PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Acceptance, adherence, and dropout rates of individuals with COPD approached in telehealth interventions: A protocol for systematic review and meta-analysis
AUTHORS	Alghamdi, Saeed; Janaudis-Ferreira, Tania; Alhasani, Rehab; Boruff, Jill; Ahmed, Sara

VERSION 1 – REVIEW

REVIEWER	Siân Russell Newcastle University, Institute of Health and Society. England, UK.
REVIEW RETURNED	01-Nov-2018

GENERAL COMMENTS	This is a worthwhile review that explores a pertinent healthcare issue: telehealth and COPD. However, I fear it is a little bio-medical and narrow in its scope. COPD is a socially patterned condition, associated with inequality; incidence and poorer outcomes have been associated with marginalised communities, socioeconomic deprivation, lower educational attainment, and childhood disadvantage. Relatedly, there are issues of literacy and health literacy that can impact upon an individual's management and understanding of the condition. Those with COPD are likely to have comorbidities such as diabetes, osteoporosis, hypertension, or lung cancer that can impact upon management (for example, diabetes may take priority for the individual). In addition to this anxiety and depression, as well as panic, have adverse implications for management, and can lead to unplanned hospital admissions. One would assume such issues would be of concern to research questions 1 to 3 of your proposed review, especially as some telehealth interventions can create a literacy barrier, and can be perceived as 'middle class' interventions. While 'level of education' is present, I wonder whether the 'population characteristics' of your proposed data extraction could be expanded in the hope of capturing some of the nuance described above? So, for example, occupation, any measure of socioeconomic status (for example, in the UK we have the Index of Multiple Deprivation), comorbidities, mental health status – which I would stress is linked yet different from health related quality of life. It would also be useful for you to extract data on ethnicity, which is oddly not listed within 'population characteristics'. Much of this may not be reported, however, being explicitly mindful of such issues during data extraction could well be illuminating for unpicking issues of acceptance, adherence and dropout. Whether these issues are reported or commented on within the papers included in your proposed review would be an interesting finding in and of itself,

	providing an opportunity for discussion as to whom these forms of intervention are being designed for – are they only targeted at a subsection of the COPD population, are they exclusionary, are trials purposefully limiting the trail populations to those more likely to accept and adhere? It would also be worth considering who is administrating the intervention; nurses, GPs, healthcare assistants, pharmacists? This, one would think, could impact upon the issues of concern to your proposed review. For example, patients may be more honest about their concerns with a nurse than a GP and have a pharmacist involved could prove vital to improvements in medication use / avoid polypharmacy and thus see improved outcomes relating to, for example, exacerbation and hospital admission.

REVIEWER	Peter Hanlon University of Glasgow, UK
REVIEW RETURNED	07-Nov-2018

GENERAL COMMENTS	This paper outlines the protocol for a systematic review to synthesise findings regarding acceptance, adherence and dropout from "telemonitoring interventions". The review will address an important issue, with relevance to the external validity of interventions in this sphere. I have major concerns, however, about the manuscript as it currently stands, as various issues are not clear. My main concerns are: - Whatever term is chosen (e.g. telemonitoring) to refer to the interventions of interest, this needs to be defined early in the introduction and be consistent with the inclusion criteria of the review. At present terminology is mixed and does not agree with the inclusion criteria. - How the authors propose to deal with the issue of adherence needs to be expanded on. This is likely to be a far more complex issue than the authors describe, particularly with the wide range of potential interventions that are be included. - Following on from this, the use of meta-regression needs to be more clearly justified and explained. Issues regarding heterogeneity and the validity of the proposed analysis are not adequately described or explored. This is a potentially very useful topic to review, however greater explanation is required around the approach to data extraction and analysis (particularly around adherence). Title The term "telemonitoring" is used in the title. However the inclusion criteria appear to be broader than the definition of telemonitoring which is given in the appendix. The terminology needs to be clearer and consistent throughout. If the authors are to use Abstract The authors use the TM (telemonitoring) abbreviation in describing their objectives. However, their inclusion criteria are much broader than simply telemonitoring (even by the definition set out in table 1). Inclusion criteria include web-based education, telerehabilitation etc… which are probably distinct from telemonitoring. More clarity and consistency over the terms used is needed. As the inclusion criteria are broad, and telehealth would appear to have a broader definition, this may be a better term to use here. Whatever term is

	chosen needs to be justified later. The authors at times refer to “experimental and non-experimental” studies and at other times “experimental and observational”. Please be consistent. Also, from the abstract and the introduction it is not totally clear what type of studies are of interest. At multiple point the authors say they will look at e.g. “dropout rates in… observational studies”. From the methods it appears that the authors mean studies of telehealth interventions which do not have a contemporaneous control group (e.g. pre-post studies, quasi-experimental studies). The terminology in the abstract and introduction could be much clearer… perhaps referring to ‘trials of telehealth interventions (including RCTs, crossover, and pre-post studies)’ or something to that effect. Introduction The authors comment that “lack of knowledge [of the impact of telehealth in COPD] might be due to non-adherence…”. While I think understanding adherence is vitally important, this is not clear from this statement as it is. Do you mean that variation in adherence could affect consistency in the findings of interventions? Non-adherence (for example if an intervention is too complex or difficult) could be a legitimate explanation for why an intervention does not work. Similarly lack of acceptance limits external validity rather than knowledge of efficacy. I agree that these are all important things to understand, and the topic of the review is important, but I don’t think the importance has been framed properly. The authors rightly point out in line 28 that” the precise impact of telehealth and telemonitoring on avoiding exacerbation and reducing hospital readmissions remains inconclusive.” However, this is not reflected earlier in this paragraph, where the evidence may be overstated. For example: “There is evidence that telehealth and/or telemonitoring is a useful tool for minimizing hospital admissions due to respiratory exacerbations, particularly in the case of individuals who are constrained by geographical barriers, or have limited access to healthcare services”. The evidence base around this is inconsistent… it may be more accurate to say some evidence that telehealth may be a useful tool… Similarly: “Clinical trials show that individuals with COPD have positive attitudes towards participating in telehealth and/or telemonitoring interventions”. The referenced studies are all small feasibility studies that do show acceptability of these intervention. This sentence should be rephrased, and perhaps balanced with other evidence that some telehealth interventions in COPD may promote dependence (e.g. the evaluation of the Light Touch intervention). Objectives See above comment regarding terminology around observational studies, interventions etc. Methods The inclusion criteria regarding interventions need to be clearer. The initial list of terms is not particularly helpful, as many are not defined (event in table 1). Specifically, telemedicine, telecare, telehomecare are not defined. This is problematic particularly as definitions are so

	variable (see Sood S, Mbarika V, Jugoo S, Dookhy R, Doarn CR, Prakash N, Merrell RC. What is telemedicine? A collection of 104 peer-reviewed perspectives and theoretical underpinnings. Telemedicine and e-Health. 2007 Oct 1;13(5):573-90.). The second statement, “In principal, any information technology tool designed for the clinical support of patients with COPD involving the exchange of data remotely between the patient and health care professional will be considered”, is more helpful, and would be more helpful if it came first (possibly qualified by examples). Would the authors include telephone interventions (there is variation between existing reviews, so would be helpful to specify)? Search strategy Do the authors plan on searching for newer articles which cite the relevant studies identified (e.g. cited reference search using Web of Science). In a rapidly moving field such as telehealth this would be a relatively quick way to look for newer articles which will not be identified by searching reference lists. I have concerns about the search terms in appendix 1. The authors use a combination of MeSH and keywords (.mp). In searching for keywords, however, they do not account for potential variation in spelling (e.g. telehealth vs tele health vs tele-health). Adjusting the terms to include optional characters (e.g. tele?health.mp in medline) would offer some reassurance that relevant articles were not being missed due to variation in spelling. On further reading the text states that these terms will be searched with and without hyphen, which is fine. However the example search in the appendix (which has presumably been conducted as there are numbers in the right hand column) does not include these terms. The search strategy needs to be reported and accurately so as to be reproducible. Terms regarding web-based monitoring may be better captured by using adjacent word searching, as terminology is unlikely to be standard. Data extraction section: The abbreviation “FEV1%” is given for Forced Expiratory Volume in one second. Should this be “FEV1” instead? Or did you mean Forced Expiratory Volume in one second as a percentage of predicted? Please clarify so the abbreviation matches the text. Perhaps I have misunderstood, but the statement “ES calculation will be performed according to results from the first postinterventional evaluation, which will reflect the impact of telehealth and/or telemonitoring interventions on outcomes.” seems unusual. If trials have multiple follow-up times are you planning to calculate the effect based on the earliest of these? If so please clarify. What about trials with different lengths of follow-up? Some clarification would be helpful. Outcomes: The section on outcomes is confusing, as the subsequent analysis does not focus on any of these. Is there going to be any synthesis of the outcomes of the interventions themselves? Is appears the review outcome is acceptance, adherence, or drop-out. However these are

	not mentioned in this outcomes section. Presumably this is because trials will not report these as outcomes, however as currently presented this is a little confusing. Clarity around how the trial outcomes will be used/synthesised (if at all) would be useful. Data analysis: The definitions of acceptance rate and dropout rates are very clear, and will be interesting outcomes to look at. Adherence, particularly for complex interventions such as telehealth, is a more difficult concept to capture, and I worry that the measure presented may oversimplify it. This is particularly important as the authors propose to include a wide range of heterogenous interventions (remote monitoring, pulmonary rehabilitation, internet-based education). "Adherence" to these interventions could mean significantly different things, which may make it problematic to calculate a rate and then aim to include these in a meta-regression. For an educational intervention, one may expect variation in the level of engagement/frequency of use etc. How would you define 'non-adherence' in such a way that you could calculate a proportion who adhered (as such as definition would have to be binary). If you were to look at completion of a programme, how would this differ from your definition of dropout ("participants who withdrew from or did not continue with the intervention"). How does adherence ("number of participants who completed the telehealth intervention according to the study protocol", line 45) differ from dropout ("did not continue with the intervention", line 48)? As the very nature of adherence is likely to be very different depending on the intervention of interest (and the inclusion criteria permit a wide range of interventions to be included in the review), is it legitimate to propose to meta-analyse these? As written, this protocol does not appear to justify this approach to analysis. The authors propose to use meta-regression to test the effect of participant, study, and intervention characteristics on the variation in outcomes (acceptance, adherence, and dropout). Will these characteristics be selected a priori, in which case what characteristics do you propose to test? If not, is there a danger that the characteristics will be selected based on a knowledge of the trial outcomes, and this bias the results. Also, the authors propose to test several characteristics in a few categories. A very large number of studies would be required to have adequate power to test multiple covariates, however this issue is not acknowledged or discussed. Perhaps a small list of likely key covariates would be appropriate? Some discussion of this complexity, at least, would be important. The following section needs revised: "Heterogeneity for the meta-analysis will be tested using the I2 statistic. The reliability of the I2 estimation will be confirmed using a 95% confidence interval. If the interventions, populations, and outcomes are homogenous, a meta-analysis will be performed." Given the nature of telehealth interventions (which have multiple components), and the broad inclusion criteria of the review, it is inconceivable that the interventions would be homogeneous. Indeed, meta-regression (as proposed) would be a tool to explain heterogeneity. The key question appears to be whither the included studies (in terms of interventions, populations, and outcomes) are too heterogeneous for a meta-analysis to be a meaningful or useful synthesis. The issues highlighted above regarding the measurement

	of adherence will be important considerations for this judgement. The decision of whither to perform the meta-analysis should surely be made on these grounds and not based on the I2 statistic (by which point the meta-analysis has already been performed). Discussion: The authors state that “To the best of our knowledge, this will be the first systematic review estimating acceptance, adherence, and dropout rates of COPD populations participating in telehealth and/or telemonitoring, as well as the associated factors influencing these rates.” However I don’t think this is the case. The authors then cite the review by Cruz et al, which does summarise adherence and dropout rates in COPD telemonitoring interventions. Cruz et al also summarise reasons for dropout, as well as factors in the interventions related to either lack of adherence or to dropout. I do not think that the author’s claim is accurate. Similarly, the authors state: “Previous systematic reviews and meta-analyses were unable to provide information about effective elements contributing to better acceptance and adherence rates; in contrast, our current study will try to explore elements of telehealth and/or telemonitoring that impact acceptance, adherence, and dropout rates”. Factors linked with adherence, and satisfaction, are discussed with the Cruz et al review, as the authors cite. It seems to me that the difference in the proposed review is the use of meta-regression to quantify the association between patient/intervention factors and dropout adherence. This would appear to be a new approach, not undertaken by previous reviewers. However, from the current text it is not clear that this is what the authors are highlighting as the novel aspect of their review. Additional files: The authors included a PRISMA checklist, however surely a PRISMA-P checklist, specific to protocols, would be the more appropriate checklist to provide. References: The references require proof-reading. An electronic reference manager has been used without checking the formatting of the references (e.g. reference 1, where the name of the Global Initiative for Chronic Obstructive Lung Disease has been treated as initials). Also some of the systematic reviews referenced are quite out of date, and more recent reviews exist.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

COPD is a socially patterned condition, associated with inequality; incidence and poorer outcomes have been associated with marginalised communities, socioeconomic deprivation, lower educational attainment, and childhood disadvantage. Relatedly, there are issues of literacy and health literacy that can impact upon an individual’s management and understanding of the condition. Those with COPD are likely to have comorbidities such as diabetes, osteoporosis, hypertension, or lung cancer that can impact upon management (for example, diabetes may take priority for the individual). In addition to this anxiety and depression, as well as panic, have adverse implications for management, and can lead to unplanned hospital admissions. One would assume such issues would be of concern to research questions 1 to 3 of your proposed review, especially as some telehealth interventions can create a literacy barrier, and can be perceived as ‘middle class’ interventions.

While ‘level of education’ is present, I wonder whether the ‘population characteristics’ of your proposed data extraction could be expanded in the hope of capturing some of the nuance described above? So, for example, occupation, any measure of socioeconomic status (for example, in the UK we have the Index of Multiple Deprivation), comorbidities, mental health status – which I would stress is linked yet different from health related quality of life. It would also be useful for you to extract data on ethnicity, which is oddly not listed within 'population characteristics'. Much of this may not be reported, however, being explicitly mindful of such issues during data extraction could well be illuminating for unpicking issues of acceptance, adherence and dropout. Whether these issues are reported or commented on within the papers included in your proposed review would be an interesting finding in and of itself, providing an opportunity for discussion as to whom these forms of intervention are being designed for – are they only targeted at a subsection of the COPD population, are they exclusionary, are trials purposefully limiting the trail populations to those more likely to accept and adhere?

It would also be worth considering who is administrating the intervention; nurses, GPs, healthcare assistants, pharmacists? This, one would think, could impact upon the issues of concern to your proposed review. For example, patients may be more honest about their concerns with a nurse than a GP and have a pharmacist involved could prove vital to improvements in medication use / avoid polypharmacy and thus see improved outcomes relating to, for example, exacerbation and hospital admission

AUTHORS' RESPONSE TO THE REVIEWER: We appreciate the detailed feedback on the manuscript. Your suggestions about adding more factors to the population characteristics and intervention characteristics will help to improve the outcomes of our current systematic review. All suggested factors have been added to the data extraction sheet (Line 273 to 305, Line 307 to 324) as follows:

"Outcomes of this review are acceptance, adherence, and dropout rates. When these outcomes are not reported in the original studies, we will calculate the rates as follows:

The acceptance rate will be calculated by taking the total number of participants who accepted, agreed, and consented to participate in this study and dividing it by the number of participants who were approached for involvement in telehealth intervention. The adherence rate will be calculated as the total number of participants who completed the telehealth intervention according to the study protocol divided by the number who started the intervention. The dropout rate will be calculated as number of participants who withdrew from or did not continue with the intervention divided by the number of participants who consented to participate on the study. All rates will be presented using an overall average"

Reviewer 2:

My main concerns are:

- Whatever term is chosen (e.g. telemonitoring) to refer to the interventions of interest, this needs to be defined early in the introduction and be consistent with the inclusion criteria of the review. At present terminology is mixed and does not agree with the inclusion criteria.

AUTHORS' RESPONSE: Thank you for your suggestion about the terminology. The definition of telemonitoring has been added to the introduction along with additional clarification of the inclusion criteria in the Methodology (Line 187 to 195) as follows:

"(3) Type of intervention: this review includes any information technology tool designed for the clinical support of patients with COPD involving the remote exchange of data between a patient and a health care professional. This includes, for example, telehealth, telecare, telehomecare, e-health, telemonitoring, telerehabilitation, telemedicine, home monitoring, digital monitoring, web-based monitoring, or internet-based monitoring as part of a COPD-management plan. "

- How the authors propose to deal with the issue of adherence needs to be expanded on. This is likely to be a far more complex issue than the authors describe, particularly with the wide range of potential interventions that are be included.

- Following on from this, the use of meta-regression needs to be more clearly justified and explained.

Issues regarding heterogeneity and the validity of the proposed analysis are not adequately described or explored.
This is a potentially very useful topic to review, however greater explanation is required around the approach to data extraction and analysis (particularly around adherence).
AUTHORS' RESPONSE: Thank you for your comments. We agree, adherence rate is a complex concept to be explained in rate and number. However, in this review, we defined the adherence rate according to the study protocol (Line 282 to 324) as follows:
"Hospitalization: admissions due to exacerbations and causes of hospitalization will be reported. Attention shall be paid to differences between count and dichotomous data (e.g., the count of participants in each group who experience at least one exacerbation event vs. number of events per intervention group).

Exacerbation rate is a commonly reported outcome [26]. As exacerbations can be reported in different ways, the data collection allows for the following numbers to be recorded: number of exacerbations or exacerbation rate (that may also be classified based on the patient disease severity), all-cause mortality, and number of patients per study group who died during the survey.

Adherence to the Action Plan: (including any measurement mentioned by the authors to report the adherence to the action plan – e.g., adherence to intervention, adherence to physiological monitoring, adherence to symptom monitoring, adherence to medication, adherence to exercise, and adherence telehealth and/or telemonitoring)

Health-related quality of life: disease-specific or non-disease-specific quality of life reported by a validated instrument.

Physical activity measurements (any type reported by a validated measurement system).

Outcome of adherence for this review:
Outcomes of this review are acceptance, adherence, and dropout rates. When these outcomes are not reported in the original studies, we will calculate the rates as follows: The acceptance rate will be calculated by taking the total number of participants who accepted, agreed, and consented to participate in this study and dividing it by the number of participants who were approached for involvement in telehealth intervention. The adherence rate will be calculated as the total number of participants who completed the telehealth intervention according to the study protocol divided by the number who started the intervention. The dropout rate will be calculated as number of participants who withdrew from or did not continue with the intervention divided by the number of participants who consented to participate on the study. All rates will be presented using an overall average".

Title
The term "telemonitoring" is used in the title. However, the inclusion criteria appear to be broader than the definition of telemonitoring which is given in the appendix. The terminology needs to be clearer and consistent throughout. If the authors are to use
AUTHORS' RESPONSE: Thank you for the feedback. The terminology in the title has been changed to "telehealth" to match with the terminology of the inclusion criteria (Line 2).

Abstract

The authors use the TM (telemonitoring) abbreviation in describing their objectives. However, their inclusion criteria are much broader than simply telemonitoring (even by the definition set out in table 1). Inclusion criteria include web-based education, telerehabilitation etc… which are probably distinct from telemonitoring. More clarity and consistency over the terms used is needed. As the inclusion criteria are broad, and telehealth would appear to have a broader definition, this may be a better term to use here. Whatever term is chosen needs to be justified later".

AUTHORS' RESPONSE: The terminology in the abstract has been adjusted to match the terminology of the inclusion criteria (Lines 51,57, 58, and 59).

The authors at times refer to "experimental and non-experimental" studies and at other times "experimental and observational". Please be consistent.
Also, from the abstract and the introduction it is not totally clear what type of studies are of interest. At multiple point the authors say they will look at e.g. "dropout rates in… observational studies". From the methods it appears that the authors mean studies of telehealth interventions which do not have a contemporaneous control group (e.g. pre-post studies, quasi-experimental studies). The terminology in the abstract and introduction could be much clearer… perhaps referring to 'trials of telehealth interventions (including RCTs, crossover, and pre-post studies)' or something to that effect.

AUTHORS' RESPONSE: Thank you for the detailed suggestions. The inclusion criteria in the Introduction has been changed to match the inclusion criteria in the Methodology section. Furthermore, the inclusion criteria have been adjusted according to the suggestions provided. (Line 186 to 198)
The inclusion criteria is now as follows:
(1) Study type: randomized or non-randomized control trials, observational single arm pre-post trials, and crossover clinical trials;
(2) Population: studies including individuals diagnosed with COPD based on reported FEV1% will be considered for this review;
(3) Type of intervention: this review includes any information technology tool designed for the clinical support of patients with COPD involving the remote exchange of data between a patient and a health care professional. This includes, for example, telehealth, telecare, telehomecare, e-health, telemonitoring, telerehabilitation, telemedicine, home monitoring, digital monitoring, web-based monitoring, or internet-based monitoring as part of a COPD-management plan.
(4) Type of outcome: outcomes include health-related quality of life, adherence to the action plan, exacerbations, duration of hospital stay, hospitalization or utilization of health services (including COPD related cost), and exercise capacity.

Introduction
The authors comment that "lack of knowledge [of the impact of telehealth in COPD] might be due to non-adherence…". While I think understanding adherence is vitally important, this is not clear from this statement as it is. Do you mean that variation in adherence could affect consistency in the findings of interventions? Non-adherence (for example if an intervention is too complex or difficult) could be a legitimate explanation for why an intervention does not work. Similarly lack of acceptance limits external validity rather than knowledge of efficacy. I agree that these are all important things to understand, and the topic of the review is important, but I don't think the importance has been framed properly.
AUTHORS' RESPONSE: We appreciate the feedback. The text has been rephrased for clarity (Line 120 to 127).
Rephrased text as follows: "Telehealth refers to the use of electronic information and communication technologies to support distance healthcare, which allows healthcare professionals and long-distance patients to exchange information and enable access to healthcare services. Various terms are used throughout the medical industry to reference specific applications and use cases for telehealth – these are presented in Table 1 [5]. For example, telehealth interventions with COPD could be used to deliver care and it can help to detect exacerbations at an early stage, minimizing the potential for emergency admissions and facilitating self-management [5-8]".

(Line 130 to 138)
Rephrased text as follows : “There is growing evidence that telehealth may be a useful tool for minimizing hospital admissions due to respiratory exacerbations, particularly in the case of individuals who are constrained by geographical barriers, or have limited access to healthcare services [5, 10]. Clinical trials have shown that individuals with COPD have positive attitudes towards participating in telehealth and that telehealth can promote patients’ independence toward self-management [11-17]. However, the precise impact of telehealth on avoiding exacerbation and reducing hospital readmissions remains inconclusive [5]. The uncertainty about the impact of telehealth may be due to non-adherence or partial adherence to intervention techniques as well as the withdrawal of participants over the course of previous studies”.

The authors rightly point out in line 28 that” the precise impact of telehealth and telemonitoring on avoiding exacerbation and reducing hospital readmissions remains inconclusive.” However, this is not reflected earlier in this paragraph, where the evidence may be overstated. For example:
“There is evidence that telehealth and/or telemonitoring is a useful tool for minimizing hospital admissions due to respiratory exacerbations, particularly in the case of individuals who are constrained by geographical barriers, or have limited access to healthcare services”. The evidence base around this is inconsistent… it may be more accurate to say some evidence that telehealth may be a useful tool…

AUTHORS’ RESPONSE: The introduction has been rephrased to reflect the current evidence (Line 130 and 133)
“There is growing evidence that telehealth may be a useful tool for minimizing hospital admissions due to respiratory exacerbations, particularly in the case of individuals who are constrained by geographical barriers, or have limited access to healthcare services [5, 10]”.

Similarly: “Clinical trials show that individuals with COPD have positive attitudes towards participating in telehealth and/or telemonitoring interventions”. The referenced studies are all small feasibility studies that do show acceptability of these intervention. This sentence should be rephrased, and perhaps balanced with other evidence that some telehealth interventions in COPD may promote dependence (e.g. the evaluation of the Light Touch intervention).
AUTHORS’ RESPONSE: The text has been modified to include additional evidence on telehealth intervention.
(Line 133 to 135)
“Clinical trials have shown that individuals with COPD have positive attitudes towards participating in telehealth and that telehealth can promote patients’ independence toward self-management [11-17]”.

Objectives
See above comment regarding terminology around observational studies, interventions etc.
AUTHORS’ RESPONSE: The terminology has been corrected as suggested and consistently throughout the text we use the terminology “pre-post studies”.

Methods
The inclusion criteria regarding interventions need to be clearer. The initial list of terms is not particularly helpful, as many are not defined (event in table 1). Specifically, telemedicine, telecare, telehomecare are not defined. This is problematic particularly as definitions are so variable (see Sood S, Mbarika V, Jugoo S, Dookhy R, Doarn CR, Prakash N, Merrell RC. What is telemedicine? A collection of 104 peer-reviewed perspectives and theoretical underpinnings. Telemedicine and e-Health. 2007 Oct 1;13(5):573-90.).

The second statement, “In principal, any information technology tool designed for the clinical support of patients with COPD involving the exchange of data remotely between the patient and health care professional will be considered", is more helpful, and would be more helpful if it came first (possibly qualified by examples).

Would the authors include telephone interventions (there is variation between existing reviews, so would be helpful to specify)?

AUTHORS' RESPONSE: Thank you for your valuable comments. All terms in the inclusion criteria have now been defined in Table 1 and we've added the reference about telemedicine. Regarding the second point, the text has been rephrased for clarity. This review will consider telephone interventions as telehealth interventions (Line 514 to 516).

Search strategy
Do the authors plan on searching for newer articles which cite the relevant studies identified (e.g. cited reference search using Web of Science). In a rapidly moving field such as telehealth this would be a relatively quick way to look for newer articles which will not be identified by searching reference lists.
I have concerns about the search terms in appendix 1. The authors use a combination of MeSH and keywords (.mp). In searching for keywords, however, they do not account for potential variation in spelling (e.g. telehealth vs tele health vs tele-health). Adjusting the terms to include optional characters (e.g. tele?health.mp in medline) would offer some reassurance that relevant articles were not being missed due to variation in spelling.
On further reading the text states that these terms will be searched with and without hyphen, which is fine. However the example search in the appendix (which has presumably been conducted as there are numbers in the right hand column) does not include these terms. The search strategy needs to be reported and accurately so as to be reproducible.
Terms regarding web-based monitoring may be better captured by using adjacent word searching, as terminology is unlikely to be standard.

AUTHORS' RESPONSE: Thank you, we appreciate the suggestions. Based on your feedback, the search has now been repeated and reported using the most relevant terms and by adjusting terms to include optional characters (line 206 – 226) as follows:
"telecare; telehomecare; telehealth; e-health; telemonitoring; telerehabilitation; telemedicine; home monitoring; digital monitoring; web-based monitoring; internet-based monitoring; Chronic Obstructive Pulmonary Disease; Chronic Obstructive lung disease, and COPD. The search strategy was developed in collaboration with a health sciences librarian (JB), to ensure the involvement of appropriate and necessary keywords in the review. Keywords and subject terms will be customized for each database. Further, all words with the prefix "tele-" will be searched both with and without a hyphen (e.g., both "tele-monitoring" and "telemonitoring"). The search strategies from Medline (Ovid) are presented in Appendix 1".

Data extraction section:
The abbreviation "FEV1%" is given for Forced Expiratory Volume in one second. Should this be "FEV1" instead? Or did you mean Forced Expiratory Volume in one second as a percentage of predicted? Please clarify so the abbreviation matches the text.

AUTHORS' RESPONSE: The abbreviation has been corrected and now reads to match the text as suggested.
line 263 -266
"Population characteristics: age; gender; level of education; GOLD grade and/or Forced Expiratory

Volume in one second as a percentage of predicted (FEV1%); smoking history; number of COPD patients who consented to participate, were approached, dropped out, and completed the study, as well as reasons for dropout".

Perhaps I have misunderstood, but the statement "ES calculation will be performed according to results from the first postinterventional evaluation, which will reflect the impact of telehealth and/or telemonitoring interventions on outcomes." seems unusual. If trials have multiple follow-up times are you planning to calculate the effect based on the earliest of these? If so please clarify. What about trials with different lengths of follow-up? Some clarification would be helpful.
AUTHORS' RESPONSE: We've added a more detailed explanation about the calculations for effect size (Line 277 to 280)
", which will reflect the earliest impact of telehealth interventions on outcomes. Any results after the first post-interventional evaluation (e.g., results from multiple follow-up points) will not be considered in the ES calculation. Also, the ES on the main outcome will be included in the analysis if the studies have more than one outcome".

Outcomes:
The section on outcomes is confusing, as the subsequent analysis does not focus on any of these. Is there going to be any synthesis of the outcomes of the interventions themselves? Is appears the review outcome is acceptance, adherence, or drop-out. However these are not mentioned in this outcomes section. Presumably this is because trials will not report these as outcomes, however as currently presented this is a little confusing. Clarity around how the trial outcomes will be used/synthesised (if at all) would be useful.

AUTHORS' RESPONSE: the outcomes mentioned in this section refer to the trial outcomes mentioned in each article, not the targeted outcomes that will be calculated for the purpose of this review; we believe that adding the targeted outcomes (i.e. the acceptance, adherence, and dropout rates) to the trials outcomes may potentially increase confusion. It is worth noting that these rates are not commonly reported as outcomes in the trials. However, to ensure a comprehensive review, the authors will calculate the rates to be used in the meta-regression (Line 274 to 324 as follow:
"OUTCOMES
All reported outcomes of COPD will be extracted, as will the effect size (ES) of telehealth intervention on these outcomes. The ES will be calculated if it is not mentioned by the author(s). ES calculation will be performed according to results from the first post-interventional evaluation, which will reflect the earliest impact of telehealth interventions on outcomes. Any results after the first post-interventional evaluation (e.g., results from multiple follow-up points) will not be considered in the ES calculation. Also, the ES on the main outcome will be included in the analysis if the studies have more than one outcome.

Outcomes
Outcomes extracted form each study:
All primary and secondary outcomes defined by each study will be extracted. These include, but are not limited to:

Hospitalization: admissions due to exacerbations and causes of hospitalization will be reported. Attention shall be paid to differences between count and dichotomous data (e.g., the count of participants in each group who experience at least one exacerbation event vs. number of events per intervention group).

Exacerbation rate is a commonly reported outcome [26]. As exacerbations can be reported in different ways, the data collection allows for the following numbers to be recorded: number of exacerbations or exacerbation rate (that may also be classified based on the patient disease severity), all-cause mortality, and number of patients per study group who died during the survey.

Adherence to the Action Plan: (including any measurement mentioned by the authors to report the adherence to the action plan – e.g., adherence to intervention, adherence to physiological monitoring, adherence to symptom monitoring, adherence to medication, adherence to exercise, and adherence telehealth and/or telemonitoring)

Health-related quality of life: disease-specific or non-disease-specific quality of life reported by a validated instrument.

Physical activity measurements (any type reported by a validated measurement system).

Outcome of adherence for this review:
Outcomes of this review are acceptance, adherence, and dropout rates. When these outcomes are not reported in the original studies, we will calculate the rates as follows:
The acceptance rate will be calculated by taking the total number of participants who accepted, agreed, and consented to participate in this study and dividing it by the number of participants who were approached for involvement in telehealth intervention. The adherence rate will be calculated as the total number of participants who completed the telehealth intervention according to the study protocol divided by the number who started the intervention. The dropout rate will be calculated as number of participants who withdrew from or did not continue with the intervention divided by the number of participants who consented to participate on the study. All rates will be presented using an overall average".

Data analysis:
The definitions of acceptance rate and dropout rates are very clear, and will be interesting outcomes to look at.
Adherence, particularly for complex interventions such as telehealth, is a more difficult concept to capture, and I worry that the measure presented may oversimplify it. This is particularly important as the authors propose to include a wide range of heterogenous interventions (remote monitoring, pulmonary rehabilitation, internet-based education). "Adherence" to these interventions could mean significantly different things, which may make it problematic to calculate a rate and then aim to include these in a meta-regression.
For an educational intervention, one may expect variation in the level of engagement/frequency of use etc. How would you define 'non-adherence' in such a way that you could calculate a proportion who adhered (as such as definition would have to be binary). If you were to look at completion of a programme, how would this differ from your definition of dropout ("participants who withdrew from or did not continue with the intervention").
How does adherence ("number of participants who completed the telehealth intervention according to the study protocol", line 45) differ from dropout ("did not continue with the intervention", line 48)?
As the very nature of adherence is likely to be very different depending on the intervention of interest (and the inclusion criteria permit a wide range of interventions to be included in the review), is it legitimate to propose to meta-analyse these? As written, this protocol does not appear to justify this approach to analysis.
AUTHORS' RESPONSE: Thank you for the valuable comments. We appreciate the detailed feedback regarding the data analysis. We fully agree that adherence could be defined according to the intervention provided. we would like to determine variations of adherence for each type of intervention. We will be able to do this as we are extracting the different components of the intervention including intervention settings, methods, frequency and components of telehealth (active

elements, targeted behavior, targeted users, the degree of tailoring, health professional assistance), and duration of intervention.
The authors propose to use meta-regression to test the effect of participant, study, and intervention characteristics on the variation in outcomes (acceptance, adherence, and dropout). Will these characteristics be selected a priori, in which case what characteristics do you propose to test? If not, is there a danger that the characteristics will be selected based on a knowledge of the trial outcomes, and this bias the results.
Also, the authors propose to test several characteristics in a few categories. A very large number of studies would be required to have adequate power to test multiple covariates, however this issue is not acknowledged or discussed. Perhaps a small list of likely key covariates would be appropriate? Some discussion of this complexity, at least, would be important.

AUTHORS' RESPONSE: The participant, study, and intervention characteristics were not selected according to the outcomes of the trials. Rather, they were selected according to empirical studies and the primary analysis (Correlation Matrix). Hence, the analysis will have included the characteristics that were associated with these rates. For example, the association between the mode of the intervention and the acceptance rate. We have defined all the characteristics in The inclusion criteria (Line 186 to 198).

The following section needs revised:
"Heterogeneity for the meta-analysis will be tested using the I2 statistic. The reliability of the I2 estimation will be confirmed using a 95% confidence interval. If the interventions, populations, and outcomes are homogenous, a meta-analysis will be performed."
Given the nature of telehealth interventions (which have multiple components), and the broad inclusion criteria of the review, it is inconceivable that the interventions would be homogeneous. Indeed, meta-regression (as proposed) would be a tool to explain heterogeneity. The key question appears to be whither the included studies (in terms of interventions, populations, and outcomes) are too heterogeneous for a meta-analysis to be a meaningful or useful synthesis. The issues highlighted above regarding the measurement of adherence will be important considerations for this judgement. The decision of whither to perform the meta-analysis should surely be made on these grounds and not based on the I2 statistic (by which point the meta-analysis has already been performed).
AUTHORS' RESPONSE: The data analysis section has been revised according to the reviewer's comments (Line 338 to 343)
"Statistical Analysis System (SAS) software will be used to run regression models. Possible variables associated with rates will be categorized and tested using the univariate analysis model. Subsequently, a random effect meta regression analysis will be used to estimate the effects of the participant, study, and intervention characteristics on acceptance, adherence, dropout rates. A separate model analysis will be conducted for each rate. If we are restricted in this regard and unable to perform a meta-analysis, we will synthesize and summarize the results narratively".

Discussion:
The authors state that "To the best of our knowledge, this will be the first systematic review estimating acceptance, adherence, and dropout rates of COPD populations participating in telehealth and/or telemonitoring, as well as the associated factors influencing these rates." However I don't think this is the case. The authors then cite the review by Cruz et al, which does summarise adherence and dropout rates in COPD telemonitoring interventions. Cruz et al also summarise reasons for dropout, as well as factors in the interventions related to either lack of adherence or to dropout. I do not think that the author's claim is accurate.
Similarly, the authors state: "Previous systematic reviews and meta-analyses were unable to provide information about effective elements contributing to better acceptance and adherence rates; in

contrast, our current study will try to explore elements of telehealth and/or telemonitoring that impact acceptance, adherence, and dropout rates". Factors linked with adherence, and satisfaction, are discussed with the Cruz et al review, as the authors cite.
It seems to me that the difference in the proposed review is the use of meta-regression to quantify the association between patient/intervention factors and dropout adherence. This would appear to be a new approach, not undertaken by previous reviewers. However, from the current text it is not clear that this is what the authors are highlighting as the novel aspect of their review.

AUTHORS' RESPONSE: We appreciate the detailed feedback. We have rephrased text in the Discussion section to incorporate the aforementioned suggestions. We agree that the distinguishing feature about this review is the use of met-regression to quantify the relationship between factors and rates
(Line 359 to 367)
"information about effective elements contributing to better acceptance, adherence and dropout rates using meta-regression analysis; in contrast, the current study will try to explore elements of telehealth that impact acceptance, adherence, and dropout rates [27, 28]. Our systematic review will analyze the literature using meta-analysis, and in doing so provide the advantage of having an opportunity to investigate and understand the correlation between pertinent factors and acceptance, adherence, and dropout rates. We will provide specific information about the trials' characteristics (RCTs vs. non-RCTs), population characteristics (i.e. mild severity vs. moderate severity), and intervention characteristics (i.e., primary care settings vs. specialty care settings), as well as how such information may facilitate users' adherence to telehealth interventions".

Additional files:
The authors included a PRISMA checklist, however surely a PRISMA-P checklist, specific to protocols, would be the more appropriate checklist to provide.
AUTHORS' RESPONSE: The PRISMA-P checklist has now been added to the resubmission.

References:
The references require proof-reading. An electronic reference manager has been used without checking the formatting of the references (e.g. reference 1, where the name of the Global Initiative for Chronic Obstructive Lung Disease has been treated as initials).
Also some of the systematic reviews referenced are quite out of date, and more recent reviews exist.

AUTHORS' RESPONSE: The reference list has been updated and reviewed (Line 417 , 421,424, 433,446,452, 459, 474, 479, 488, 491,497, 519,524,532,and 543)

VERSION 2 – REVIEW

REVIEWER	Sian Russell Institute of Health & Society, Newcastle University, England, UK
REVIEW RETURNED	08-Jan-2019

GENERAL COMMENTS	The authors have not fully addressed my comments on the original draft, which is a shame. The purpose of my comments was to suggest issues that the authors could consider that could add nuance to their findings. I can, however, accept the author's choice to keep their protocol more streamlined and they appear to have responded appropriately the the concerns of reviewer 2.

REVIEWER	Peter Hanlon

	University of Glasgow, UK
REVIEW RETURNED	04-Jan-2019

GENERAL COMMENTS	Thank you for the opportunity to review the revision of this interesting review protocol. The authors have responded well to the suggestions and I think have strengthened the protocol, which is now clearer. One minor issue is the formatting of the referencing. For example reference 1 still requires attention. I suspect this is an issue with referencing software and not checking/reformatting.