PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

(This paper received three reviews from its previous journal but only two reviewers agreed to published their review.)

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effect of CPAP therapy on kidney function in patients with obstructive sleep apnea and chronic kidney disease: a protocol for a randomized controlled clinical trial
AUTHORS	Rimke, Alex N; Ahmed, Sofia; Turin, Tanvir C; Pendharkar, Sachin R; Raneri, Jill K; Lynch, Emma J; Hanly, Patrick J

VERSION 1 – REVIEW

REVIEWER	Craig L Phillips University of Sydney, Australia
REVIEW RETURNED	02-Jul-2018

GENERAL COMMENTS	This protocol is for an open label pilot RCT in patients with CKD and co-morbid OSA and is aimed at assessing the effect of OSA treatment with CPAP to slow the rate of decline in renal function (eGFR). It seeks to answer a clinically relevant question and focuses on a clinical population not specifically studied in OSA therapy research. The authors appropriately recognize their study limitations and have proposed several strategies to address them. Recruitment began in July 2015 and the study will finish in August 2019. Overall this protocol is clearly written however it would have been more desirable to write it according to SPIRIT guidelines. Specific Comments/Questions: 1. Inclusion criteria: The RDI>5 and SaO2T90 > 12% criteria may lead to inclusion of nocturnal hypoventilation as the primary pathology even with normal daytime PaO2 and PaCO2. What was the rationale for not considering the more mainstream ODI as a measure of intermittent hypoxia? 2. Inclusion Criteria: Given that the HSAT device does not measure sleep (and arousals) could the authors clarify the definition of the RDI used? 3. Inclusion Criteria: Do the authors have a strategy for dealing with false negatives from the HSAT due to poor sleep? 4. Exclusion criteria: Are patients with co-morbid significant cardiopulmonary disease (eg COPD) that might have mild OSA but whose primary problem is a lower baseline hypoxia during sleep excluded? 5. Randomisation: Are patients stratified for baseline CKD stage

	when randomising to CPAP versus usual care? 6. Randomisation: Given the open label design, is a random block size being used to ensure allocation concealment? 7. Intervention: Please clarify the mode of CPAP - will it be auto-CPAP and if so, what pressure range? 8. Intervention: Will the second HSAT study be performed on auto-CPAP? 9. Intervention: If OSA or nocturnal hypoxaemia persists on this second HSAT study, what adjustments will be made (convert to fixed, higher pressure range on auto)? Alternatively, will patients have an in-lab titration study? 10. Intervention: Regarding repeat HSAT at end of study – will there be a subgroup analysis for those in the active arm depending on whether CPAP remains effective at the end of study? If yes, will this analysis look at residual exposure to OSA (which could be as much as 3-4 hours after removing CPAP) or will they only consider compliance? 11. DSMC: Please clarify according to 21a of the SPIRIT guideline. 12. Outcomes analysis: Will investigators involved in the analysis be blinded to treatment allocation? 13. Outcomes collection: Regarding ACR testing – will the collection time be consist - eg first morning voids or will it be a random ACR. 14. Statistical analysis: Usually the mixed models ANOVA uses the maximum likelihood ratio to impute missing values. Could the authors comment on why they chose LOCF instead? 15. Statistical analysis: Adjustments will be made for differences in baseline BMI, diabetes and hypertension status as well as for co-variates of etiology of disease, gender, severity of CKD and OSA. The statistical plan should state more clearly which parameters will be adjusted for. Could the authors guarantee they have the power with n=30 in each group to make multiple adjustments? 16. Statistical analysis: How will the researchers manage the data from participants who progress to dialysis or have an acute kidney injury during the one-year trial or introduction of medications that have significant impact on eGFR/ACR? 17. Secondary outcome: Will adverse events due to therapy be recorded and presented? 18. Limitations: The authors state that eGFR and ACR have intrinsic variability that may result in them being unable to detect any change in eGFR due to the intervention. They plan to look at the variability from previous measurements and correct for this in their analysis. It is unclear how this will be done and it would be useful to know why this variability was not assessed prior to sample size calculations to ensure that it is taken into account. 19. Limitations: Do previous studies support a clinically meaningful change in eGFR with CPAP over the planned 12 months intervention? 20. Limitations: Will CPAP compliance be averaged over 12 months or will it be inserted as a nested factor in the time-series analyses? 21. Trial Registration: Is the current protocol reflected by the trials registry the same as this manuscript? If not then please explain the differences.

REVIEWER	Wisit Cheungpasitporn, MD, FASN University of Mississippi Medical Center, Jackson, Mississippi, USA
REVIEW RETURNED	08-Jul-2018

GENERAL COMMENTS	I totally agree with the investigators that this is an important study that we need since OSA is common problem and associated with many worse clinical outcomes. In addition, CKD is irreversible and slow progression of CKD is challenging in clinical practice. While I support this study, I have several important comments that I would like to raise; in order to help identify the true benefit on renal function. My main concerns are disadvantages of the eGFR by creatinine and potential of inadequate power. -This is the first randomized controlled trial to evaluate the impact of CPAP on renal function in patients with CKD. This is debating statement, since this study result has not completed and there is another ongoing randomized controlled trial (NCT03319888) that also evaluates Effect of CPAP in the Worsening of Renal Function in Patients with Chronic Kidney Disease (RENAS; prospective, multicentric, randomized and controlled study); but that multicenter RCT study is planned to assess the effect of CPAP on Early-stage renal disease (G1-3 KDIGO); rather than stages 3 and 4 CKD as in your study - I am afraid that one year, since the data on hard outcomes, e.g., the need for dialysis or mortality are limited, evaluation of renal function change by eGFR by creatinine-based formula will not see the actual benefit of CPAP in this CKD patient population. We know that short-term, CPAP may help improve exercise tolerance for patients with OSA, these patients in short-term usually have no changes in BMI (PMID: 27840271); but likely have higher muscle mass/strength; and muscle mass may affect and result in higher creatinine in another group which patients without CPAP may have renal function decline and higher creatinine (or these patients may lose muscle mass and then may not have creatinine as high as it should be); per se, creatinine is not a proper measurement for this setting; if you can use cystatin C based formula; or other methods e.g. iothalamate clearance; to help confirm; then this may help with this issue. -Power Calculation: RE “The absence of previous randomized studies to evaluate the use of CPAP for OSA in CKD patients poses a challenge when estimating the sample size required for this study. Consequently, a convenience sample of 60 CKD patients (30 with stage 3 CKD and 30 with stage 4 CKD) with OSA and nocturnal hypoxemia will be enrolled.” I agree that it is difficult to calculate the power as the investigators mentioned. However, I am really afraid convenience samples of 60 CKD patients will again make a concern about lack of power. In your prior study evaluating renal function in patients with cardiovascular disease (Am J Respir Crit Care Med. 2017 Dec 1;196(11):1456-1462); I agree there was lack of power because most patients had relatively good kidney function or no significant proteinuria. -How many patients with CKD stage 3-4 do your clinics have had for the past year? Can you recruit all eligible patients rather than only 60 CKD? Otherwise, I am afraid that 1-year evaluation is not long enough to see the differences. - Please describe more details on Randomization; block randomization? Mixed block randomization? - Can you plan for subgroup analysis based on the risk of kidney function decline? By using Kidney Failure Risk Equation (8 Variable; PMID: 26757465); would require age, sex, eGFR, urine albumin to creatinine, serum calcium, serum phosphorus, bicarb, albumin, patient’s location at the time of enrollment; these are

	common testing in Nephrology clinic. - Are you planning to record sleep duration as well? Duration of sleep may also affect renal function/proteinuria (PMID: 27190375). - Medications are planned to be recorded; want to make sure that analysis will take blood pressure and the need for ACEIs/ARBs into consideration.

REVIEWER	Zhiying You University of Colorado Anschutz Medical Campus, USA
REVIEW RETURNED	13-Sep-2018

GENERAL COMMENTS	1. In general it is clear paper of a high quality design 2. There is a need of more details about assessment of adherence or compliance 3. If possible, adjustment for measure of compliance in effect analysis would be very preferable 4. While the change in eGFR can be calculated at multiple time points (i.e. month 3, 6, and 12), it is unclear at which month the change (from baseline) in eGFR will be defined as the primary outcome in case that different conclusions were generated at different time points, even reader would assume month 12. 5. While analyzed as intention-to-treat, per protocol, and based on actual treatment used have been proposed, it is unclear from which analysis the conclusion about intervention effect will be made in case that different conclusions were made from different analyses. 6. There is a lack of abbreviation for PaO2 and PaCO2 when first showed up

VERSION 1 – AUTHOR RESPONSE

REVIEWER 1
Comments
This protocol is for an open label pilot RCT in patients with CKD and co-morbid OSA and is aimed at assessing the effect of OSA treatment with CPAP to slow the rate of decline in renal function (eGFR). It seeks to answer a clinically relevant question and focuses on a clinical population not specifically studied in OSA therapy research. The authors appropriately recognize their study limitations and have proposed several strategies to address them. Recruitment began in July 2015 and the study will finish in August 2019.

Overall this protocol is clearly written however it would have been more desirable to write it according to SPIRIT guidelines.
Response: We thank the reviewer for this feedback. We hope that the clarity of the manuscript and the inclusion of the SPIRIT checklist will satisfy the journal's requirements. If this is not the case, we can revise the manuscript further to meet those requirements.

Comment 1: Inclusion criteria: The RDI>5 and SaO2T90 > 12% criteria may lead to inclusion of nocturnal hypoventilation as the primary pathology even with normal daytime PaO2 and PaCO2. What was the rationale for not considering the more mainstream ODI as a measure of intermittent hypoxia?
Response: Although RDI was the term used to report respiratory events when the Remmers Sleep Recorder was developed over 30 years ago, the data is collected though automated analysis of the oximetry signal, specifically, each 4% desaturation followed by re-saturation is scored as a respiratory event. Consequently, this is more accurately described as an ODI. In addition, there is a qualitative assessment of airflow by the interpreting physician to confirm that these episodes of oxygen

desaturation are accompanied by a transient reduction or absence of airflow. We have clarified this in the manuscript (page 4, comment R1C1).

Comment 2: Inclusion Criteria: Given that the HSAT device does not measure sleep (and arousals) could the authors clarify the definition of the RDI used?
Response: As indicated in the response to comment #1 above, the data taken from the Remmers Sleep Recorder is actually an ODI rather than an RDI, which, as the reviewer implies, would require monitoring of sleep to meet criteria for scoring hypopneas and RERAs.

Comment 3: Inclusion Criteria: Do the authors have a strategy for dealing with false negatives from the HSAT due to poor sleep?
Response: When patients use the Remmers Sleep Recorder they are asked to report how long they slept while the monitor was worn. If patients report that they slept less than 50% of the time that the monitor was worn, they are asked to repeat the study. We have outlined this in the manuscript (page 5, comment R1C3).

Comment 4: Exclusion criteria: Are patients with co-morbid significant cardiopulmonary disease (eg COPD) that might have mild OSA but whose primary problem is a lower baseline hypoxia during sleep excluded?
Response: Individuals who require supplemental oxygen therapy at nighttime or during the daytime are excluded from the study. However, patients with comorbidities, such as COPD, who do not require supplemental oxygen therapy, are not excluded. We are confident that we can identify a false positive diagnosis of OSA on the automated oximetry analysis by the Remmers Sleep Recorder since we routinely correlate episodes of oxygen desaturation with changes in the airflow signal. This enables us to distinguish episodes of oxygen desaturation that are due to sleep apnea from episodes of desaturation that are due to minor changes in ventilation in a patient with baseline hypoxemia. Approximately 2,500 home sleep apnea tests are done annually at our Sleep Centre with the Remmers Sleep Recorder, which has provided extensive experience with this device. We have clarified this in the manuscript (page 4, comment R1C4).

Comment 5: Randomisation: Are patients stratified for baseline CKD stage when randomising to CPAP versus usual care?
Response: Patients are stratified into either CKD stage 3 or 4 at baseline for both groups. We have clarified this in the manuscript (page 4, Comment R1C5).

Comment 6: Randomisation: Given the open label design, is a random block size being used to ensure allocation concealment?
Response: Block randomization is employed through the random number generation website to ensure allocation concealment. We have clarified this in the manuscript (page 4, comment R1C6).

Comment 7: Intervention: Please clarify the mode of CPAP - will it be auto-CPAP and if so, what pressure range?
Response: All patients are started on auto CPAP (15/5 cmsH2O). The effectiveness of auto CPAP is reviewed at the time of the first CPAP download, one month after randomization, and the accompanying home sleep apnea test with the Remmers Sleep Recorder. If the patient's apnea and hypoxemia are satisfactorily controlled the patient remains on those auto CPAP settings. However, if the patient has persistent hypoxemia or persistent apnea, appropriate changes are made such as adjustment of the auto CPAP setting or conversion to fixed CPAP. The home sleep apnea test is repeated until CPAP efficacy has been optimized. The patient remains on whichever CPAP mode and settings works best to control their apnea and nocturnal hypoxemia. These details are recorded and will be reported. We have clarified this in the manuscript (page 5, comment R1C7).

Comment 8: Intervention: Will the second HSAT study be performed on auto-CPAP?
Response: The second HSAT will be performed on auto-CPAP. However, as stated in the response to comment #7 above, the HSAT will be repeated again if adjustment of CPAP is required, until control of the patient's apnea and nocturnal hypoxemia has been optimized. We have clarified this in the manuscript (page 5, comment R1C7).

Comment 9: Intervention: If OSA or nocturnal hypoxaemia persists on this second HSAT study, what adjustments will be made (convert to fixed, higher pressure range on auto)? Alternatively, will patients have an in-lab titration study?
Response: As outlined above, CPAP will be adjusted to optimize control of sleep apnea and nocturnal hypoxemia. The options chosen will depend on what is responsible for sub-optimal treatment and include both adjustment of auto-CPAP and conversion to fixed CPAP. We are confident that this can be managed in the ambulatory setting and do not plan to provide CPAP titration in the sleep laboratory. We have clarified this in the manuscript (page 5, comment R1C7).

Comment 10: Intervention: Regarding repeat HSAT at end of study – will there be a subgroup analysis for those in the active arm depending on whether CPAP remains effective at the end of study? If yes, will this analysis look at residual exposure to OSA (which could be as much as 3-4 hours after removing CPAP) or will they only consider compliance?
Response: Collection of HSAT data at the end of the study will provide the opportunity to compare variability in the effectiveness of CPAP on renal outcomes. This variability can include persistent apnea and persistent hypoxemia, regardless of adherence with CPAP therapy. We have clarified this in the manuscript (page 5, comment R1C10).

Comment 11: DSMC: Please clarify according to 21a of the SPIRIT guideline.
Response: Although our original protocol indicated that we would have a DSMC, we do not feel it is required for this study. As discussed in section 21a of the SPIRIT guidelines, a formal committee is not required in trials "with known minimal risks". The intervention in our trial (CPAP therapy) has minimal risk and our sleep centre and the CPAP providers in the community whom we collaborate with have extensive experience with this treatment. Furthermore, our exclusion criteria were chosen to avoid recruitment of patients in whom CPAP therapy may not be appropriate. We have clarified this in the manuscript (page 8, comment R1C11).

Comment 12: Outcomes analysis: Will investigators involved in the analysis be blinded to treatment allocation?
Response: Investigators involved in the analysis of the outcomes will not be blinded to treatment allocation. We did not feel this was necessary since our outcome measurements are objective and unlikely to be influenced by investigator bias. We have clarified this in the manuscript (page 4, comment R1C12).

Comment 13: Outcomes collection: Regarding ACR testing – will the collection time be consist - eg first morning voids or will it be a random ACR.
Response: The time of ACR collection is determined by patient availability. As such the collection times will be random. We have clarified this in the manuscript (page 5, comment R1C13).

Comment 14: Statistical analysis: Usually the mixed models ANOVA uses the maximum likelihood ratio to impute missing values. Could the authors comment on why they chose LOCF instead?
Response: Response: We acknowledge that mixed model ANOVA generally imputes missing values using the maximum likelihood ratio, but to accommodate the progressive nature of the change in kidney function over time, we chose to use LOCF. Moreover, maximum likelihood ratio is a suitable approach when the number of subjects is sufficiently large, and the proportion of missing data is

small. In our case, we have a small sample, which may not be suitable for maximum likelihood ratio. LOCF is the preferred method of analysis since it is more conservative than using observed cases only.

Comment 15: Statistical analysis: Adjustments will be made for differences in baseline BMI, diabetes and hypertension status as well as for co-variates of etiology of disease, gender, severity of CKD and OSA. The statistical plan should state more clearly which parameters will be adjusted for. Could the authors guarantee they have the power with n=30 in each group to make multiple adjustments?
Response: We acknowledge that our relatively small sample size (convenience sample) may lack the power to make multiple adjustments. However, assessment for confounders (BMI, diabetes, and hypertension) will allow us to appreciate the impact of these conditions on the outcome to some extent even if the study is underpowered. As there have been no studies of this kind previously we will use this to gain a better understanding for larger trials. This has been clarified in the manuscript (page 7, R1C15)

Comment 16: Statistical analysis: How will the researchers manage the data from participants who progress to dialysis or have an acute kidney injury during the one-year trial or introduction of medications that have significant impact on eGFR/ACR?
Response: Patients who progress to dialysis within the 12-month trial will be flagged to determine if there was an acute event that was responsible for this rapid progression. Similarly, patients who have a rapid decline in GFR will be reviewed to determine if an acute event was responsible for this. If we find evidence of a significant kidney injury over and above what might be expected from nocturnal hypoxemia, we will assess the impact of this on our results. We have clarified this in the manuscript (page 7, comment R1C16).

Comment 17: Secondary outcome: Will adverse events due to therapy be recorded and presented?
Response: Although we do not anticipate serious adverse events due to CPAP therapy, these will be recorded. We have clarified this in the manuscript (page 5, comment R1C17).

Comment 18: Limitations: The authors state that eGFR and ACR have intrinsic variability that may result in them being unable to detect any change in eGFR due to the intervention. They plan to look at the variability from previous measurements and correct for this in their analysis. It is unclear how this will be done and it would be useful to know why this variability was not assessed prior to sample size calculations to ensure that it is taken into account.
Response: The variability in GFR and ACR prior to recruitment is not an inclusion or exclusion criterion; nor will it be used in our formal statistical analysis. However, patients with high variability in GFR and ACR prior to enrolment may respond differently to CPAP than those with low variability. We will investigate this possibility with an exploratory analysis by comparing the response to CPAP between those with high and low variability in GFR and ACR prior to enrolment. This has been clarified in the manuscript (page 9, comment R1C18)

Comment 19: Limitations: Do previous studies support a clinically meaningful change in eGFR with CPAP over the planned 12 months intervention?

Response: There are 2 previous observational studies that have shown a significant change in eGFR with CPAP over 12 months or less. Koga et al reported that eGFR increased from 72.9±12 to 79.3±17.9 (p=0.014) in patients with stage 2 CKD (Intern Med 52:345-349,2013). Puckrin et al reported that the rate of decline was slower in patients adherent with CPAP therapy compared to those who used CPAP less frequently (-0.07 mL/min/1.73m2 vs -3.15 mL/min/1.73m2 (Int Urol Nephrol 47:1839-1845,2015) Furthermore, in the patient population we are targeting, small changes in eGFR can have a significant impact on clinical outcomes (N Engl J Med 351:1296-305, 2004).

Comment 20: Limitations: Will CPAP compliance be averaged over 12 months or will it be inserted as a nested factor in the time-series analyses?
Response: CPAP adherence will be averaged over 12 months. This has been outlined in the manuscript (page 5, R3C2)

Comment 21: Trial Registration: Is the current protocol reflected by the trials registry the same as this manuscript? If not then please explain the differences.
Response: There are minor differences between the current protocol registered in clinicaltrials.gov (ID: NCT02420184) and the manuscript submitted to BMJOPEN. We have added the following secondary outcomes: Albumin/creatinine ratio (ACR), the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), and the Kidney Disease Quality of Life (KDQoL). The protocol in the trial's registrar has been updated to include these additions.

REVIEWER: 2
Comments
I totally agree with the investigators that this is an important study that we need since OSA is common problem and associated with many worse clinical outcomes. In addition, CKD is irreversible and slow progression of CKD is challenging in clinical practice. While I support this study, I have several important comments that I would like to raise; in order to help identify the true benefit on renal function. My main concerns are disadvantages of the eGFR by creatinine and potential of inadequate power.

Comment 1: This is the first randomized controlled trial to evaluate the impact of CPAP on renal function in patients with CKD. This is debating statement, since this study result has not completed and there is another ongoing randomized controlled trial (NCT03319888) that also evaluates Effect of CPAP in the Worsening of Renal Function in Patients with Chronic Kidney Disease (RENAS; prospective, multicentric, randomized and controlled study); but that multicenter RCT study is planned to assess the effect of CPAP on Early-stage renal disease (G1-3 KDIGO); rather than stages 3 and 4 CKD as in your study
Response: We thank the reviewer for bringing our attention to this other proposed randomized controlled trial. As pointed out by the reviewer, this trial is focusing on patients with mild CKD in contrast to our study, which may impact the results and their implications. We have modified our statement to highlight that our proposed study is the first randomized controlled trial to evaluate the impact of CPAP on renal function in patients with stages 3 and 4 CKD. We have clarified this in the manuscript (page 2, comment R2C1).

Comment 2: I am afraid that one year, since the data on hard outcomes, e.g., the need for dialysis or mortality are limited, evaluation of renal function change by eGFR by creatinine-based formula will not see the actual benefit of CPAP in this CKD patient population. We know that short-term, CPAP may help improve exercise tolerance for patients with OSA, these patients in short-term usually have no changes in BMI (PMID: 27840271); but likely have higher muscle mass/strength; and muscle mass may affect and result in higher creatinine in another group which patients without CPAP may have renal function decline and higher creatinine (or these patients may lose muscle mass and then may not have creatinine as high as it should be); per se, creatinine is not a proper measurement for this setting; if you can use cystatin C based formula; or other methods e.g. iothalamate clearance; to help confirm; then this may help with this issue.
Response: We chose a creatinine-based measurement of GFR because this is used uniformly by all practicing nephrologists in our health region. As such, our results will have general applicability for the patient population we are recruiting and the healthcare providers who care for them. Secondly, GFR estimated by the CKD-EPI formula is as accurate as GFR measured with cystatin C for patients with stage 3 and 4 CKD. Thirdly, we do not anticipate muscle mass to increase in our patient population

due to the potential for CPAP to increase exercise tolerance, since this has not been something, we have observed in our sleep clinics over several years of practice. We also record changes in weight which will help to address this issue, at least partially.

Comment 3: Power Calculation: RE “The absence of previous randomized studies to evaluate the use of CPAP for OSA in CKD patients poses a challenge when estimating the sample size required for this study. Consequently, a convenience sample of 60 CKD patients (30 with stage 3 CKD and 30 with stage 4 CKD) with OSA and nocturnal hypoxemia will be enrolled.”
I agree that it is difficult to calculate the power as the investigators mentioned. However, I am really afraid convenience samples of 60 CKD patients will again make a concern about lack of power. In your prior study evaluating renal function in patients with cardiovascular disease (Am J Respir Crit Care Med. 2017 Dec 1;196(11):1456-1462); I agree there was lack of power because most patients had relatively good kidney function or no significant proteinuria.
Response: We acknowledge the reviewer’s comments regarding potential lack of power to find significant differences between the CPAP and control groups in our study. As outlined in our manuscript, this is a pilot study to obtain preliminary data to test the notion that treating sleep apnea and nocturnal hypoxemia may benefit kidney function. Since there are no previous well-controlled studies to test this hypothesis, we believe that our pilot study is worthwhile, even if differences in renal function between the two groups do not reach statistical significance. At the very least, it will enable us to more accurately calculate the sample size required for a larger and more definitive study

Comment 4: How many patients with CKD stage 3-4 do your clinics have had for the past year? Can you recruit all eligible patients rather than only 60 CKD? Otherwise, I am afraid that 1-year evaluation is not long enough to see the differences.
Response: Approximately 3,500 patients with stage 3 and 4 CKD are seen in our nephrology clinics annually. However, we have learned from previous studies that there are many barriers to recruitment and this data will also be used to project what would be necessary for a larger, multicentre trial. At the current time, we believe that in a single centre study, 60 patients who are prepared to commit to a one-year pilot trial is a realistic number.

Comment 5: Please describe more details on Randomization; block randomization? Mixed block randomization?
Response: Block randomization is being employed to ensure allocation concealment. To ensure even allocation, randomization occurs in blocks of six for each stratum. This has been clarified in the manuscript (page 4, comment R1C6).

Comment 6: Can you plan for subgroup analysis based on the risk of kidney function decline? By using Kidney Failure Risk Equation (8 Variable; PMID: 26757465); would require age, sex, eGFR, urine albumin to creatinine, serum calcium, serum phosphorus, bicarb, albumin, patient’s location at the time of enrollment; these are common testing in Nephrology clinic.
Response: We thank the reviewer for this recommendation. Unfortunately, we do not have measurements of serum calcium, serum phosphorus, and bicarbonate levels in all of our patients, which precludes evaluation of the Kidney Failure Risk Equation (KFRE) with 8 variables.

Comment 7: Are you planning to record sleep duration as well? Duration of sleep may also affect renal function/proteinuria (PMID: 27190375).
Response: We are aware of previous literature that has proposed that sleep disruption and sleep loss may impact kidney function. Our hypothesis is that nocturnal hypoxemia is a more likely candidate to accelerate the decline in kidney function. Consequently, we are focusing on that and have not included measurements of sleep duration in our study design.

Comment 8: Medications are planned to be recorded; want to make sure that analysis will take blood pressure and the need for ACEIs/ARBs into consideration.
Response: We will record changes in blood pressure and medications, including ACEIs/ARBs, and will include them in the analysis of our results. We have clarified this in the manuscript (page 5, Comment R2C8).

REVIEWER 3
Comments
Comment 1: In general it is clear paper of a high quality design.
Response: Thank you.

Comment 2: There is a need of more details about assessment of adherence or compliance.
Response: CPAP adherence will be monitored daily for the entire 12 months after randomization. These daily measurements will be averaged for each month of the study. CPAP adherence will be quantified for each of these months as the number of hours CPAP was used each day and the percentage of each month that CPAP was used more than 4 hours per night. Both of these measurements are used as indices of CPAP adherence in clinical practice. We have clarified this in the manuscript (page 5, comment R3C2).

Comment 3: If possible, adjustment for measure of compliance in effect analysis would be very preferable.
Response: The detailed monitoring of CPAP adherence in our study, described above, will facilitate adjustment for CPAP adherence in the effect analysis. Our intention to treat analysis will likely include some patients in the CPAP group who discontinue CPAP therapy. However, we will also undertake an exploratory analysis using both per protocol and as treated design. We have clarified this in the manuscript (page 5, comment R3C2).
Comment 4: While the change in eGFR can be calculated at multiple time points (i.e. month 3, 6, and 12), it is unclear at which month the change (from baseline) in eGFR will be defined as the primary outcome in case that different conclusions were generated at different time points, even reader would assume month 12.
Response: If CPAP therapy benefits renal function in an individual patient and that patient remains adherent with therapy, one would expect the improvement in renal function to be apparent and sustained at the end of the study, i.e. 12 months after randomization. However, it is possible that the benefits of CPAP on GFR may be present sooner and this will be addressed by the analysis every three months. We have outlined this in the manuscript (page 7, comment R3C4).

Comment 5: While analyzed as intention-to-treat, per protocol, and based on actual treatment used have been proposed, it is unclear from which analysis the conclusion about intervention effect will be made in case that different conclusions were made from different analyses.
Response: We will use intention-to-treat principle in our main analysis. Intention-to-treat is a more conservative approach and tends to under-estimate an effect but at the same time reduces the risk of a type-I error. However, an exploratory analysis using per protocol and as treated design will also be used to help us in planning a larger, more definitive trial. We have clarified this in the manuscript (page 7, comment R3C5).

Comment 6: There is a lack of abbreviation for PaO2 and PaCO2 when first showed up
Response: The abbreviations for the partial pressure of oxygen and carbon dioxide have been added to the manuscript (page 4, comment R3C6)

VERSION 2 – REVIEW

REVIEWER	Craig L Phillips Woolcock Institute of Medical Research, University of Sydney, Australia
REVIEW RETURNED	18-Nov-2018

GENERAL COMMENTS	The authors state "Block randomization is being employed to ensure allocation concealment. To ensure even allocation, randomization occurs in blocks of six for each strata." Please clarify this. Usually, "random" block sizes (not fixed sizes) are used to ensure treatment allocation concealment. This random blocking can be used within strata to ensure a balance between treatment groups. The random block sizes must be multiples of the number of treatments and the sizes are usually stated in the methods - eg. 2, 4 and 6 for 2 treatments. It will be crucial that treatment allocation is concealed in order for you to publish this study and it should be clear how this was ensured.

REVIEWER	Wisit Cheungpasitporn, MD University of Mississippi Medical Center
REVIEW RETURNED	31-Oct-2018

GENERAL COMMENTS	Thank you for clarification and addressing my comments and concerns. This protocol is well written. Despite limitations, the investigators have addressed all of my concerns and I think this manuscript is acceptable for publication.

REVIEWER	Zhiying You University of Colorado Denver USA
REVIEW RETURNED	31-Oct-2018

GENERAL COMMENTS	All comments have be addressed.

VERSION 2 – AUTHOR RESPONSE

REVIEWER COMMENT
The authors state "Block randomization is being employed to ensure allocation concealment. To ensure even allocation, randomization occurs in blocks of six for each strata." Please clarify this. Usually, "random" block sizes (not fixed sizes) are used to ensure treatment allocation concealment. This random blocking can be used within strata to ensure a balance between treatment groups. The random block sizes must be multiples of the number of treatments and the sizes are usually stated in the methods - e.g. 2, 4 and 6 for 2 treatments. It will be crucial that treatment allocation is concealed in order for you to publish this study, and it should be clear how this was ensured.

REVISED TEXT IN MANUSCRIPT
Education session
All patients who meet these criteria and agree to participate in the study will be identified by a recruiter (ANR) who will obtain informed consent. Following this, a CPAP education and acclimatization session will be scheduled with a research coordinator (JKR), who will provide a standardized 20-minute presentation on OSA and CPAP therapy. The research coordinator will fit the patient with a comfortable interface (mask) and show them how to use a CPAP unit set at a pressure of 4 cmH2O.

Randomization, allocation concealment, and blinding

Following the education session, patients stratified by stage 3 and stage 4 CKD will be randomly allocated equally (1:1) to receive either usual medical treatment for CKD (Control group) or usual medical treatment with CPAP (CPAP group). Randomization will be done using a web-based system http://www.randomization.com which will provide the research co-ordinator with the patient's assignment. Randomization will be performed by means of a random number generator for an initial block of 20 patients for stage 3 CKD and 20 patients for stage 4 CKD. For further recruitment, to ensure even allocation, randomization will occur in blocks of 6 for each CKD stage strata. To ensure allocation concealment, we will follow a stringent procedure to ensure enrolment before randomization. Recruitment and randomization will be performed by different individuals, as outlined above, and without the involvement of other investigators. The allocation will be concealed and will be broken by the research co-ordinator only after the participant has met all selection criteria and completed the education session. Neither the patients nor the research staff will be blinded to the intervention (CPAP) or medical treatment for CKD.