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Telehealth for Chronic Obstructive Pulmonary Disease (COPD) Patients: a Systematic Review and Meta-analysis Protocol

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Telehealth for Chronic Obstructive Pulmonary Disease (COPD) Patients: a Systematic Review and Meta-analysis Protocol

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ABSTRACT

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a highly prevalent chronic disease characterized by persistent respiratory symptoms. A major focus of COPD interventional studies is directed towards prevention of exacerbations leading to hospital readmissions. Telehealth as a method of remote patient monitoring and care delivery may be implemented to reduce hospital readmissions and improve self-management of chronic disease. Prior reviews have not systematically assessed the efficacies of various telehealth functionalities on COPD patients at different stages of disease severity. We aim to evaluate which COPD telehealth interventions, classified by their functionalities, are most effective in improving COPD patient management measured by both clinical and resource utilization outcomes.

Methods and analysis

We will conduct a systematic review which will include randomized controlled trials comparing the efficacy of telehealth interventions versus standard care in COPD patients with confirmed disease severity based on FEV% levels. Trials will be identified from searches of multiple electronic databases (CENTRAL, MEDLINE, EMBASE and CINAHL). Telehealth is described as remote monitoring and delivery of care where patient data or clinical information is routinely or continuously collected and/or computed, presented to the patient and transferred to a clinical care institution for feedback, triage and intervention by a clinical specialist. Two authors will independently screen articles for inclusion, assess risk of bias and extract data. We will pool studies into a meta-analysis if the interventions, technologies, participants and underlying clinical questions are homogenous enough. We will use a random-effects model, as we expect some heterogeneity between interventions. In cases where a meta-analysis is not possible, we will synthesize findings qualitatively. We will also assess the quality of evidence for the main outcomes using GRADE.

Ethics and Dissemination

Research ethics approval is not required. The findings will be disseminated through publication in a peer-reviewed journal.

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294

Strengths and limitations of this study

- This systematic review will update the knowledge on efficacy of telehealth interventions in management of COPD patients. We will propose to look at all telehealth applications and functionalities and to provide a typology for the telehealth interventions of the COPD patient's remote service delivery
- This article will help clinicians working in the COPD field to select the most effective telehealth intervention for the different COPD severity groups to improve COPD management;
- Despite considerable heterogeneity in reporting in published clinical trials and limited data, we expect to demonstrate considerable promise for the successful implementation of telehealth services to remotely manage COPD patients.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a highly prevalent disease that is characterized by persistent respiratory symptoms due to airway and/or alveolar abnormalities caused by significant exposure to noxious particles or gases.[1] COPD results in high societal healthcare expenditures and resource utilization.[2,3] The estimated annual economic burden of COPD in terms of conventional direct (healthcare utilization) and indirect (lost production) costs is 141.4 billion euros in Europe (2011).[4] The costs of COPD are strongly related to disease severity. The major components of direct costs are hospitalizations (for very severe COPD) and drugs (all other severity stages).[5]
Telehealth involves the remote exchange of data between patients and healthcare professionals as part of the patient's diagnosis and healthcare management.[6,7] Telehealth interventions for management of COPD patients were introduced more than 20 years ago, but the evidence base for the value of telehealth is limited and contradictory.[8] Published systematic reviews on telehealth interventions for the clinical management of COPD patients only focus on the application of specific services (e.g. hospital to home)[9,10], specific functions (e.g. smart phone intervention)[11,12] or the experience of clinical professionals (e.g. nursing professionals).[13]Even if a recent systematic reviews focuses on a particular telehealth application or functionality, a lack of established taxonomy in the field greatly limits their value for clinicians. In our systematic review, we propose to look at all telehealth applications and functionalities and to provide a typology for the telehealth interventions of the COPD patient's remote service delivery. This will allow us to describe the use of different telehealth functions across a range of healthcare fields, from health behavior change interventions to remote patients monitoring such as vital signs observations. This allows us to focus on similarities in mechanisms of action for a particular device or function and to suggest where it might be useful in new remote service selections for the COPD patients' clinical management. A number of systematic reviews have evaluated the efficacy of telehealth interventions on clinical outcomes in patients diagnosed with COPD. However, the findings vary widely; they are diverse[13,14] and of poor methodological quality.[15] This may be due to lack of reporting on important patient characteristics, lack of validated data collection instruments and lack of high quality reporting. [12,14] However, telehealth interventions are very complex to evaluate because of their dynamic nature: they are designed for a very specific setting and efficacy is impacted by the behavior of those delivering (resistance to new ICT applications) as well as receiving the intervention (non-adherence to intervention).[15,16] This lack of evidence is a barrier for further deployment or scaling up of telehealth services.

OBJECTIVES

The aim of this systematic review will be 1) describe how telehealth may be used for the remote management of COPD patients that have been evaluated in randomized controlled trials; 2) derive typology on these telehealth solutions for COPD patients remote management based on their application for clinical services and specific functionalities 3) assess the effectiveness of telehealth solutions for improving health and health service outcomes in COPD patients stratified according to disease severity.

METHODS

This systematic review protocol was registered in the Prospero Registry (Number obtained: CRD42018083671). The systematic review will be conducted according to the Cochrane Handbook for Systematic Reviews of Interventions[17] and reported according to the PRISMA-P (the Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols 2015) methodology.[18,19]

Eligibility criteria

The PICO components (Population, Intervention, Comparator and Outcomes) and study design were used to define study selection criteria.

Participants
Eligible for inclusion are studies involving patients with a COPD diagnosis based on reported FEV1% (or reported as a COPD GOLD grade). [1] If a reported patient population is mixed, for instance including patients presenting with asthma, this study will be excluded.[20] Studies that include additional medical conditions as well as COPD will be retained if the outcomes specific to the COPD group are reported separately.

Intervention group: telehealth services
The intervention group is described as patients receiving telehealth as part of a COPD management plan. Telehealth involves the remote exchange of data between a patient and healthcare professionals as part of the patient's diagnosis and healthcare management.[6,7]
The telehealth intervention can involve any IT tool designed for clinical support: an assessment, consultation, triage or intervention performed by the care provider (telemedicine nurse, clinician or service provider, or back-office feedback).
The telehealth component of the management plan may consist of the following functional components: care provider consultations, vital signs monitoring, education/prevention modules, lifestyle coaching, etc. We will exclude studies reporting home mechanical ventilation procedures.

Comparator: standard care
The definition of standard care, if retrievable, will be reported. Standard care is controversial and may vary widely between hospitals and countries[21] therefore we include the study if a description of the care has been provided without further restrictions on the type of standard care (care without telehealth component).

Study design
Eligible studies for inclusion are:
Randomized clinical trials (RCTs);
Cluster RCTs;
Controlled trials, if they have a randomization component (feasibility and pilots studies are included[22])

Search strategy
Electronic databases
We will identify studies through systematic searches of the following electronic databases: MEDLINE via PubMed, EMBASE, The Cochrane Central Register of Controlled Trials (CENTRAL) and CINAHL. The preliminary search strategy for CINAHL (Appendix 1) will be adapted for use in the other databases. The Cochrane sensitivity-maximizing RCT filter will be applied to MEDLINE and adaptations of it to the other databases except CENTRAL. We will search all databases from 2000 to the present and will impose no restriction on language.

Hand searching literature
We will supplement the main search strategy with manual searches of reference lists of all relevant primary studies and systematic reviews to identify any additional studies not captured by our original search. We will also contact field experts and search the ClinicalTrials.gov Registry for potentially eligible studies.

Reference management
The bibliographic details of all retrieved articles will be stored in Mendeley, a reference management software package. Duplicates will be identified and removed using the Mendeley reference management software.

Study selection and data extraction strategy

Screening and selection of studies

Two authors will independently assess the title and abstract of all identified papers as well as the articles that passed the title and abstract screening based on pre-defined eligibility criteria. Any disagreements between reviewers will be resolved through discussion or adjudication by a third reviewer. The data extraction form[23] will be adapted to our systematic review and adjusted for optimal data collection through a pilot of several full texts of several included RCTs. Any disagreement arising in the full text screening stage between reviewers will be resolved through discussion. If agreement cannot be reached, a third reviewer will mediate. All studies that do not fulfil all of the criteria will be excluded and the reasons for their exclusion will be noted. We will identify and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review.

Data extraction and management

Data will be independently extracted from the included studies by the first author (VG) and recorded on a predesigned extraction form. A second reviewer will check the data for consistency against the published manuscripts to identify any errors. In case of missing data, we will contact the corresponding authors of the included studies where possible. Among other elements, the following data will be captured from studies to be included in the review:

Study characteristics: study design, comparator, duration, sample size, setting, country, participant characteristics: age and sex; FEV%, comorbidities, asthma profile (with/without), smoking status

Intervention characteristics: functionality description (goal, technical details, how service works), how data is collected, how data is reported, adverse events reporting, sustainability of intervention.

Feedback criteria: healthcare provider; timing: synchronous or asynchronous; nature: manual or automated;

Outcomes: Clinical outcomes collection

Although we will extract all reported outcomes, we will report on the most common outcomes for COPD clinical trials only.[24]

Primary outcomes

Hospital readmissions. COPD-related hospitalizations and all-cause hospitalizations will be reported. We will differentiate between count and dichotomous data (e.g. the number of participants in each intervention group who experience at least one event vs. number of events in each intervention group).

Exacerbations – Exacerbation rate is a commonly reported outcome.[24] The definition of exacerbations and their severity needs to be standardized to allow comparisons between different interventions in different settings.[25,26] As exacerbations can be reported in different ways, the data collection form allows the following to be recorded: number of exacerbations, or exacerbation rate and etc. (it can be classified based on patient disease severity as well).

All-cause mortality. Number of patients who died during the study per study group.

Secondary outcomes

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 validated measurement).

COPD related costs (total and program related; if available also indirect costs).

Risk of bias assessment

Two authors will independently assess risk of bias for each study included in the review using the Cochrane Collaboration Risk of Bias criteria, which assess the following domains: sequence generation; allocation concealment; blinding of participants and personnel (performance bias);

blinding of outcome assessment, whether incomplete outcome data were adequately addressed; and whether there was selective outcome reporting.[27]
In accordance with the Cochrane risk of bias assessment tool, we will grade each potential source of bias as high, low or unclear and provide a quote from the study report together with a justification for our judgment in the 'Risk of bias' table.

Data synthesis
Risk ratios (RR) will be determined for outcome measures of dichotomous variables. Where possible, RR will be pooled using a random effects model. The standard mean difference will be calculated for continuous data variables in the absence of significant clinical heterogeneity.[28]Statistical heterogeneity will be analyzed using the I2 statistic. To confirm reliability of the summary estimate, 95% confidence intervals (CI) will be calculated. If there is important clinical heterogeneity among the included studies or data are reported using different scales, we will summarize the findings of the studies narratively by direction of effect and/or statistical significance.

Quality of Evidence Assessment
A Quality of Evidence Assessment is performed to determine the extent to which we can be confident that an estimate of effect is close to the true quantity/value, i.e. it is not distorted by internal or external bias within and across studies. The assessment will be done with the GRADE system.[29] Quality of evidence assessment will be performed by outcome of interest.

Dealing with missing data
Authors will be contacted to obtain unreported data.

Assessment of heterogeneity and reporting biases
We will assess clinical heterogeneity between studies by comparing the characteristics of the study populations, interventions and outcome measures. Statistical heterogeneity will be assessed with the I2 and $\chi 2$ (chi-square) statistic measures. The assessment of reporting biases for the primary outcomes of interest will be explored using funnel plots if we are able to pool more than 10 trials per outcome of interest.

DISCUSSION

Overall, the systematic review outlined in this protocol aims to identify, assess and synthesize using meta-analytic methods all available evidence on the effects of telehealth interventions for the management of COPD patients. Our systematic review will evaluate which COPD telehealth interventions, classified by their functionalities, are most effective in improving COPD patient management measured by both clinical and resource utilization outcomes. It will allow better clinical service selection, which aims to tailor the telehealth services to the specific COPD disease severity and patient needs.[30] Based on published randomized clinical trials, it will describe the telehealth solutions usability and efficacy in terms of clinical outcomes and service utilization for the COPD patients' remote management. Clinical outcomes reporting will be focused on the patient profile (comorbidities, FEV%, no asthma cases) which strengthens this systematic review and facilitates the evidence implementation in the future's individual patient service selection procedures. Heterogeneous reporting in trials on telehealth and the limited number of trials for some of the interventions, foreseen based on a scoping search, may limit our ability to draw conclusions on telehealth efficacy following the meta-analysis. The gathered information will help to derive the typology of telehealth solutions for COPD patients' remote management based on their application for the clinical services and specific functionalities

Ethics and dissemination

Violeta Gaveikaite, Steffen Pauws and Helen Schonenberg are employees of Philips research, Eindhoven, the Netherlands. Other authors declare that they have no conflict of interest.
No research ethics approval is required for this systematic review as no confidential patient data will be used. The findings will be disseminated through publication in a peer-reviewed journal.

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Authors' contributions

VG, SK, SP, HS, CF developed the idea and designed the study protocol. VG, SK designed and wrote the search strategy and the first protocol draft; VG, SK, SP planned the data extraction and statistical analysis; HS, IC, SP, JR, NM provided critical insights. All authors have approved and contributed to the final written manuscript.

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Appendix 1: CINAHL data base search

1. (MH "Pulmonary Disease, Chronic Obstructive+")
2. (MH "Lung Diseases, Obstructive")
3. TI (COPD OR COAD OR COBD OR AECB) OR AB (COPD OR COAD OR COBD OR AECB) **7551**
4. TI (chronic airway disease OR chronic pulmonary disease or chronic lung disease or emphysema) OR AB (chronic airway disease OR chronic pulmonary disease or chronic lung disease or emphysema)
5. TI "chronic*" W3 "bronchiti*" OR AB "chronic*" W3 "bronchiti*"
6. TI ("obstruct*" W3 ("pulmonary" OR "airway*" OR "airflow*" OR "lung*" OR "bronch*" OR "respirat*" OR "emphysema*")) OR AB ("obstruct*" W3 ("pulmonary" OR "airway*" OR "airflow*" OR "lung*" OR "bronch*" OR "respirat*" OR "emphysema*"))
7. S1 OR S2 OR S3 OR S4 OR S5 OR S6

8. (MH "Remote Consultation")
9. (MH "Telemedicine")
10. (MH "Telerehabilitation")
11. (MH "Telemetry")
12. (MH "Videoconferencing")
13. (MH "Monitoring, Physiologic")
14. TI (remote monitor* OR remote consult* OR remote care* OR councel*) OR AB (remote monitor* OR remote consult* OR remote care* OR councel*)
15. TI (videoconferenc* OR video group) OR AB (videoconferenc* OR video group)
16. TI (telemetr* OR telemat* OR telemonitor* OR tele-monitor*) OR AB (telemetr* OR telemat* OR telemonitor* OR tele-monitor*)
17. TI (telehome* OR tele-home OR tele home) OR AB (telehome* OR tele-home OR tele home)
18. TI (telenurse* OR telesupport* OR telecommunic*) OR AB (telenurse* OR telesupport* OR telecommunic*)
19. TI telepharmac* OR AB telepharmac*
20. TI (ehealth* OR e health* OR e-health*) OR AB (ehealth* OR e health* OR e-health*)
21. TI (telehealth OR tele health OR tele-health) OR AB (telehealth OR tele health OR tele-health)
22. TI connected health OR AB connected health
23. TI (telemedicine OR tele medicine OR tele-medicine) OR AB (telemedicine OR tele medicine OR tele-medicine)
24. S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23
25. TI (e-coach OR ecoach OR e coach) OR AB (e-coach OR ecoach OR e coach)
26. TI (e-learning OR elearning or e learning) OR AB (e-learning OR elearning or e learning)
27. TI (telemanagem* OR tele-managem*) OR AB (telemanagem* OR tele-managem*)
28. S25 OR S26 OR S27
29. (MH "Decision Support Techniques+")
30. (MH "Drug Therapy, Computer Assisted")
31. (MH "Mobile Applications")
32. (MH "Text Messaging")

33. TI (("cell*" OR "mobile*") W3 "phon*") OR AB (("cell*" OR "mobile*") W3 "phon*")
34. TI (smartphone* OR smart-phone* or mobile phone*) OR AB (smartphone* OR smart-phone* or mobile phone*)
35. TI (m health* OR mhealth* OR m-health* OR mobile health*) OR AB (m health* OR mhealth* OR m-health* OR mobile health*)
36. TI (handheld* OR hand held*) OR AB (handheld* OR hand held*)
37. TI (computer* OR pc OR laptop*) OR AB (computer* OR pc OR laptop*)
38. TI (smart watch* OR smart-watch*) OR AB (smart watch* OR smart-watch*)
39. TI tablet* OR AB tablet*
40. S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40
41. S24 OR S28 OR S41

42. S42 AND S7

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ABSTRACT

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a highly prevalent chronic disease characterized by persistent respiratory symptoms. A focus of COPD interventional studies is directed towards prevention of exacerbations leading to hospital readmissions. Telehealth as a method of remote patient monitoring and care delivery may be implemented to reduce hospital readmissions and improve self-management of disease. Prior reviews have not systematically assessed the efficacies of various telehealth functionalities on COPD patients at different stages of disease severity. We aim to evaluate which COPD telehealth interventions, classified by their functionalities, are most effective in improving COPD patient management measured by both clinical and resource utilization outcomes.

Methods and analysis

We will conduct a systematic review which will include randomized controlled trials comparing the efficacy of telehealth interventions versus standard care in COPD patients with confirmed disease severity based on FEV% levels. An electronic search strategy will be used to identify trials published since 2000 in MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL),CINHAL. Telehealth is described as remote monitoring and delivery of care where patient data/clinical information is routinely or continuously collected and/or processed, presented to the patient, and transferred to a clinical care institution for feedback, triage, and intervention by a clinical specialist. Two authors will independently screen articles for inclusion, assess risk of bias, and extract data. We will merge studies into a meta-analysis if the interventions, technologies, participants, and underlying clinical questions are homogenous enough. We will use a random-effects model, as we expect some heterogeneity between interventions. In cases where a meta-analysis is not possible, we will synthesize findings narratively. We will assess the quality of the evidence for the main outcomes using GRADE.

Ethics and Dissemination

Research ethics approval is not required. The findings will be disseminated through publication in a peer-reviewed journal.

Word count

300

Strengths and limitations of this study

- This systematic review will update the knowledge on efficacy of telehealth interventions in management of COPD patients. We will propose to look at all telehealth applications and functionalities and to provide a typology for the telehealth interventions of the COPD patient's remote service delivery
- This article will help clinicians working in the COPD field to select the most effective telehealth intervention for the different COPD severity groups to improve COPD management;
- We expect to provide robust evidence supporting the successful implementation of telehealth services to remotely manage COPD patients, despite considerable heterogeneity in the reporting of published clinical trials and limited data.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a highly prevalent disease that is characterized by persistent respiratory symptoms due to airway and/or alveolar abnormalities caused by significant exposure to noxious particles or gases.[1] COPD results in high societal healthcare expenditures and resource utilization.[2, 3] The estimated annual economic burden of COPD in terms of conventional direct costs (healthcare utilization) and indirect costs (lost production) is approximately 141.4 billion euros in Europe (2011).[4] Where the main costs of COPD are strongly related to disease severity, the other major components of direct costs are hospitalizations (for very severe COPD) and medication (all other severity stages).[5]

Telehealth involves the remote exchange of data between patients and healthcare professionals as part of the patient's disease status and healthcare management.[6, 7] Telehealth interventions for management of COPD patients were introduced more than 20 years ago, but the evidence for the value of telehealth is limited and contradictory.[8] Published systematic reviews on telehealth interventions for the clinical management of COPD patients only focus on the application of specific services (e.g. '*hospital to home*')[9, 10], specific functions (e.g. smart phone intervention)[11, 12], or the experience of clinical professionals (e.g. nursing professionals).[13]Even if recent systematic reviews [14–16] focus on a particular telehealth application or functionality, a lack of established taxonomy in the field greatly limits their value for clinicians. In our systematic review, we propose to look at all telehealth applications and functionalities, as well as to provide a typology for the telehealth interventions of the COPD patient's remote service delivery. This will allow us to describe the use of different telehealth functions across a range of healthcare fields, from health behavior change interventions to remote patients monitoring such as vital signs observations. This allows us to focus on similarities in mechanisms of action for a particular device or function and to suggest where it might be useful in new remote service selections; all towards the clinical management of COPD patients. A number of systematic reviews have evaluated the efficacy of telehealth interventions on clinical outcomes in patients diagnosed with COPD.[14–16] However, the findings vary widely; they are diverse[13, 17], and of poor methodological quality.[18] This may be due to lack of reporting on important patient characteristics, lack of validated data collection instruments, and lack of high quality reporting. [12, 17] However, telehealth interventions are very complex to evaluate because of their dynamic nature; they are designed for a very specific setting; their efficacy is impacted by the behavior of those delivering who might be resistant to new ICT applications, as well as those receiving the intervention who might fail to comply.[18, 19] This lack of evidence acts as a barrier for further deployment or scaling up of telehealth services.

OBJECTIVES

The aim of this systematic review will be 1) describe how telehealth may be used for the remote management of COPD patients that have been evaluated in randomized controlled trials, 2) derive typology on these telehealth solutions for COPD patients' remote management based on their application for clinical services and specific functionalities, and 3) assess the effectiveness of telehealth solutions for improving health and health service outcomes in COPD patients stratified according to disease severity.

METHODS

This systematic review protocol was registered in the Prospero Registry (Number obtained: CRD42018083671). The systematic review will be conducted according to the Cochrane Handbook for Systematic Reviews of Interventions [20] and reported according to the PRISMA-P (the Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols 2015) methodology.[21], [22]

Eligibility criteria

The PICO components (Population, Intervention, Comparator and Outcomes) and study design were used to define study selection criteria for eligibility.

Participants

Eligible for inclusion are studies involving patients with a COPD diagnosis based on reported FEV_1% (or reported as a COPD GOLD grade). [1] If a reported patient population is mixed, for instance including patients presenting with asthma, this study will be excluded.[23] Studies that include additional medical conditions as well as COPD will be retained if the outcomes specific to the COPD group are reported separately.

Intervention group: telehealth services

The intervention group is described as patients receiving telehealth as part of a COPD management plan. Telehealth involves the remote exchange of data between a patient and healthcare professionals as part of the patient's disease status and healthcare management.[6, 7]
The telehealth intervention can involve any IT tool designed for clinical support: an assessment, consultation, triage or intervention performed by the care provider (telemedicine nurse, clinician or service provider, or back-office feedback).
The telehealth component of the management plan may consist of the following functional components: care provider consultations, vital signs monitoring, education/prevention modules, lifestyle coaching, etc. We will exclude studies reporting home mechanical ventilation procedures.

Comparator: standard care

The definition of standard care, if retrievable, will be reported. Standard care is controversial and may vary widely between hospitals and countries[24] therefore we include the study if a description of the care has been provided without further restrictions on the type of standard care (care without telehealth component).

Study design

Eligible studies for inclusion are:

- Randomized clinical trials (RCTs);
- Cluster RCTs;
- Controlled trials, if they have a randomization component (feasibility and pilots studies are included[25])

Search strategy

Electronic databases

Studies will be identified through systematic searches of the following electronic databases: MEDLINE via PubMed, EMBASE, The Cochrane Central Register of Controlled Trials (CENTRAL) and CINAHL. The preliminary search strategy for CINAHL (Appendix 1) will be adapted for use in the other databases. The Cochrane sensitivity-maximizing RCT filter will be applied to MEDLINE and adaptations of it to the other databases except CENTRAL. We will search all databases from 2000 to the present and will impose no restriction on language.

Hand searching literature

We will supplement the main search strategy with manual searches of reference lists of all relevant primary studies and systematic reviews to identify any additional studies not captured by our original search. We will also contact field experts and search the ClinicalTrials.gov Registry for potentially eligible studies.

Reference management

The bibliographic details of all retrieved articles will be stored in Mendeley, a reference management software package. Duplicates will be identified and removed using the Mendeley reference management software.

Study selection and data extraction strategy

Screening and selection of studies

Two authors will independently assess the title and abstract of all identified papers as well as the articles that passed the title and abstract screening based on pre-defined eligibility criteria. Any disagreements between reviewers will be resolved through discussion or adjudication by a third reviewer. The data extraction form [26] will be adapted to our systematic review and adjusted for optimal data collection through a pilot of several full texts of several included RCTs. Any disagreement arising in the full text screening stage between reviewers will be resolved through discussion. If agreement cannot be reached, a third reviewer will mediate. All studies that do not fulfil all of the criteria will be excluded and the reasons for their exclusion will be noted. We will identify and collate multiple reports of the same study so that each study is the unit of interest in the review, rather than each report.

Data extraction and management

Data will be independently extracted from the included studies by the first author (VG) and recorded on a predesigned extraction form. A second reviewer will check the data for consistency against the published manuscripts to identify any errors. In case of missing data, we will contact the corresponding authors of the included studies where possible. Among other elements, the following data will be captured from studies to be included in the review:

1) Study characteristics: study design, comparator, duration, sample size, setting, country;
2) Participant characteristics: age and sex; FEV%, comorbidities, asthma profile (with/without), smoking status
3) Intervention characteristics: functionality description (goal, technical details, how service works), how data is collected, how data is reported, adverse events reporting, sustainability of intervention, and
4) Feedback criteria: healthcare provider; timing: synchronous or asynchronous; nature: manual or automated;

Valuable qualitative data, such as patient safety will be extracted.

Outcomes: Clinical outcomes collection

Six outcomes, commonly reported in COPD clinical trials, were selected to provide relevant information regarding our research question. Studies will be included if at least one of these six outcomes were reported.[27]

Primary outcomes

Hospital readmissions: COPD-related hospitalizations and hospitalization causes will be reported. We will differentiate between count and dichotomous data (e.g. number of events in each intervention group vs the number of participants in each intervention group who experience at least one event).
Exacerbations: Exacerbation rate is a commonly reported outcome.[27] The definition of exacerbations and their severity needs to be standardized to allow comparisons between different interventions in different settings.[28, 29] As exacerbations can be reported in different ways, the data collection form allows the following to be recorded: number of exacerbations, or exacerbation rate (e.g. it can be classified based on patient disease severity as well).
All-cause mortality: Number of patients who died during the study per study group.

Secondary outcomes

Health-related Quality of Life (HRQoL): disease specific or non-disease specific quality of life reported by a validated instrument.

Physical activity measurements: any type reported by validated measurement.
COPD related costs: total and program related and indirect costs if available.

Risk of bias assessment

Two authors will independently assess risk of bias for each study included in the review using the Cochrane Collaboration Risk of Bias criteria, which assesses the following domains: sequence generation, allocation concealment, blinding of participants and personnel (performance bias), blinding of outcome assessment, whether incomplete outcome data were adequately addressed, and whether there was selective outcome reporting.[30]
In accordance with the Cochrane risk of bias assessment tool, we will grade each potential source of bias as high, low or unclear and provide a quote from the study report together with a justification for our judgment in the 'Risk of bias' table.

Data synthesis

Risk Ratios (RR) will be determined for outcome measures of dichotomous variables. Where possible, RR will be pooled using a random effects model. The standard mean difference will be calculated for continuous data variables in the absence of significant clinical heterogeneity.[31] Statistical heterogeneity will be analyzed using the I2 statistic. To confirm reliability of the summary estimate, 95% confidence intervals (CI) will be calculated. If there is important clinical heterogeneity among the included studies, or data are reported using different scales, we will provide a qualitative summary of the findings of the studies by direction of effect and/or statistical significance.

Quality of Evidence Assessment

A Quality of Evidence Assessment is performed to determine the extent to which we can be confident that an estimate of effect is close to the true quantity/value, i.e. it is not distorted by internal or external bias within and across studies. The assessment will be done with the GRADE system.[32] Quality of evidence assessment will be performed by outcome of interest.

Dealing with missing data

Authors will be contacted to obtain unreported data.

Assessment of heterogeneity and reporting biases

We will assess clinical heterogeneity between studies by comparing the characteristics of the study populations, interventions, and outcome measures. Statistical heterogeneity will be assessed with the I2 and χ^2 (chi-square) statistic measures. The assessment of reporting biases for the primary outcomes of interest will be explored using funnel plots if we are able to pool more than 10 trials per outcome of interest.

Patients and Public Involvement

This is a protocol for a systematic review of prior randomized controlled trials. Therefore, no human subjects/patients were directly involved in the design and/or execution of this research study. A plain language summary with the main findings of the review will be provided in a straightforward style that can be understood by consumers of health care.

DISCUSSION

Overall, the systematic review outlined in this protocol aims to identify, assess, and synthesize using meta-analytic methods available in the evidence of the effects of telehealth interventions for the management of COPD patients. Our systematic review will evaluate which COPD telehealth interventions, classified by their functionalities, are most effective in improving COPD patient management measured by both clinical and resource utilization outcomes. It will allow better clinical service selection, which aims to tailor the telehealth services to the specific COPD disease severity and patient needs.[33] Based on published randomized clinical trials, it will describe the telehealth solutions usability and efficacy in terms of clinical outcomes and service utilization for the COPD patients' remote management. Clinical outcomes reporting will be focused on the patient profile (comorbidities, FEV%, and no asthma cases) which strengthens this systematic review and facilitates the evidence implementation in a future individual patient service selection procedure. Heterogeneous reporting in trials on telehealth, and the limited number of trials for some of the interventions, which are foreseen based on a scoping search, may limit our ability to draw conclusions on telehealth efficacy following the meta-analysis. The gathered information will help to derive the typology of telehealth solutions for COPD patients' remote management based on their application for the clinical services and specific functionalities

Ethics and dissemination

Violeta Gaveikaite, Steffen Pauws and Helen Schonenberg are employees of Philips research, Eindhoven, the Netherlands. Other authors declare that they have no conflict of interest.
No research ethics approval is required for this systematic review as no confidential patient data will be used. The findings will be disseminated through publication in a peer-reviewed journal.

Acknowledgements

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Authors' contributions

VG, SK, SP, HS, CF, NM developed the idea and designed the study protocol. VG, SK designed and wrote the search strategy and the first protocol draft; VG, SK, SP planned the data extraction and statistical analysis; HS, IC, SP, JR, NM provided critical insights. All authors have approved and contributed to the final written manuscript.

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Appendix 1: CINAHL data base search

1. (MH "Pulmonary Disease, Chronic Obstructive+")
2. (MH "Lung Diseases, Obstructive")
3. TI (COPD OR COAD OR COBD OR AECB) OR AB (COPD OR COAD OR COBD OR AECB) **7551**
4. TI (chronic airway disease OR chronic pulmonary disease or chronic lung disease or emphysema) OR AB (chronic airway disease OR chronic pulmonary disease or chronic lung disease or emphysema)
5. TI "chronic*" W3 "bronchiti*" OR AB "chronic*" W3 "bronchiti*"
6. TI ("obstruct*" W3 ("pulmonary" OR "airway*" OR "airflow*" OR "lung*" OR "bronch*" OR "respirat*" OR "emphysema*")) OR AB ("obstruct*" W3 ("pulmonary" OR "airway*" OR "airflow*" OR "lung*" OR "bronch*" OR "respirat*" OR "emphysema*"))
7. S1 OR S2 OR S3 OR S4 OR S5 OR S6

8. (MH "Remote Consultation")
9. (MH "Telemedicine")
10. (MH "Telerehabilitation")
11. (MH "Telemetry")
12. (MH "Videoconferencing")
13. (MH "Monitoring, Physiologic")
14. TI (remote monitor* OR remote consult* OR remote care* OR councel*) OR AB (remote monitor* OR remote consult* OR remote care* OR councel*)
15. TI (videoconferenc* OR video group) OR AB (videoconferenc* OR video group)
16. TI (telemetr* OR telemat* OR telemonitor* OR tele-monitor*) OR AB (telemetr* OR telemat* OR telemonitor* OR tele-monitor*)
17. TI (telehome* OR tele-home OR tele home) OR AB (telehome* OR tele-home OR tele home)
18. TI (telenurse* OR telesupport* OR telecommunic*) OR AB (telenurse* OR telesupport* OR telecommunic*)
19. TI telepharmac* OR AB telepharmac*
20. TI (ehealth* OR e health* OR e-health*) OR AB (ehealth* OR e health* OR e-health*)
21. TI (telehealth OR tele health OR tele-health) OR AB (telehealth OR tele health OR tele-health)
22. TI connected health OR AB connected health
23. TI (telemedicine OR tele medicine OR tele-medicine) OR AB (telemedicine OR tele medicine OR tele-medicine)
24. S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23
25. TI (e-coach OR ecoach OR e coach) OR AB (e-coach OR ecoach OR e coach)
26. TI (e-learning OR elearning or e learning) OR AB (e-learning OR elearning or e learning)
27. TI (telemanagem* OR tele-managem*) OR AB (telemanagem* OR tele-managem*)
28. S25 OR S26 OR S27
29. (MH "Decision Support Techniques+")
30. (MH "Drug Therapy, Computer Assisted")
31. (MH "Mobile Applications")
32. (MH "Text Messaging")

33. TI (("cell*" OR "mobile*") W3 "phon*") OR AB (("cell*" OR "mobile*") W3 "phon*")
34. TI (smartphone* OR smart-phone* or mobile phone*) OR AB (smartphone* OR smart-phone* or mobile phone*)
35. TI (m health* OR mhealth* OR m-health* OR mobile health*) OR AB (m health* OR mhealth* OR m-health* OR mobile health*)
36. TI (handheld* OR hand held*) OR AB (handheld* OR hand held*)
37. TI (computer* OR pc OR laptop*) OR AB (computer* OR pc OR laptop*)
38. TI (smart watch* OR smart-watch*) OR AB (smart watch* OR smart-watch*)
39. TI tablet* OR AB tablet*
40. S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40
41. S24 OR S28 OR S41

42. S42 AND S7

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Page (in the submitted manuscript)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	(CRD42018083671) 1,4
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	9
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	9
Sponsor	5b	Provide name for the review funder and/or sponsor	9
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	9
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	4-5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	12-13
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	6

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) 6
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators 6
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications 6
Outcomes and prioritization	13	6
Risk of bias in individual studies	14	6
Data synthesis	15a	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale 6-7
	15b	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis 6-7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) 6-7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned 7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies 6-7
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) 7

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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