section about studying CPAP in specific populations. We do not provide future research recommendations for analyses outside the scope of our review (i.e., studies that would not have been eligible). These include predicting outcomes using molecular or genetic markers or promotion of adherence to therapy. It is also not clear to us that studies of CPAP withdrawal would provide better evidence (although, we likely would have included any such studies).

Commentator & Affiliation	Section	Comment	Response
		The specific recommendations we propose be integrated into the section on future research include discussion of: 1. Potential challenges in conducting RCTs and the need for alternative trial designs, such as adaptive trials and studies of CPAP withdrawal. 2. Alternative non-randomized study designs, including carefully designed propensity score matching studies, when RCTs may not be possible. 3. Studies needed to predict outcomes using molecular biomarkers and genetic markers. 4. The need to recruit and study patients who will likely benefit from CPAP for a specific outcome. 5. Specific studies to establish successful interventions which promote long-term adherence to therapy.	
AASM, CHEST, AAN, ATS, SRS, representing others	General	We provide further rationale for these recommendations below. Design of Future RCTs The draft report advocates for new, larger RCTs; however, the situation is not as simple as the authors of the AHRQ report envisage. Benefits of CPAP with respect to multiple outcomes have been documented in shorter-term studies (see earlier section on sleepiness). The report acknowledges that there is high SoE of CPAP to improve symptoms,1, 2 such as excessive sleepiness. Given these acknowledged benefits, clinicians in practice and who participate with institutional review boards (IRBs) have been reluctant to have patients participate in randomized studies that include the possibility of receiving no treatment for multiple years, as would be required for RCTs to assess long-term benefits. There are also potential safety	We have added language to the Future Research section acknowledging the difficulties of conducting future RCTs. We describe issues related to adherence. As the reported evidence allow, we describe analyses of (adherent) users versus nonusers. These analyses were consistent with the ITT analyses, where reported.

Commentator & Affiliation	Section	Comment	Response
		concerns, such as an increased risk of motor vehicle crashes15 in patients with OSA and the potential harm their sleepiness may present to others on the road. Given that participants enrolled in longer-term RCTs are usually less symptomatic due to referring clinicians not being in equipoise, it is not surprising that CPAP adherence in these studies is much lower than that described in a study of millions of typical clinical patients with OSA.44 Thus, the trials reviewed in the AHRQ report are not providing evidence that CPAP does not have cardiovascular benefit in patients with OSA. Rather, these studies are providing evidence that CPAP does not have cardiovascular benefits in relatively asymptomatic patients without excessive sleepiness who have poor CPAP adherence (partial treatment). This is not a surprising conclusion.	
AASM, CHEST, AAN, ATS, SRS, representing others	General	While designing RCTs to address whether treatment of OSA with CPAP or other interventions improves cardiovascular and other long-term clinically important outcomes will be challenging, strategies to make these study designs more efficient have been described.45 Specifically, adaptive enrichment designs may be one approach, where through pre-specified interim analyses, more promising at-risk groups (e.g., excessively sleepy, higher nocturnal hypoxemic burden) may be identified, which allow eligibility criteria to be modified to oversample participants in that subgroup. This has the advantage of potentially decreasing both the time needed to complete an RCT and the ultimate sample size required. In addition, SMART (sequential, multiple assignments, randomized trials) designs have also been	In the Future Research section, we have added suggestions about using adaptive enrichment designs. We have also added further text about other non-RCT designs.

Commentator & Affiliation	Section	Comment	Response
		advocated.45 This approach allows for non-adherent participants to be subsequently re-randomized to an alternative treatment intervention (e.g., oral appliance therapy, hypoglossal stimulation, surgical intervention, or pharmacotherapy). Such an approach would help optimize adherence to a treatment intervention in order to assess long-term outcomes more adequately. Randomized trials with a withdrawal design (i.e., withdrawal of treatment) have several benefits that can provide data on the ability of OSA treatments to suppress symptoms and control blood pressure over long periods. Particular outcomes of interest include symptomatic benefit for sleep quality, excessive sleepiness symptoms, nocturia, quality of life of the patient and bedpartner, headaches, concentration and attention, mood and anxiety. Withdrawal studies can provide data on the sustained effects of long-term treatment of OSA in much shorter time frames and at lower costs than a typical randomized trial. They can potentially minimize bias from suboptimal CPAP adherence and incomplete therapeutic effects. They can minimize sample bias by enriching study populations with patients with comorbidities of interest (e.g., hypertension or cognitive impairment) prior to CPAP initiation. Given the shorter time frame, blinded randomization with sham treatment (e.g., sham CPAP) could be performed. RECOMMENDATION: We recommend that the draft report section on “Future Research” be revised to acknowledge the need for alternative RCT designs as described to determine if treatment of OSA with CPAP or	

Commentator & Affiliation	Section	Comment	Response
		other therapies improves clinically important long-term outcomes.	
AASM, CHEST, AAN, ATS, SRS, representing others	General	Propensity Score Matching Studies When conducting longer-term RCTs is challenging, other study designs should be considered. In this situation, non-randomized, prospective cohort studies with a carefully conducted propensity score matching design may be appropriate.46 This type of observational design is often used in similar circumstances where RCTs are problematic. Although the AHRQ report gives weight to studies employing propensity score matching, the analyses reviewed were typically conducted post-hoc after the RCT was completed, i.e., this was not the primary design. The Center for Devices and Radiologic Health (CDRH) of the FDA has accepted well-conducted propensity score designs as the basis for the approval of a number of medical devices, and FDA review statisticians have written extensively concerning best practices.49, 50 Importantly, these study designs need to control for healthy user and healthy adherer bias.51-53 Studies indicate, however, that RCTs and observational designs can lead to the same conclusions when applied to the same groups of subjects with the same outcomes.54, 55 Moreover, well-conducted propensity score matching studies have been shown to replicate the findings of RCTs at a fraction of the cost.56 RECOMMENDATION: There is a major need for well-designed propensity score matching studies addressing, in particular, the major likely confounders and using state-of-the-art analytical strategies. Therefore, we strongly	We have added a paragraph about other non-RCT designs, including propensity score analyses.

Commentator & Affiliation	Section	Comment	Response
		encourage the draft report section on “Future Research” be revised to include discussion of prospective, non-randomized studies with propensity score matching a s the primary design.	
AASM, CHEST, AAN, ATS, SRS, representing others	General	New Approaches to Define Disease Severity The authors of the report have appropriately drawn attention to the need for metrics of disease burden rather than event rate. In addition, a fundamental argument against the sole use of the AHI as a measure of disease severity is the low level of correlation with different outcomes of the disorder (e.g., excessive sleepiness and hypertension). A recent report of the Sleep Research Society (SRS)57 addresses the strengths and weaknesses of the AHI. It emphasizes three potential sources that serve to limit the predictive ability of the AHI: 1) Precision - does the AHI measure accurately the burden of disease? 2) Individual differences in response to OSA 3) Competing (non-OSA) causes of outcomes of interest As outlined in the SRS report, one should not solely rely on physiological measures to provide prediction of outcomes.57 We also need to utilize molecular biomarkers59 and genetic studies to develop polygenetic risk scores. All tools should be initially utilized to provide enhanced prediction of outcomes so that the optimal approach can be developed. It should not simply be based on only physiological measures. There are, however, new physiologic metrics such as hypoxic burden60 and heart rate response to arousal61 that have been shown to be predictors of future cardiovascular events.	Since we did not evaluate these metrics, we do not comment on them in the Discussion. It is the case that we did not include a section on the limitations of AHI, per se. This topic was not asked in the CQs and we did not expand on scope of the questions. The CQ addresses new metrics. Assessment of molecular biomarkers and genetic studies and other new physiologic metrics are beyond the scope of our review.

Commentator & Affiliation	Section	Comment	Response
		These new metrics need to be more thoroughly investigated. RECOMMENDATION: With this background, we encourage AHRQ to revise the draft report section on “Future Research” to describe the importance of doing studies with molecular biomarkers (multiple OMIC strategies), genetic markers, and novel physiologic measures to enhance prediction of outcomes.	
AASM, CHEST, AAN, ATS, SRS, representing others	General	Specific Patient Populations There is considerable heterogeneity in patients with OSA both from a clinical symptomatic perspective62, 63 that affects risk of CV disease64 and other outcomes from a physiological viewpoint.65 There is also individual variation in outcomes in patients with this disorder. Thus, future studies should seek to recruit and study individuals who will likely benefit from CPAP for a specific outcome. Examples of this include studying blood pressure changes in patients who are hypertensive, studying the impact of CPAP on neurocognition in patients with observed deficits in cognition before starting therapy, and studying depression changes in patients who are depressed. RECOMMENDATION: We recommend that the AHRQ report make specific recommendations for studies on selected patient groups. We strongly encourage that the draft report section on “Future Research” be expanded to provide suggestions of specific populations with OSA that should be studied, such as those with depression, anxiety, cognitive impairment, and specific cardiovascular disorders. Stating specific populations that should be studied is an opportunity to advance strategies to obtain the evidence that is needed.	Thank you. We have added these concepts to the Future Research section.

Commentator & Affiliation	Section	Comment	Response
AASM, CHEST, AAN, ATS, SRS, representing others	General	Enhancing CPAP Adherence Fundamental to studying long-term outcomes of CPAP is to ensure adherence to the therapy. Adherence to CPAP in recent long-term RCTs has been problematic and is not typical of what is found in clinical samples.44 This likely reflects the relatively asymptomatic nature of subjects who were recruited.46 In the future research section, the AHRQ report suggests that evidence is needed to address issues of non-adherence and how these issues can be minimized. Although we agree with the draft report's premise, more specific recommendations could be presented to stimulate the research community. Methods to enhance CPAP adherence can be divided into four broad categories—education at initiation of therapy, behavioral interventions, troubleshooting interactions, and tele-monitoring. Much of the literature on methods to enhance CPAP adherence has only been performed for a few months.40, 66 There are very limited data on the effects of interventions to enhance CPAP adherence over the long term (e.g., multiple years). There has been a recent review outlining strategies to manage CPAP adherence in clinical trials, with the need to assess the validity and value of this approach for implementation in long-term studies. RECOMMENDATION: Therefore, we strongly encourage that the section on "Future Research" acknowledges the specific need for studies of CPAP adherence in patients with OSA to optimize strategies for long-term RCTs and NRCS in the treatment of OSA.	While we agree it is an important clinical question how to improve adherence, this topic is beyond the scope of our review. We did not review the evidence base, thus do not have specific insights into the future research needs.
AASM, CHEST, AAN, ATS, SRS,	General	The summary statements were unclear. We are concerned that the language used in the AHRQ report to create summary	We have revised the findings to more clearly focus on the scope of the review and the type of evidence reviewed. Thus we now state that

Commentator & Affiliation	Section	Comment	Response
representing others		statements, which integrate the strength of evidence (SoE) with the directionality of effect for each clinical outcome, will be confusing to readers of the report and lead to misinterpretation. For example, there are several statements on outcomes from the executive summary which may confuse the reader, as the statements are presented as "double negatives" (see italics added): • ". . .there was *low SoE* that CPAP does *not* affect the risk of cardiovascular (CV) death." • ". . .provide *low SoE* that CPAP does *not* affect the risk of stroke or acute myocardial infarction." • ". . .there is *low SoE* that CPAP use does *not* affect the risk of all-cause mortality, stroke, myocardial infarction, composite CV outcomes, driving accidents, and incident diabetes." • ". . .there is *low* SoE that CPAP does *not* yield clinically meaningful changes in depression and anxiety symptoms, cognitive function, or QoL. RECOMMENDATION: We encourage AHRQ to revise and more clearly state the observations in the report to prevent misinterpretation by first making a statement about the direction of effect and then providing meta-analysis results when available and the level of confidence as follows: "[CPAP use (does or does not) affect X (show meta-analysis results) (low SOE)]."	comparative studies do not provide evidence that CPAP affects outcomes (low SoE). We also clarify the focus of the review in terms of included outcomes and study designs.
AASM, CHEST, AAN, ATS, SRS, representing others	General	Conclusions This AHRQ report has the potential to shape future research endeavors and strengthen the medical knowledge base, while improving the care of patients, for which the authors are to be commended. We acknowledge that the current scientific evidence has not resulted in	It is the case that our review was focused in scope and evaluated only a specific portion of the full evidence base. We have stated this up front more explicitly. The scope of the review is not at all meant to trivialize outcomes and other evidence outside our scope.

Commentator & Affiliation	Section	Comment	Response
		strong evidence regarding the effect of CPAP on improving composite CV outcomes for patients with OSA. However, the methodology chosen by the draft denies the recognition of the powerful effects of CPAP treatment for other outcomes. In the preceding detailed sections and summarized in the following paragraphs, we express our deep concerns regarding the trivialized effect of CPAP on patient-centered symptoms, such as excessive sleepiness as a long-term outcome, and safety-oriented outcomes such as motor vehicle crashes.	
AASM, CHEST, AAN, ATS, SRS, representing others	General	There are further issues regarding the sole focus on incident and normalized blood pressure as CV outcomes, and the correlation of change in AHI to the change in clinical outcomes to validate the AHI as an intermediate measure. In addition, we reviewed the AHRQ discussion on future studies and recommended to especially emphasize the explicit need for alternative study designs, as randomized clinical trials of CPAP may not be possible for some long-term outcomes and may never be reasonably or ethically undertaken for motor vehicle crashes. We are also concerned about the emphasis and language used to provide the conclusions. It should not be the charge of the report to conclude when it is or is not appropriate to prescribe CPAP as stated in the abstract: “The published evidence mostly does not support that CPAP prescription affects long-term, clinically important outcomes." The report finally concludes: “Specifically, with low SoE RCTs do not demonstrate that CPAP affects all-cause mortality, various CV outcomes, clinically important changes in psychosocial measures,	We are not proposing that separate trials are required each with a separate primary outcome. For example, we would not suggest that a long-term clinical trial is needed primarily evaluating motor vehicle accidents. However, it should be feasible for existing and future long-term studies to evaluate a multitude of important outcomes (including accidents). We have rephrased to stated that comparative studies mostly do not provide evidence that CPAP affects long-term outcomes. We did not mean to imply that we evaluated, or have summarized, all sources of evidence. We state more explicitly the types of evidence that were reviewed and that the conclusions refer to.

Commentator & Affiliation	Section	Comment	Response
		or other clinically important outcomes." The corollary of this statement can also be true in that the low SoE does not confirm that CPAP did not demonstrate an effect on various CV outcomes. In other words, the low SoE of evidence for benefit is not evidence of absence of benefit.	
AASM, CHEST, AAN, ATS, SRS, representing others	General	Sleepiness is the most common OSA symptom for which patients seek treatment and is the strongest clinical indication for prescription of CPAP by clinicians, and it often determines patients' adherence to long-term therapy. The draft report itself recognized the strong evidence for the impact of CPAP on excessive sleepiness, as noted deep into the report (see pages 117-118 of the draft report): "The generally low SoE regarding the use of CPAP to prevent long-term clinical outcomes (for most outcomes) is in contrast with high SoE of the effect of CPAP to improve AHI and other sleep and symptom measures, as evaluated by ESS." We have described that the major limitation of the draft is that excessive daytime sleepiness (measured by the ESS) is exclusively viewed as an intermediate or surrogate outcome, rather than a key clinically important, patient-centered outcome for people with OSA.	We have stated more explicitly that we did not evaluate sleepiness. We have added the focused scope to the Limitations section. We have also added a description to the Discussion about findings from prior reviews (including the 2019 AASM review) about a range of outcomes, including sleepiness.
AASM, CHEST, AAN, ATS, SRS, representing others	General	We also detailed how non-commercial motor vehicle crash data supported by prior governmental reports have previously concluded that OSA is an important risk factor that CPAP can benefit. Although the body of data may not achieve the SoE thresholds set by the AHRQ report, appropriate conclusions would be made much clearer by a statement reflecting the methodologic limitations inherent in restricting the evidence base to RCT design to address this question. The	We included all eligible studies, including older studies published prior to 2010. However, we relied on previous SRs for the older studies. We have stated the focused scope, including by study design and duration, more explicitly. This included that we did not evaluate pre-post studies or short-term outcomes.

Commentator & Affiliation	Section	Comment	Response
		patient benefit and public safety implications of motor vehicle crashes are also important. The AHRQ report should acknowledge that there is NRCS evidence supporting a CPAP effect on reducing motor vehicle crashes, especially the many studies excluded that were published more than 10 years ago. This could be rectified if the question of effect on motor vehicle crashes included important studies, especially NRCS prior to 2010, and shorter-term studies.	
AASM, CHEST, AAN, ATS, SRS, representing others	General	We provided extensive discussion of the direct effect of CPAP on changes in blood pressure in short and long-term studies as well. The authors of the draft report have focused on incident hypertension and normalization of blood pressure. Despite a large body of research on the effect of CPAP on blood pressure, the AHRQ limited their evaluation to one long-term study on incident blood pressure and one on blood pressure normalization. However, hypertension has a multi-factorial etiology with only some of those pathways potentially affected by CPAP treatment. Furthermore, it is also important not to underappreciate evidence that small improvements in individual blood pressure may be profound when looked at across a large population. We recommend that the AHRQ reassess the outcome of blood pressure to include reduction in blood pressure measurements as a clinically significant, long-term outcome.	We have more explicitly stated the focused scope, including by outcome, more explicitly. An evaluation of BP is beyond the scope of our review. We have added this to the Limitations.
AASM, CHEST, AAN, ATS, SRS, representing others	General	When examining the AHI as an intermediate outcome, we argued that the chosen method was inappropriate. This approach did not provide needed information regarding a potential dose-response effect between reductions in AHI	It is the case that we did not evaluate sleepiness as an outcome within our scope. Based on prior SRs, including one conducted for AASM, we have added to the Discussion summaries of the effect of CPAP on

Commentator & Affiliation	Section	Comment	Response
		and improvements in clinical outcome such as sleepiness, especially since CPAP use was not accounted for. CPAP is very effective for the goal of minimizing the AHI, best when utilized for the entire period of sleep. Thus, changes in AHI with CPAP treatment are more likely to be a function of the baseline severity of OSA for an individual or group. The approach presented in the AHRQ report should not be used in determining whether the AHI is an appropriate intermediate or surrogate measure for clinical outcomes.	sleepiness and other outcomes we did not review. We have better clarified that we evaluated the validity of *changes* in intermediate measures, not single measurements alone, as predictors of clinical outcomes (that were assessed by this SR). The approach described in "Ideal Study Design to Establish Validity of Mediator (Intermediate) and Surrogate Measures" is the methodologically correct approach to assess intermediate outcomes. The terms "intermediate outcome" and "surrogate outcome" have precise (mathematical) definitions. Well-developed theory describes the designs that can be used to distinguish mediators (intermediate outcomes that are causally related to the response) from non-mediator surrogate outcomes (outcomes that are correlated with the response but are not on the causal path). The study designs summarized in the section "Ideal Study Design to Establish Validity of Mediator (Intermediate) and Surrogate Measures" are the appropriate designs to assess whether AHI or other measurements are a mediator, a non-mediator surrogate, or unrelated to e.g., a downstream clinical outcome.
AASM, CHEST, AAN, ATS, SRS, representing others	General	As pointed out when we explore the need for future studies, we noted that the AHRQ report provides a very compelling rationale for why more studies to address the impact of CPAP on longer term outcomes are required. This report does not, however, acknowledge the obstacles inherent with randomization of excessively sleepy patients to a control treatment arm, the most obvious example being the risk of motor vehicle crashes.	We have added in language about difficulties in conducting future RCTs; although we note that a number of RCTs have been conducted despite these obstacles. We have added text about other study designs that could inform the questions under review.

Commentator & Affiliation	Section	Comment	Response
		Complementary, alternative study designs should be considered for future trials of OSA on long-term outcomes, including innovative RCT designs, propensity score matching, and targeting specific patient groups.	
AASM, CHEST, AAN, ATS, SRS, representing others	General	In addition, identifying biomarkers and genetic predictors of risk and response and innovative approaches to promote long-term CPAP adherence are other areas in need of research.	This topic is beyond the scope of our review.
AASM, CHEST, AAN, ATS, SRS, representing others	General	We are concerned for the millions of patients who have benefitted from the long-term treatment of their OSA and those yet to be diagnosed. The AHRQ report should not present the findings in a way that may appear as an indictment of the current practice for OSA treatment, based on the narrow scope of review chosen by AHRQ from the totality of the evidence available and the exclusion of key, long-term clinical outcomes. The draft report, in its current form, does not accurately reflect the long-term clinical, patient-centered benefits of CPAP.	We have endeavored to clarify the focused scope of the review and to acknowledge that other aspects (including other outcomes, shorter duration follow-up, or other study designs) may be important for patients and other decisionmakers.
AASM, CHEST, AAN, ATS, SRS, representing others	General	Finally, we appreciate the opportunity to present our suggested revisions and would welcome future discussion with AHRQ regarding matters that have such a significant impact on the improvement of care for patients with OSA using CPAP.	Thank you for your comments.
Baystate Regional Sleep Program, University of Massachusetts Medical School, Sunnybrook Health Sciences Centre, LSU Health	General	We thank the AHRQ for this review of recent literature of clinical trials on the effect of CPAP on the treatment of long-term outcomes of OSA. While we agree there are limitations to the strength of evidence regarding the effect of CPAP on stroke and TIA outcomes, we have several recommendations to ensure that the report provides a comprehensive review of the relevant literature and clearly explains the implications of this review within	Thank you

Commentator & Affiliation	Section	Comment	Response
Shreveport, University of Arizona College of Medicine, Stanford/VA Alzheimer's Research Center		the greater comprehensive body of literature about the effects on OSA on stroke and TIA incidence, stroke risk factors and the effects of CPAP on stroke incidence and stroke recovery.	
Baystate Regional Sleep Program, University of Massachusetts Medical School, Sunnybrook Health Sciences Centre, LSU Health Shreveport, University of Arizona College of Medicine, Stanford/VA Alzheimer's Research Center	General	The primary AHRQ conclusions on stroke state "4 RCTS provide low SoE that CPAP does not affect risk of stroke or acute MI" and "there is inadequate evidence to support whether any particular group of patients may benefit to a greater or lesser degree from CPAP treatment to reduce clinical outcomes." Both the double-negative language of these statements and the broad claim of inadequate evidence based only on studies encompassed by this review (long-term clinical trials primarily in last 10 years) without explanation of the broader science on the strong link between OSA and stroke and TIA, and the limited applicability of the available research to the most relevant clinical populations lead to a strong potential for misinterpretation by non-expert readers.	We have re-stated our conclusions to better clarify that the conclusions are based on comparative study data only. It is beyond the scope of this report to provide a narrative review of the broader science.
Baystate Regional Sleep Program, University of Massachusetts Medical School, Sunnybrook Health Sciences Centre, LSU Health Shreveport, University of Arizona College	General	Clarity of conclusions and presentation of data When a neurologist or sleep medicine specialist is presented with the decision of whether to initiate CPAP therapy in patients with OSA, speaking only about indications related to stroke or TIA, there are 4 main scenarios: (1) primary prevention of stroke and TIA events, (2) secondary prevention of stroke and TIA events, (3) secondary prevention of mortality or other cardiovascular events in patients with prior stroke/TIA, and (4) the effect on recovery after stroke. While we agree that definitive high-grade evidence	We agree

Commentator & Affiliation	Section	Comment	Response
of Medicine, Stanford/VA Alzheimer's Research Center		is still lacking, especially as relates to primary prevention of cardiovascular events in patients without sleepiness, the jury is still out especially on recurrent stroke and recovery-related outcomes, and patients with sleepiness and severe hypoxia. Future research will be critical.	
Baystate Regional Sleep Program, University of Massachusetts Medical School, Sunnybrook Health Sciences Centre, LSU Health Shreveport, University of Arizona College of Medicine, Stanford/VA Alzheimer's Research Center	General	It is important for clinicians, patients and payers to understand that lack of high-grade evidence does not equate to lack of evidence. In the case of stroke and TIA, we have high quality data and metanalysis showing 1-4 increased risk of stroke and TIA in patients with OSA that aligns with proven pathophysiological effects of OSA that contribute to known mechanisms and risk factors of stroke. A selection of the data supporting the effects of OSA on stroke risk includes increasing sympathetic nerve activity5 and blood pressure 6-8, endothelial damage and atherosclerosis that is worse in carotid arteries presumably due to direct traumatic effects of snore vibrations,9 10-13 increasing silent white matter lesions,14,15 increasing inflammation and oxidative damage,16,17 altering cerebro-hemodynamics,18-20 causing intrathoracic pressure fluctuations that increase right to left shunting and PFO incidence,21,22 increasing hypercoagulability,23-25 increasing atrial fibrillation incidence, 26-28 and patients with OSA and atrial fibrillation are more likely to have strokes than those without OSA.29,30 While these data on risk and physiology do not replace high quality treatment trials, in the absence of applicable studies they do support that a particular group MAY benefit to a greater degree from CPAP treatment. This weaker evidence and data on non-clinical	We have endeavored to further clarify that our scope and conclusions are focused on specific study designs, durations, and outcomes. We do not evaluate intermediate outcomes. We agree that clinicians and researchers need to consider a broader range of evidence.

Commentator & Affiliation	Section	Comment	Response
		outcomes are the type of data that clinicians and policy makers must use when there is a paucity of applicable high grade treatment trial data to make clinical decisions about the patient sitting in our office.	
Baystate Regional Sleep Program, University of Massachusetts Medical School, Sunnybrook Health Sciences Centre, LSU Health Shreveport, University of Arizona College of Medicine, Stanford/VA Alzheimer's Research Center	General	We recommend the AHRQ present the data in this report in such a way that it will provide clear analyzable information for clinicians and policy makers. Statements can be written in the format "There is evidence that CPAP has a "direction" effect on "X" (meta-analysis results) which "reaches/does not reach" clinical threshold (level of evidence)" and provide clear summarized reasons for grading the level of evidence and limitations that exist regarding the applicability of the available data to relevant populations. For areas where data is missing or limited, recognition that other data sources need to be considered at this point until further research is done.	We have rewritten findings in the format the comparative studies do not provide evidence that CPAP affects outcome (low SoE). We have added summary effect sizes to the Main and Key Points.
Baystate Regional Sleep Program, University of Massachusetts Medical School, Sunnybrook Health Sciences Centre, LSU Health Shreveport, University of Arizona College of Medicine, Stanford/VA Alzheimer's	General	The SAVE trial cited by the AHRQ report provided low-level evidence that patients who are adherent with PAP therapy may benefit in terms of incident stroke. However, SAVE was underpowered for determining secondary prevention of stroke, and was not directly applicable to our patients in higher risk categories, having excluded patients with recent stroke/TIA and those >75 years old in addition to sleepy patients and those with severe hypoxia. This suggests that a clearer benefit may be found in those patients. This supports the need for further research that is appropriately powered and representative of the stroke population and continued	We agree, but we did not evaluate CPAP use in the stroke population.

Commentator & Affiliation	Section	Comment	Response
Research Center		consideration of CPAP therapy depending on individual patient risks until that time.	
Baystate Regional Sleep Program, University of Massachusetts Medical School, Sunnybrook Health Sciences Centre, LSU Health Shreveport, University of Arizona College of Medicine, Stanford/VA Alzheimer's Research Center	General	The AHRQ report appropriately downgraded the level of evidence of the findings in the large long-term SAVE trial31 on reduction in stroke and composite cerebral events in adherent patients in a propensity score matched analysis. However, the downgrading was ascribed to the analysis not being fully explained. There was a statistically significant effect for propensity score-matched analysis for subjects adherent to CPAP (HR 0.56 (0.32-1.0, p =0.05) for stroke, and for composite cerebral events (0.52 (0.3-0.90 p=0.02). It would have been preferable to fully explain the limitations and applicability of the SAVE trial, given the sample bias and underpowering for the outcome of interest.	We have provided a fuller description, and limitations, of the SAVE trial.
Baystate Regional Sleep Program, University of Massachusetts Medical School, Sunnybrook Health Sciences Centre, LSU Health Shreveport, University of Arizona College of Medicine, Stanford/VA Alzheimer's Research Center	General	We recommend that summary statements reflect what data is present and include clear explanations of strengths and limitations of available data that may affect utility in clinical decision making.	We are concerned that the Main Points are already quite lengthy. The full explanations of strengths and limitations are described in the main report.

Commentator & Affiliation	Section	Comment	Response
Baystate Regional Sleep Program, University of Massachusetts Medical School, Sunnybrook Health Sciences Centre, LSU Health Shreveport, University of Arizona College of Medicine, Stanford/VA Alzheimer's Research Center	General	Relevant Studies not Included Because of different key questions and literature search criteria in the prior 2011 AHRQ report, adjusted non-randomized comparative studies (NRCS) that fit current criteria, but were published prior to 2010, were not included. We recommend performing a complete search for relevant long-term studies on stroke and TIA incidence prior to 2010 including: Martinez Garcia et al Chest 2005.32 An 18-month adjusted prospective study of 95 stroke or TIA comparing those who tolerated and did not tolerate CPAP found 6.7% vs 36.1% p=0.03- new vascular events with OR 5.09 adjusted for vascular risk factors and neurologic indexes Martinez Garcia et al. Am J Respir Crit Care Med. 2009.33 A 5-year prospective study of survival in 223 stroke or TIA patients with OSA AHI>20 who tolerated or did not tolerate CPAP. The study showed an increased adjusted risk of mortality (hazards ratio [HR], 2.69; 95% confidence interval [CI], 1.32-5.61) compared with patients with an AHI of less than 20 (n = 70), and an increased adjusted risk of mortality (HR, 1.58; 95% CI, 1.01-2.49; P = 0.04) compared with patients with moderate to severe OSA who tolerated CPAP (n = 28). There were no differences in mortality among patients without OSA, patients with mild disease, and patients who tolerated CPAP. Other long-term NRCS that were not mentioned in the report or appendix may meet criteria but are from earlier time periods include Marin Lancet 200534	We believe we conducted a full search of all studies, including older studies (pre-2010). However, we have added missed studies. Thank you. We have added Campos-Rodriguez 2005. Martinez Garcia 2005 and 2009, Parra 2015, and Haba-Rubio 2019 were excluded for population (stroke patients were excluded). Marin 2005 compared CPAP with healthy controls. Doherty 2005 did not report a plausible adjusted analysis, having used an invalid analysis method. Studies that were excluded at the title/abstract level are not included in the appendix list of studies excluded at full text. Buchner 2007 evaluated any treatment (PAP or MAD), and was thus excluded.

Commentator & Affiliation	Section	Comment	Response
		Doherty Chest 200535 Campos-Rodriguez Chest 200536 Bucchner Am J Resp Crit Care Med 200737 A 2015 study after the evaluation period was not included in the analysis of all-cause and cardiovascular mortality that was performed in patients with prior stroke. Parra et al. J Sleep Res 202038 This study had 5.3 h CPAP average use and showed difference in cardiovascular survival (excluding non-cardiovascular deaths) 89.9 % vs 100% (p=0.015) but not a statistical difference although a trend in cardiovascular event free survival (cardiovascular deaths and events) at 68 mo 75.4% vs 89.5%(p-0.059). A not included NRCS possibly from just after the time period (not listed in appendix so unclear why excluded) Haba-Rubio 201939 A 2 year prospective adjusted cohort study of stroke recurrence and death. In multivariate analysis the SDB+ CPAP+ group was associated with a significant reduction of stroke recurrence and mortality (odds ratio 0.13, 95% confidence interval 0.00-0.86, P = .031)	
Baystate Regional Sleep Program, University of Massachusetts Medical School, Sunnybrook Health Sciences Centre, LSU Health Shreveport, University of Arizona College	General	Exclusion of stroke recovery as a clinically important outcome The AHRQ report fails to evaluate an important long-term outcome for Medicare beneficiaries—stroke recovery. Stoke affects more than 750,000 individuals each year and is the leading cause of serious long-term disability in the united states. Nearly ¾ of strokes occur in the Medicare population over age 65. Not only is stroke recovery an important clinical outcome, it is an important economic outcome; caring for disabled stroke patients costs $34 billion annually.40	It is the case that, per protocol, we excluded studies of patients with prior/existing strokes. The focus of this review was on the more “general” population.

Commentator & Affiliation	Section	Comment	Response
of Medicine, Stanford/VA Alzheimer's Research Center		Additionally data support that OSA is associated with worse stroke recovery outcomes including more depression, delirium, activities of daily living dependence, lower functional recovery, longer hospital stays, longer rehabilitation stays, cognitive outcomes and lower 1 year survival.41,42,43-45 While many of the studies are short and results have not been consistent, a recent meta-analysis found a benefit of CPAP therapy on a combined outcome standardized mean difference in NIH stroke scale and Canadian neurological evaluation (CNE) 0.54 (0.03-1.05) in favor of CPAP treatment.46 It is also likely necessary to use more specific functional scales to fully appreciate benefits of treatment on different aspects of stroke recovery. These are likely at least in part driven by sleepiness, which studies have shown improvement with CPAP during post-stroke recovery period.31,47,48	
Baystate Regional Sleep Program, University of Massachusetts Medical School, Sunnybrook Health Sciences Centre, LSU Health Shreveport, University of Arizona College of Medicine, Stanford/VA Alzheimer's	General	While there are a couple long term studies that could clearly fit into this review, we also recommend evaluating studies with shorter term data as the largest gains after stroke are seen within months and there is no clinical reason to suggest that recovery that is gained early will be lost.	The scope of our review was specifically on long-term outcomes.

Commentator & Affiliation	Section	Comment	Response
Research Center			
Baystate Regional Sleep Program, University of Massachusetts Medical School, Sunnybrook Health Sciences Centre, LSU Health Shreveport, University of Arizona College of Medicine, Stanford/VA Alzheimer's Research Center	General	2 RCT with ≥1 year follow up that were not included were: Gupta et al. JCSM 201848 The study was listed in the appendix as excluded due to not included population- but it is unclear why this would be. Possibly due to age (mean 53) was younger than the typical Medicare population, but stroke patients are often disabled which would qualify them for Medicare. This was an Indian RCT of stroke patients followed for 1 year with average CPAP use of 4.2 hours. While it did not find a significant different in recurrent vascular events which can be due to under-power, there was a clear trend (3.3% vs 15% p=0.23) and significant benefit was shown in improvement in modified Rankin score and sleepiness at 6 months and 12 months. Bravata et al J Am Heart Assoc 201849 It was unclear why the following study was not evaluated as it is not mentioned in the appendix The RCT compared control vs standard CPAP (3.9 h use) vs enhanced CPAP protocol (4.3 h use) for 1 year with starting treatment approximately 2-3 month after stroke or TIA. No change was found in combined recurrent cardiovascular events, but more CPAP use was associated with improved NIH stroke scale (NIHSS) and modified Rankin score.	We excluded studies of patients with prior stroke. We have stated this more explicitly in several places. Studies excluded at the abstract level (without full-text review) are not included in the appendix list of excluded articles.
Baystate Regional Sleep Program, University of Massachusetts Medical School,	General	Future Research Given the current lack of studies that fully address the typical clinical scenarios, this report can have an important role in summarizing the limitations and applicability of current studies and addressing gaps.	Thank you

Commentator & Affiliation	Section	Comment	Response
Sunnybrook Health Sciences Centre, LSU Health Shreveport, University of Arizona College of Medicine, Stanford/VA Alzheimer's Research Center			
Baystate Regional Sleep Program, University of Massachusetts Medical School, Sunnybrook Health Sciences Centre, LSU Health Shreveport, University of Arizona College of Medicine, Stanford/VA Alzheimer's Research Center	General	Particular concerns regarding the effect of CPAP in stroke patients include 1. Effect of timing of treatment initiation after stroke or TIA on secondary prevention 2. Effect of timing of treatment initiation after stroke on recovery outcomes 3. Ensuring adequate adherence with CPAP allows for full understanding of impact 4. Effect of heterogeneous OSA phenotypes as well as different stroke etiologies 5. Effect of CPAP on primary prevention of stroke of different etiologies, especially atrial fibrillation Ongoing well-designed studies like the ongoing Sleep SMART50 trial may be able to answer some of these concerns in 6 months after stroke.	We did not evaluate CPAP in stroke patients. This is stated more explicitly in several places.
Baystate Regional Sleep Program, University of Massachusetts Medical School, Sunnybrook Health Sciences Centre, LSU	General	However longer-term primary and secondary prevention trials will likely be limited by ethical safety considerations regarding inclusion of patients with excessive daytime sleepiness and severe hypoxia like the SAVE trial. Additionally, CPAP adherence may continue to be a limitation. Other research designs including adaptive randomized trials to allow for patients to move to other treatment	We discuss these issues in the Future Research section.

Commentator & Affiliation	Section	Comment	Response
Health Shreveport, University of Arizona College of Medicine, Stanford/VA Alzheimer's Research Center		modalities and propensity matching and predictive heterogeneity analysis may allow for fuller evaluation of certain populations and address phenotypic differences.	
Baystate Regional Sleep Program, University of Massachusetts Medical School, Sunnybrook Health Sciences Centre, LSU Health Shreveport, University of Arizona College of Medicine, Stanford/VA Alzheimer's Research Center	General	In summary, our particular requests regarding the CPAP therapy for OSA and stroke/TIA in the AHRQ report are as follows: We recommend rewording conclusion statements to remove double negatives and clearly summarize the effects, reasons for grade of evidence and strengths and limitations that may affect applicability and size of effect.	We cannot change the protocol to include studies of stroke patients. We have stated more explicitly that the review does not cover this population. We have revised findings to focus more directly on the scope of the review.
Baystate Regional Sleep Program, University of Massachusetts Medical School, Sunnybrook Health Sciences Centre, LSU Health Shreveport, University of	General	We recommend consideration of expansion of the literature search for relevant long-term adjusted non-randomized comparative studies (NRCS) to before and after the study current period or otherwise addressing the findings	We cannot change the protocol, including the eligible study designs. The scope of the review has been clarified in numerous places.

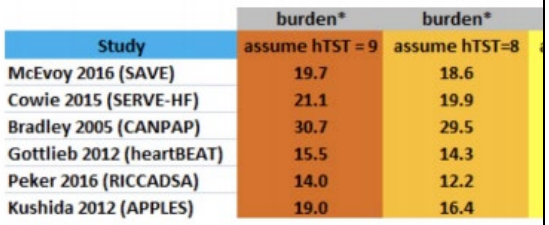
Commentator & Affiliation	Section	Comment	Response
Arizona College of Medicine, Stanford/VA Alzheimer's Research Center			
Baystate Regional Sleep Program, University of Massachusetts Medical School, Sunnybrook Health Sciences Centre, LSU Health Shreveport, University of Arizona College of Medicine, Stanford/VA Alzheimer's Research Center	General	We recommend including stroke recovery as a patient-centered clinically relevant outcome of interest and include shorter-term studies on especially physical stroke recovery measures as they will represent long term benefits.	While this is an important issue, it is beyond the scope of the current review.
Baystate Regional Sleep Program, University of Massachusetts Medical School, Sunnybrook Health Sciences Centre, LSU Health Shreveport, University of Arizona College of Medicine, Stanford/VA	General	We recommend inclusion of a section about interpretation of the findings in the report in the larger context of available literature. For example, that failure of the 4 included randomized trials including stroke outcomes does not disprove the suggestion from prior NRCS that an impact does not exist. The strengths, limitations and applicability of the included trials should be summarized. Where there are limitations and possibility of benefit, the report should recommend future research and address that in the meanwhile it is important not to limit treatment options to individual patients based on these results.	We summarize prior systematic reviews that included a broader scope of study designs and outcomes. But this is not meant to be all-encompassing. We do not address CPAP treatment in stroke patients.

Commentator & Affiliation	Section	Comment	Response
Alzheimer's Research Center			
Baystate Regional Sleep Program, University of Massachusetts Medical School, Sunnybrook Health Sciences Centre, LSU Health Shreveport, University of Arizona College of Medicine, Stanford/VA Alzheimer's Research Center	General	We recommend that the "Future Studies" section acknowledge that future research should include randomized control trials targeting early treatment of stroke patients on stroke recurrence and recovery outcomes and for longer-term primary prevention trials to consider alternative study designs including prospective non-randomized propensity score matching studies and consideration of predictive heterogeneity analysis to best identify patients who may benefit most.	We did not evaluate, and thus do not make conclusions regarding, CPAP for stroke patients.
Baystate Regional Sleep Program, University of Massachusetts Medical School, Sunnybrook Health Sciences Centre, LSU Health Shreveport, University of Arizona College of Medicine, Stanford/VA Alzheimer's Research Center	General	We recommend that the "Future Studies" section acknowledge need of research designs that will safely enhance the inclusion of high-risk populations to limit the effect of sample bias.	Thank you. We have added to the Future Research section a discussion of specific future studies of high-risk populations.

Commentator & Affiliation	Section	Comment	Response
Baystate Regional Sleep Program, University of Massachusetts Medical School, Sunnybrook Health Sciences Centre, LSU Health Shreveport, University of Arizona College of Medicine, Stanford/VA Alzheimer's Research Center	General	We recommend that the "Future Studies" section acknowledge support of future research that will study methodology to promote adherence to CPAP and early initiation of treatment to benefit stroke recovery and secondary prevention given the highest risk of recurrent events is in the first 3 months.	These topics, while important, are beyond the scope of our review.
Baystate Regional Sleep Program, University of Massachusetts Medical School, Sunnybrook Health Sciences Centre, LSU Health Shreveport, University of Arizona College of Medicine, Stanford/VA Alzheimer's Research Center	General	We recommend that the "Future Studies" section acknowledge support of research that addresses the heterogeneity of stroke causes that OSA may differentially affect (ie. atrial fibrillation, small vessel disease, hemorrhagic strokes) as well as the phenotypic heterogeneity of OSA that is not fully explained by AHI, requiring the need for further physiological, molecular and genetic biomarkers. Further basic science research will be needed in this regard.	This review does not address the causes of strokes or intermediate outcomes.
Baystate Regional Sleep Program,	General	We recommend that the "Future Studies" section acknowledge support of future basic science research targeting OSA and Stroke	This is beyond the scope of our review.

Commentator & Affiliation	Section	Comment	Response
University of Massachusetts Medical School, Sunnybrook Health Sciences Centre, LSU Health Shreveport, University of Arizona College of Medicine, Stanford/VA Alzheimer's Research Center		interface with development of animal models of OSA, and studying natural history of OSA as a risk factor for cardio- and cerebro-vascular disease.	
NR	General	Hello, I am writing in regards to the review "Continuous Positive Airway Pressure Treatment for Obstructive Sleep Apnea". I am hoping to bring to the attention of the authors a vantage point that may be helpful for the audience. The concept pertains to the well-known reality that CPAP compliance is nearly always "partial". The first and most obvious implication of partial compliance is the challenge that while randomization distributes subjects at therapy allocation, it cannot distribute across levels of compliance. Thus, the common criticism that PP methods are confounded (and thus ITT is preferred) will always put CPAP trials at relative disadvantage to show outcome benefits.	Thank you. To the extent possible, we evaluated both ITT and PP analyses. Our conclusions from ITT analyses pertain more to the prescription of CPAP, which we distinguish from effect of CPAP, per se.
NR	General	The arguably more intriguing consequence of partial compliance with CPAP is that the AHI value during off-PAP sleep is not measured in trials (or in practice), yet it is well known to vary across individuals from immediate to several days delayed return to baseline	This is an important concept. However, we did not systematically address the validity of different definitions of adherence/compliance.

Commentator & Affiliation	Section	Comment	Response
		("diagnostic") levels. Because the threshold acceptable level of "compliance" (4 hours, 70% of nights) represents less than 50% of the total sleep amount for most subjects, we are blind to the actual "exposure" AHI for most individuals. The actual exposure for a subject (i.e., the AHI over the whole night including on-PAP and off-PAP sleep) could range from normal to severe levels, depending on how much off-PAP sleep occurs and what the AHI is during such sleep time. Blindness to this reality could impact our view of CPAP benefit in both directions: there could be "non-compliant" subjects with relatively normal overall AHI values (if they are in the "delayed return" phenotype during off-PAP sleep), as well as compliant subjects with relatively severe AHI values (if they are in the "immediate return" phenotype during off-PAP sleep). The concept of considering the full night AHI is not new, but different groups have named it differently (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5070750/, https://pubmed.ncbi.nlm.nih.gov/25441743/, and https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3001787/, for example).	
NR	General	Although we cannot overcome the variable compliance issue with randomization, it seems that we can and should recognize something we could potentially capture: measuring AHI during off-PAP sleep. Doing so would reduce a known source of variance that biases any CPAP study toward a null finding. Dr Robert Thomas and I wrote about this in a 2017 review:	This is very interesting. However, it is beyond the scope of our review.

Commentator & Affiliation	Section	Comment	Response
		https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5406947/ As an illustrative example, can calculate the predicted overall-AHI ("burden" AHI) based on data from recent trials that failed to meet objective endpoints, across a range of habitual TST values, by simply extrapolating the baseline AHI value to the off-PAP sleep duration. If, as is predicted by prior literature, about 50% of subjects have this kind of immediate return of AHI in off-PAP sleep, many of the "treated" individuals still have substantial AHI values (i.e., exposure to sleep apnea).  (unpublished figure)	
NR	General	Recognizing that measuring off-PAP sleep is not standard practice, and has not been used in trials yet, it is understandable to feel the concept remains untested. However, I wondered if the AHRQ authors might consider the topic worthy of discussion, even speculative, as a potential source of variance that at least in principle could be addressed in future trials, perhaps in the section detailing recommendations for future research. For example, devices like WatchPAT can be easily worn overnight spanning time onPAP and off-PAP, to provide quantification of full night AHI. Best regards, and thank you for the opportunity to comment on the AHRQ piece.	While we find this interesting, it is beyond the scope of our review.

Study	burden* assume hTST = 9	burden* assume hTST=8
McEvoy 2016 (SAVE)	19.7	18.6
Cowie 2015 (SERVE-HF)	21.1	19.9
Bradley 2005 (CANPAP)	30.7	29.5
Gottlieb 2012 (heartBEAT)	15.5	14.3
Peker 2016 (RICCADSA)	14.0	12.2
Kushida 2012 (APPLES)	19.0	16.4

Commentator & Affiliation	Section	Comment	Response
Brigham and Women's Hospital, University of Washington, University of Pittsburgh	General	We read with great interest the 2021 Draft Technology Assessment entitled "Continuous positive airway pressure treatment for obstructive sleep apnea." Overall, the draft document is well-conceived and achieves its stated goal – to accurately convey the state of current knowledge about the impact of CPAP on the outcomes selected for assessment in this document, including the limitations in the current evidence base. However, we are concerned the draft document does not directly address the most common indication for continuous positive airway pressure (CPAP) in patients with OSA – the treatment of symptoms directly attributable to OSA.	We agree that outcomes we did not review are important to patients and clinicians, including symptoms. We have stated more clearly that we do review these outcomes, such as sleepiness.
Brigham and Women's Hospital, University of Washington, University of Pittsburgh	General	The draft document also conflates short-term and long-term time frames for expected treatment effects with the short-term and long-term treatment goals of patients and clinicians.	It is the case that we focus on long-term treatment and follow-up. This is not to downplay the importance to patients and clinicians of short term outcomes, but they are beyond the scope of our review.
Brigham and Women's Hospital, University of Washington, University of Pittsburgh	General	The draft document fails to make clear that CPAP effectively treats symptoms attributable to OSA. By not acknowledging this indication anywhere in the document, a non-expert reader is left with a biased impression that there is no justification for patients with OSA to use CPAP. The draft document appears to relegate OSA symptoms to the category of "short-term" clinical outcomes, and so irrelevant to an assessment of long-term effects of CPAP. However, while OSA symptoms respond to CPAP in the short-term (as evidenced in dozens of randomized trials), there is also strong evidence from several long-term randomized trials that short-term improvements in sleepiness with CPAP are maintained long-term. Among the trials	We agree that outcomes we did not review are important to patients and clinicians, including symptoms, whether short- or long-term. We have stated more clearly that we do review these outcomes, such as sleepiness.

Commentator & Affiliation	Section	Comment	Response
		demonstrating this long-term benefit are APPLES and SAVE, trials included in this assessment for other outcomes.	
Brigham and Women's Hospital, University of Washington, University of Pittsburgh	General	As such, we strongly encourage AHRQ to consider revising the draft document to state explicitly that the effectiveness of CPAP in improving or resolving OSA symptoms such as fatigue, sleepiness, and bothersome snoring was not within the scope of this work. Without such a statement, the reader is left with the impression that there is no evidence that CPAP has any clinical benefit. In fact, the draft document states repeatedly that there is little evidence that CPAP therapy has benefit on any long-term clinically important outcomes, using clinically important outcomes as shorthand for clinical outcomes evaluated in this assessment. As currently written, we fear stakeholders have a high likelihood of misinterpreting the findings in this draft document as suggesting there is no evidence for benefit from CPAP in any "long-term clinically important outcome" among patients with OSA. Such an interpretation could lead to patients suffering from symptoms of OSA being denied access to CPAP therapy.	We have endeavored to clarify the scope more explicitly.
Brigham and Women's Hospital, University of Washington, University of Pittsburgh	General	The Food and Drug Administration in approving the use of modafinil, armodafinil, and solriamfetol for treating excessive daytime sleepiness in patients with OSA concluded sleepiness was a clinically important outcome. Certainly, AHRQ recognizes that improvement in OSA symptoms, such as excessive daytime sleepiness, is clinically important and also recognizes that patients value the treatment of excessive daytime sleepiness and other OSA	We do not believe we have made any implied statements about OSA-related symptoms.

Commentator & Affiliation	Section	Comment	Response
		symptoms in both the short and long-term. As such, we would encourage revision of the draft document to avoid misinterpretation of the findings as suggesting CPAP does not improve OSA-related symptoms, which are clinically important outcomes in the long-term.	
Sleep Centers of Middle Tennessee, MTSU Sleep Research Consortium	General	Regarding AHRQ Technology Assessment (TA) for Continuous Positive Airway Pressure (CPAP) Treatment for Obstructive Sleep Apnea (OSA), the TA is a thorough evaluation of the current literature regarding long-term outcomes with CPAP. However, I have great concern regarding the statement in the conclusion of the abstract, "The published evidence mostly does not support that CPAP prescription affects long-term, clinically important outcomes." I believe this statement without the full knowledge of the context to those outside the field of sleep medicine will likely lead to increased morbidity and mortality from untreated OSA. The knowledge of sleep medicine outside of our field is very poor. On a daily basis we have to explain what OSA is and is not to the outside world. The most recent estimate of OSA prevalence among US adults is 37% (1). It is estimated that > 85% of cases go undiagnosed (2). While as many as 60-82% of cardiology patients have OSA (3-6), as few as < 5% undergo testing (7). While as many as 86% of Type 2 diabetes mellitus patients have OSA (8), < 5% are on treatment for OSA (9). In a recent short review (10), we contrast the prevalence and mortality of OSA to hyperlipidemia (HL) and in another article released this month I contrast it to hypertension (HTN) (11). The result is that the awareness of OSA is greatly lacking compared to HL and HTN. Your summary	We have revised to be more specific about the scope of the review and the conclusions (specifically evaluating long-term comparative studies, and not symptoms).

Commentator & Affiliation	Section	Comment	Response
		statement quoted above will likely worsen this situation and potentially lead to unnecessary morbidity and mortality.	
Sleep Centers of Middle Tennessee, MTSU Sleep Research Consortium	General	When the SAVE study was published in September 2016 (12), I had cardiologists texting me the next day about the results and immediately their referrals dropped off. They said, "New England journal says CPAP doesn't work." This obviously was not the authors intent, or the intent of the TA authors. The authors of the TA need to understand the reactive consequences of their words to those uninformed providers outside the field of sleep, and how this statement will be pulled from the report and will potentially keep many patients from the potential benefits of CPAP found in the literature.	We have revised our findings to pertain more specifically to the breadth of the evidence reviewed, namely comparative studies of long-term outcomes. We hope this will improve clarity and reduce misinterpretations.
Sleep Centers of Middle Tennessee, MTSU Sleep Research Consortium	General	In the SAVE study (12), the treatment group only averaged 3.5 hours of usage per night over the first year, and that is after a run-in phase which eliminated 15% of participants before randomization. If you include those participants, the average usage of the treatment group would have been 2.9 hours per night. Secondary analysis of the SAVE study (as well as other RCTs) did show positive outcomes for CPAP in those with > 4hours of usage (10). RCTs, like the SAVE study, are plagued with poor adherence and ethical constraints leading to exclusions of patients most likely to benefit from treatment (10).	We reported on the secondary analyses of adherent users versus nonusers. For the outcomes of interest to this review, there were not substantive differences in findings.
Sleep Centers of Middle Tennessee, MTSU Sleep Research Consortium	General	It is the TA authors' specific statement that "...published evidence mostly does not support..." that contains the negative bias and says the glass is half empty. Since you are addressing a disorder with a mortality as high as 40% over 13-15 years (13,14) and limited treatment options where CPAP is clearly	We have revised the findings to state that comparative studies do not provide evidence that CPAP affects outcomes (low SoE). We have conclusions that include nonrandomized studies that mostly agree with the RCT evidence.

Commentator & Affiliation	Section	Comment	Response
		superior, you need to word your statement where the glass is half full. A better wording might be: Because of poor adherence as well as ethical constraints in randomization, it is difficult to currently confirm and quantify the long-term benefits of CPAP found in the observational data. This statement is not only true, but it does not suggest a summary judgement against CPAP. A judgement which insinuates that CPAP fails to provide long-term benefits to those outside the field of sleep medicine. Inside the field we understand what you mean. Outside our field, they will not.	
Sleep Centers of Middle Tennessee, MTSU Sleep Research Consortium	General	CPAP usage does not have to be poor. We recently published a large trial (15) looking at CPAP adherence where the treatment group had a median average use of 5.2 hours per night over the first year. That was 90% more usage than the control group during the first year, and 80% more usage than in the SAVE study (including those removed in the run-in phase). Furthermore, our age group was limited to age 18-64. Age 65-80 was excluded from the treatment group because of Stark law, however in the control group age 65-80 had 39% greater adherence than age 18-64. If the treatment group had included ages 65-80, the adherence would have likely been much higher as well. The 3.5-hour result over the first year for the SAVE study corresponded to only 42% still using at one year. Our treatment group (age 18-64) had 66% still using at one year, and if we had had the same mean age of the SAVE study, we likely would have had close to 80% still using at one year. As the TA authors conclude, further trials are needed.	Thank you.

Commentator & Affiliation	Section	Comment	Response
		We believe these trials need greater usage as we, and others (16), have demonstrated. Thank you for the opportunity to respond, and although I have other issues with the TA, again my major issue is with the one statement. Please change your wording to not mislead those outside our field who will not understand the nuances of your words and further restrict access to treatment for OSA.	
Society of Behavioral Sleep Medicine	General	Within the sleep field, there has been considerable angst about the Agency for Healthcare Research and Quality (AHRQ) Technology Assessment Review of Continuous Positive Airway Pressure (CPAP) Treatment for Obstructive Sleep Apnea. Those who treat patients with sleep apnea are well aware that treatment of the disorder leads to tremendous benefit for many of our clients. Unfortunately, the AHRQ review was not able to identify evidence of substantial clinical benefit of CPAP across several clinical outcomes. Although these results are disappointing, the review highlights many ways in which the efforts of sleep specialists across the continuum could be improved. Rather than providing a methodological critique of the review or the research within, the ensuing comment from the Society of Behavioral Sleep Medicine will focus on the need for a multimodal approach in the treatment of sleep disorders. Achieving successful clinical outcomes requires attention to the patient as a complex biopsychosocial being driven by behaviors that impede or enhance health. Thus, it is unsurprising that a single intervention (e.g., CPAP) is not always successful. Dr. Meeta Singh reminds us that, at its most basic level, sleep is a behavior. Positive outcomes are	Thank you. These are important considerations that are beyond the scope of our review

Commentator & Affiliation	Section	Comment	Response
		attained by embracing the synergistic relationship between medical and behavioral interventions targeting conditions known to affect sleep (e.g., circadian rhythm disruptions, gastrointestinal problems, chronic pain, obesity, cardiovascular problems). The following evidence-based examples highlight the necessity of including behavioral modalities in the treatment of chronic illnesses to maximize outcomes for patients experiencing sleep disorders, including sleep apnea. The bidirectional relationship between sleep and other chronic conditions is well documented. Insufficient sleep is associated with obesity through dysregulation of hormonal and neuronal pathways that control appetite and metabolism.1 Mounting evidence supports the use of behavioral interventions to treat sleep disorders through the management of obesity as well as reciprocal behavioral weight loss strategies as a component of the treatment of sleep disorders.2 Lifestyle modification is an effective component in treating obstructive sleep apnea in adults.3 Chronic insomnia affects at least half of chronic pain patients4 and can lead to the development or worsening of pain.5 Common pharmacological and behavioral treatments specifically for pain often fail to provide effective long-term pain relief. Growing evidence indicates sleep may provide an important pathway for targeting chronic pain.6-8 Tang and colleagues9 meta-analysis of non-pharmacological insomnia interventions in chronic pain patients (11 RCTs) found large sleep quality improvements and small to moderate pain	

Commentator & Affiliation	Section	Comment	Response
		reductions following treatment. Chronic pain patients often experience heightened brain activity, altered connectivity patterns and cortical thinning compared to healthy individuals.10,11 New pilot research shows cognitive behavioral therapy for insomnia (CBT-I), multi-component behavioral sleep intervention, can reverse cortical thinning in several brain regions in fibromyalgia.12 This suggests behavioral sleep techniques may impact pain, at least in part, through their impact on the brain. Obstructive sleep apnea (32%) and restless legs syndrome (32%) are also common in chronic pain.13 Opioid therapy may contribute to calmer sleep with fewer body/leg movements and awakenings, but may also concurrently increase sleep-disordered breathing and shorten rapid eye movement (REM) sleep latency.14 Behavioral modalities that improve not only sleep, but also pain may have broader implications for chronic pain patients, particularly those with comorbid insomnia and sleep apnea (COMISA). There is growing interest in the relationship between circadian disruption as a contributor to cardiovascular risk,15 irritable bowel syndrome, inflammatory bowel disease, and digestive cancers.16 Insomnia has also been linked to cardiovascular risk17 and insomnia commonly co-exists with sleep apnea (COMISA) and circadian disruption. Meira, Salles, and Gozal (2021)18 reported the relative frequencies of HT and diabetes were significantly higher in the COMISA group (54.3% and 13.3%) compared to the isolated SDB (41.9% and 10.1%) or the isolated insomnia group (10.1% and 1.8%) ($p<0.001$).	

Commentator & Affiliation	Section	Comment	Response
		Behavioral sleep specialists navigate the crossroads of a seemingly unending relationship to virtually every bodily system. Stabilizing circadian rhythms, assisting patients to lose weight, addressing fears and anxieties, and assisting patients to adapt to their sleep technology, and, in some instances, to sleep without medication for the first time in years are some of the benefits of a behavioral approach to sleep health. Behavioral sleep medicine is empowering to patients, ultimately enhancing other prescribed plans of treatment. Although CPAP has changed the lives of many it may not be the right tool for everybody. Perhaps this "shot across the bow" is just one more reason for the field of sleep medicine to fully embrace its roots in the fields of psychology and medicine and adopt a more integrated and comprehensive disease management approach to the management of sleep apnea and other sleep disorders. Opportunities abound for those who are willing to adapt.	
Meir Kryger MD FRCPC Yale School of Medicine Past President American Academy of Sleep Medicine, Canadian Sleep Society Past Board Chair, National Sleep Foundation	General	The current draft version of the report, in my opinion, has several important shortcomings. It does not convey the notion that sleep apnea is not a single entity, but that there are several clinical and physiological phenotypes and that apnea during sleep may have different presentations and consequences related to comorbidities, physiology, etiology, gender, and race.1-6 If published as is, the report may result in the denial of treatment to millions of patients, especially the poor, African Americans, Hispanics, and harm the public.	The purpose of the systematic review is to summarize specific evidence pertaining to the effect of CPAP (and related issues). We do not attempt to provide a narrative review of OSA and its features. We believe that our findings are focused in that they pertain to the specific study designs and outcomes investigated. We have added in the need for future research regarding healthcare disparity populations.
Meir Kryger MD FRCPC	General	Not one of the authors of the report has treated a single apnea patient. We have	This review does not address diagnostic tests or the specific channels used in sleep studies

Commentator & Affiliation	Section	Comment	Response
Yale School of Medicine Past President American Academy of Sleep Medicine, Canadian Sleep Society Past Board Chair, National Sleep Foundation		treated more than 20,000. The authors do not seem to appreciate the heterogeneity of sleep apnea, and that this inherent heterogeneity makes research looking at outcomes so difficult. The authors also seem unaware that one of the core measurements used in apnea evaluation and research (SaO2) disadvantages people with dark skin.7-14 Related to this notion is that the authors do not seem to appreciate is that when patients stop breathing what we worry about is hypoxemia. The words *hypoxia* and *hypoxemia* do not appear even once in the report.	(or their problems), except to the extent that researchers have failed to use standardized methods to define sleep and breathing measures or to define OSA. The scope does not include a narrative review of all aspects of OSA, including which attributes of OSA (like hypoxemia) may be causes of symptoms or clinical effects of the condition.
Meir Kryger MD FRCPC Yale School of Medicine Past President American Academy of Sleep Medicine, Canadian Sleep Society Past Board Chair, National Sleep Foundation	General	Until the mid-1980s tracheostomies were done to treat sleep apnea patients with severe hypoxemia. It is a given that hypoxemia is dangerous and life-threatening when severe. We challenge the authors of the report to find a single RTC on the use of oxygen for life-threatening hypoxemia.	The review is focused on CPAP. We do not evaluate supplemental oxygen to treat hypoxemia.
Meir Kryger MD FRCPC Yale School of Medicine Past President American Academy of Sleep Medicine, Canadian Sleep Society	General	RTCs are not the only way to determine whether a disorder should be treated, by what, and for how long.	We agree

Commentator & Affiliation	Section	Comment	Response
Past Board Chair, National Sleep Foundation			
Meir Kryger MD FRCPC Yale School of Medicine Past President American Academy of Sleep Medicine, Canadian Sleep Society Past Board Chair, National Sleep Foundation	General	There is also an ethnic/racial dimension when discussing a treatment for sleep apnea. African Americans are commonly affected by sleep apnea, and as a group their adherence rate to CPAP is about half of American Caucasians, but adherence is greater if their apnea is more severe.15 However African Americans who were adherent to therapy had had a mortality benefit similar to Caucasians.16 Hispanic patients with OSA with insomnia as a comorbidity had a lower CPAP adherence rate.17 Hispanic veterans in Puerto Rico when treated for OSA had a significant long term improvement in BP, and an "extreme improvement in the quality of life". 18 Yet, the writers of the AHRQ draft focus (among many other studies) on a large RTC with patients from China (80%), with 20% from Australia, Spain, Brazil Australia, with almost 80% of the patients already being treated for cardiovascular disease.19 The patients were much thinner than the average US patient. A screening device (rather than a diagnostic device) was used to document apnea. Patients were recruited into the study if their adherence on study run-in was 3 or more hours – indeed the adherence of the patients on CPAP averaged only 3.3 hours/night. There is no way that this study could be generalizable to the diverse US population.	Unfortunately, the studies that met eligibility criteria did not consider differences based on race or ethnicity. We do not agree with the comment that our report focuses on the SAVE trial; although, it is the case that it is the largest RCT and reported on many outcomes of interest for our review. As we point out in several places, for most outcomes there was consistency across RCTs (including SAVE) and usually also consistency with the NRCSs. The issues related to where the study was done and regarding its restrictive eligibility criteria relate to the applicability of the evidence. We discuss this for each outcome (and in the Discussion). We also describe the eligibility criteria and other issues mentioned. We have added further details to the Applicability section of the Discussion.
Meir Kryger MD FRCPC Yale School of Medicine	General	In this comment I will not focus on the shortcomings of the research cited; others have done this.20 I will summarize by saying that the research cited has suffered from poor	We agree that our review does not cover all outcomes that are important to patients and clinicians. We have endeavored to make our focus more explicit.

Commentator & Affiliation	Section	Comment	Response
Past President American Academy of Sleep Medicine, Canadian Sleep Society Past Board Chair, National Sleep Foundation		design, exclusion of the most severely affected, patient selection issues, and which primary outcome is relevant, and ignoring public health issues. One does not treat patients simply to reduce mortality or morbidity. One treats patients to improve the lives of patients and their families and to reduce risk to the public. Do the authors expect us to stop treating locomotive engineers and pilots for their sleep apnea? Would the authors of the report suggest that we should not treat broken bones because there are no significant comorbidities associated with untreated broken bones?	
Meir Kryger MD FRCPC Yale School of Medicine Past President American Academy of Sleep Medicine, Canadian Sleep Society Past Board Chair, National Sleep Foundation	General	**Why do we treat sleep apnea?** There are links between OSAS and several important comorbidities. There is a clear association of OSAS with the development of hypertension,21-23 stroke,24-26 congestive heart failure,27 coronary artery disease,28-30 and even early mortality.31,32 In addition there are neurocognitive sequelae and quality of life issues that are also important reasons to treat patients. The consequences of undiagnosed and untreated OSAS are medically serious and, based on many estimates, economically costly.33 Continuous positive airway pressure (CPAP) is considered the gold standard of treatment for OSAS but, despite many technological advances of the CPAP apparatus, compliance remains a significant problem.34,35 Studies have shown that when used as directed, CPAP improves sleep quality, reduces the risk of OSAS related co-morbidities, and improves patient quality of life.28,36 There are many reasons to treat OSA because there are many consequences of untreated patients.	We agree these are important considerations, but these are beyond the scope of our review.

Commentator & Affiliation	Section	Comment	Response
		Medical consequences of untreated OSA The consequences of undiagnosed and untreated OSAS are numerous and serious.37-51 There is an increase in heart rate and surge in blood pressure during apnea events and, as a result, stress the heart and circulatory system repetitively throughout the night.52,53 Arousals at apnea termination cause a sympathetic nervous system response.54 This sympathetic persists during the day.55,56 OSAS patients tend to have higher heart rates, less heart rate variability, and higher blood pressure than healthy controls.52 It is not surprising that multiple studies have found OSAS patients to be at increased risk for cardiovascular morbidities and hypertension.21-23,25-29 These same patients are also at an increased risk for early all-cause mortality and as one might expect, cardiovascular mortality risk is high (adjusted hazard ratio = 5.2 (95% CI 1.4, 19.2)).31,32 OSAS has been associated with metabolic disorders.57-59 There appears to be an elevated risk for cancer and mortality among OSAS patients particularly for those with severe OSAS (AHI > 30).60,61 Neurocognitive consequences of untreated OSA The main presenting symptom of OSAS is day time sleepiness, decreased cognitive function and are at an increased risk for co-morbidities and accidents. OSAS patients report lower quality of life than non-OSAS patients. 62-64 The bed partners of OSAS patients also have a reduced quality of life.65 Depression is also prevalent in the OSAS population.66,67 Studies have also shown that when the patient's OSAS is treated, quality of life goes up and depression symptoms improve.36,66	

Commentator & Affiliation	Section	Comment	Response
		Transportation consequences of untreated OSA Related to the neurocognitive sequelae there is an increased risk of motor vehicle crashes among untreated OSA patients, 68-71 resulting in significant costs (in lives and dollars). In 2004, Sassani and colleagues estimated that OSAS related motor vehicle crashes cause 810,000 collisions annually, resulting in 1,400 fatalities and costing roughly $15.9 billion.72 They reported that treatment with CPAP (assumed CPAP compliance was 70% - commonly achieved in many clinics) found that CPAP use would prevent roughly 500,000 collisions, save 1,000 lives and reduce the cost by $11.1 billion. The cost of CPAP was used to calculate the dollars saved.72 Workplace consequences of untreated OSA Also related to neurocognitive sequelae patients with snoring and daytime sleepiness are at an increased risk for workplace accidents.73 OSAS patients report excessive daytime sleepiness and are at greater risk of workplace disability than those with no OSAS and no daytime sleepiness, odds ratio of 13.7 (95% confidence interval [CI], 3.9–48). There is an increased risk of long-term duty/job modification as a result of their OSA.74 Economic consequences of untreated OSA Case-controlled studies have reported that healthcare utilization costs are higher for undiagnosed OSAS patients. Three such studies include Kapur et al 1999, Tarasiuk et al 2005 and Albarrak et al 2005.75-77 It has been estimated that increased healthcare spending to treat undiagnosed OSAS patients is between $1,950 and $3,899, per patient, per year.	

Commentator & Affiliation	Section	Comment	Response
		An analysis conducted by Berger et al in 2006 78 analyzed healthcare costs for 337 commercial vehicle drivers, before beginning CPAP treatment and post-CPAP treatment. They found an overall reduction in healthcare costs of 48%, from $906.28 per member per month to $472.69 per member per month. They also found a significant reduction in the accident rate from 93% pre-CPAP treatment to 25% post-CPAP treatment.78 Hoffman et al in 2010 in a retrospective analysis of 248 commercial motor vehicle drivers that compared treated OSAS patients versus untreated controls. They reported that annual healthcare costs decreased by 37% one year post-treatment and noted a 41% decrease in annual healthcare costs when comparing the second year with treatment to pre-treatment healthcare costs.79 They also found that the percentage of drivers taking short-term disability leave decreased by about 50% in the 2 years following treatment compared to a year before treatment.79	
Meir Kryger MD FRCPC Yale School of Medicine Past President American Academy of Sleep Medicine, Canadian Sleep Society Past Board Chair, National Sleep Foundation	General	**The report ignored population-based and administrative data base studies** As is apparent from the above, OSA is a complex disorder with many symptoms and potential comorbidities, and choosing a clinical trial design and endpoint(s) for analysis is complicated. Population-based data was ignored in the report. For example, it has been shown that health care utilization is decreased after treatment with CPAP.75 An administrative database study (also cited above) reported African Americans who were adherent to therapy had had a mortality benefit similar to Caucasians.16	You are correct that we included only randomized and other comparative studies. This does not imply that other evidence is not also important. We have stated this more explicitly.

Commentator & Affiliation	Section	Comment	Response
Meir Kryger MD FRCPC Yale School of Medicine Past President American Academy of Sleep Medicine, Canadian Sleep Society Past Board Chair, National Sleep Foundation	General	**Final thoughts** Millions of people around the world have OSA. Based on our knowledge of physiology, at least some patients with severe hypoxemia require treatment and before CPAP, to save their lives tracheostomy was commonly done. There are many endpoints that are possible (accident rate, comorbidities, quality of life, mortality, cognitive function, depressive symptoms, etc). There are several possible phenotypes. This report may be interpreted as suggesting that PAP should not be prescribed for OSA, ignoring the fact that many patients have excellent adherence and are doing well. The key research protocols published to date cited by the writers of the draft report have been suboptimal: adherence has been poor, and the most severely affected patients were excluded. The studies cited focused primarily on males and completely ignored African Americans and Hispanics. We believe the report needs a major revision with input from sleep specialist.	We aim only to address the scope of the evidence as described in our protocol. We discuss the limitations to the studies within the scope of the review.
Shahrokh Javaheri MD et al. US, European, and Brazilian Medical Centers	General	The undersigned individuals, American, European, and South American lifelong researchers, and clinicians who have taken care of dozens of thousands of patients with sleep-disordered breathing have carefully studied the draft technology assessment entitled, “Continuous Positive Airway Pressure (CPAP) Treatment for Obstructive Sleep Apnea (OSA),” prepared for the Evidence-based Practice Center (EPC) program at AHRQ at the request of the Centers for Medicare & Medicaid Services (CMS). We welcome this timely draft, However, some elements of the report can be misinterpreted. Daytime sleepiness is by far the main reason individuals seek therapy and are referred to	We have made it more explicit that we do not address sleepiness, an important outcome and reason to consider CPAP use. We have also added this to the Limitations. We have added further information in the Discussion Applicability question regarding exclusion of patients with excessive daytime sleepiness.

Commentator & Affiliation	Section	Comment	Response
		sleep physicians for treatment. As noted below, severely sleepy subjects, for ethical reasons were excluded from the randomized controlled trials, referenced in the AHRQ draft. In other words, the subjects enrolled in the trials reviewed do not represent the patients typically referred. Multiple studies and metanalyses have shown that treatment of sleepy OSA subjects improves daytime sleepiness and reduces car crashes. Sleep apnea has been implicated in many high-profile accidents in the transportation industry. It is therefore critical that the authors of the AHRQ report consider daytime sleepiness, the main symptom for which patients come to see us, as an important outcome of CPAP treatment of OSA. The AHRQ report is therefore out of sync with the US Government approach to sleepiness and sleep apnea as will now be reviewed.	
Shahrokh Javaheri MD et al. US, European, and Brazilian Medical Centers	General	The vast majority of OSA patients have as their main complaint excessive daytime sleepiness. The AHRQ report understates the importance of sleepiness as an important issue in public health and flies in the face of government initiatives to deal with sleep issues. Here are some examples: The US government-sponsored public health initiative by the CDC, Healthy People 2020, now includes a dedicated section on sleep health to promote public awareness of the ill effects of sleep loss and sleep disorders.1 The U.S. Army has adopted a program called Performance Triad that includes sleep as one of the three pillars of health and performance alongside nutrition and physical activity.2 The rationale for government programs to mitigate sleepiness	We agree that sleepiness is an important outcome for patients and clinicians, but it is outside the scope of the review. In the Discussion we have added a summary of prior systematic reviews on this and other outcomes.

Commentator & Affiliation	Section	Comment	Response
		These are as a result of research and the understanding that sleepiness played an important role in some catastrophes and near catastrophes. For example, the Three Mile Island nuclear reactor disaster of 1979 resulted from human error and mechanical factors that allowed a large amount of nuclear reactor coolant to escape into the environment. Fatigue was implicated in the accident, not surprisingly because the accident occurred at 4 AM.3 Another fatigue-related accident occurred in 1989 when the oil tanker Exxon Valdez struck a reef off the coast of Alaska and spilled 11 to 32 million gallons of crude oil. It was at the time the largest and most devastating human-caused environmental disaster.4 Although multiple factors played a role in the accident, crew fatigue was identified as a major factor. Fatigue has also been implicated in the Chernobyl nuclear5 and Challenger space shuttle disasters.5 Other examples of preventable fatigue-related accidents abound in the transportation and health care industries. In response to these catastrophic events and to promote public safety, many governmental regulations have been established over the years. Railroad. The recognition that sleepiness and fatigue needed to be regulated came early in the US, decades before the field of sleep medicine even existed. The first public policy attempting to address fatigue-related accidents, the “Hours of Service Act of 1907” (45 USC Sect. 61; 1907). In response to several fatal rail accidents in 2002 and 2008, Congress passed the Rail Safety Improvement Act of 2008 (49 USC 21101; 2008), which enabled the Federal Railroad	

Commentator & Affiliation	Section	Comment	Response
		Administration (FRA), a member of the U.S. Department of Transportation (USDOT), to mandate new safety regulations governing different aspects of railroad safety, including hours of service requirements. Aviation. In 1938, the Civil Aeronautics Board issued its first rules dealing with fatigue.6 Commercial drivers. The U.S. Interstate Commerce Commission (ICC), which then had regulatory authority over motor carriers, introduced the first governmental regulations in 1938. Marine. The first regulations concerning the marine industry were drafted in 1978 by the International Marine Organization, an agency of the United Nations. Evolution of US government regulations Regulations continue to evolve based on science and the common sense understanding that a sleepy person controlling a train, automobile, an aircraft, or a sea-going craft is a danger to the public. To give an example, in late 2013, the FAA decided to modify rules governing untreated OSA, a disqualifying condition for airmen and traffic controllers when untreated. The current guidelines require that “an integrated assessment of history, symptoms, and physical/clinical findings” be used to determine the risk of OSA.7 Transport companies have also embraced measures regarding sleepiness and sleep apnea. Among 348 drivers diagnosed with sleep-disordered breathing and who were treated, medical costs and accident rates declined by 57.8% and 73%, respectively. The driver retention rate of continuous positive airway pressure (CPAP)-treated individuals was 2.29 times greater than the total company driver population.8	

Commentator & Affiliation	Section	Comment	Response
		As a result of the science and the above, The National Transportation Safety Board issued on its Most Wanted List for Safety Improvement for 2019-2020: “Screen for and Treat Obstructive Sleep Apnea”.9 Below, we briefly review scientifically the pitfalls of the RCTs and why they failed, as reviewed by the writers of the draft, and respectfully ask for their consideration. We submit this letter to you on behalf of thousands of symptomatic patients we have seen over few decades of practice of sleep medicine and their gratitude and appreciation of our services to them. It appears the writers of the draft are not sleep physicians, and in that case, they may not have had the patient experience as the writers of this letter. The draft as written has important negative implications for symptomatic patients, depriving them of the most effective treatment of OSA. We10 and others11 have already written about these issues in peer-reviewed publications and will now expand further. 1. Excessive daytime sleepiness. This is the main reason for referral and should be considered a clinically important outcome because of the public health issues mentioned above and because animal models of OSA have shown that hypoxemia could permanently damage the neuronal cells involved in the maintenance of wakefulness.12 Additionally, this symptom (EDS) has important implications in regards to its association with a) CPAP adherence and b), cardiovascular outcomes of OSA.10,13 In regards to the latter, studies have shown that it is this phenotype of OSA, which is associated with incident adverse cardiovascular consequences of OSA. Again,	

Commentator & Affiliation	Section	Comment	Response
		such subjects were excluded from the long-term RCTs for ethical reasons and concerns that such individuals could be involved in car accidents or similar catastrophic events. RCTs which randomized the duration of CPAP therapy to 1 night, 14 nights, and 42 nights showed that EDS (documented objectively) improved significantly after one night, and improved further after 14 nights, but no further improvement was documented after 42 nights.14 Meanwhile, consistent with hypoxemia damaging (due to inflammation, apoptosis, gliosis) awake neuronal cells of the brain, is the persistence of EDS in almost 30 % of OSA subjects, particularly the hypoxemic phenotype, who use CPAP, even 7 hours or more /night.15 Indeed, FDA has approved several drugs to treat EDS in OSA subjects with persistent EDS despite adequate use of CPAP.	
Shahrokh Javaheri MD et al. US, European, and Brazilian Medical Centers	General	For this reason, we have proposed (for details please see reference 10) an RCT of sleepy OSA phenotype, randomized to CPAP vs usual care, and use of FDA-approved wake-promoting medication for sleep subjects. This RCT is a critical one, to once and for all answer the equipoise whether CPAP is effective or not in preventing hard CV outcomes.	Thank you. We have expanded our Future Research section, in part along the lines of your article.
Shahrokh Javaheri MD et al. US, European, and Brazilian Medical Centers	General	2. Other reasons accounting for the failure of the RCTs reviewed in the AHRQ draft. Aside from EDS [excessive daytime sleepiness] as an exclusion, there were multiple other reasons for the failure of the RCTs and we respectfully ask the writers of the draft to study our publication (see reference 10) on this issue. Some underlying reasons were the	We have discussed the potential limitations regarding the applicability of the RCTs in the Discussion Applicability section, including issues related to eligibility based on EDS. We have also discussed limitations of the SAVE study more extensively.

Commentator & Affiliation	Section	Comment	Response
		inclusion of less severe OSA subjects, and those with less severe hypoxemia, and poor adherence to CPAP. Importantly, in the SAVE trial, most of the subjects enrolled were Chinese and the results are not necessarily generalizable.16 The SAVE trial used a type 4 device (a first-generation Apnea link, with only 2 channels), to determine the presence of OSA; according to AASM, the device is best used for screening, not for diagnosis.	
Shahrokh Javaheri MD et al. US, European, and Brazilian Medical Centers	General	3. OSA and hypertension and the effects of CPAP on blood pressure. The clinical importance of improved blood pressure, as a critical intermediary mechanism for downstream cerebro-cardiovascular consequences of OSA appears not to have been somewhat underestimated. In fact, the effect of CPAP on hypertension has been widely investigated, and the available evidence from multiple RCTs and several recent meta-analyses demonstrate that CPAP significantly reduces BP in OSA patients. Studies using 24-h BP monitoring consistently report drops of 2 to 2.5 mm Hg and 1.5 to 2 mm Hg in systolic blood pressure (SBP) and diastolic blood pressure (DBP), respectively, compared with subtherapeutic or conservative treatment (Figure 1), with greater reductions in patients with resistant hypertension (between 4.7 to 7.2 mm Hg and 2.9 to 4.9 mm Hg for SBP and DBP, respectively).17 Because long-term reductions of 2 to 3 mm Hg in SBP are associated with a 4% to 8% reduction in the future risk of stroke and coronary heart disease, long-term treatment of OSA in hypertensive patients could eventually reduce incident cardiovascular burden. Certainly, the effect of CPAP should be far more profound in resistant	We agree that decrease in BP, even without a change in diagnosis of hypertension, is clinically important. Unfortunately, it was outside the scope of our review. We state this more explicitly.

Commentator & Affiliation	Section	Comment	Response
		hypertension. We, therefore, suggest that writers of the AHRQ draft consider improvement in hypertension as an important intermediary outcome.	
Shahrokh Javaheri MD et al. US, European, and Brazilian Medical Centers	General	Future Directions. This has been addressed in our recent publication where we detail the necessity of a true RCT, in which subjects with EDS are included, hypoxemia burden is considered not an exclusion, a 2 month trial of sham CPAP, and inclusion of only adherent individuals in a long-term trial.10 The proposed trial allows the clinician to use wakefulness-promoting FDA-approved drugs for sleepy OSA subjects during follow up. This will eliminate the ethical consideration for excluding sleepy subjects. Other details regarding the power of the trial for inclusion/exclusion have been detailed. 10 We thank the writers of the AHRQ report to consider our comments and refocus the report to emphasize the main reason patients seek attention: excessive daytime sleepiness.	We hope your study will successfully add important information to the evidence regarding CPAP and treatment of OSA.