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Review article

A systematic map and in-depth review of European telehealth interventions efficacy for chronic obstructive pulmonary disease

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ABSTRACT

Background: Evidence to support the implementation of telehealth (TH) interventions in the management of chronic obstructive pulmonary disease (COPD) varies throughout Europe. Despite more than ten years of TH research in COPD management, it is still not possible to define which TH interventions are beneficial to which patient group. Therefore, informing policymakers on TH implementation is complicated. We aimed to examine the provision and efficacy of TH for COPD management to guide future decision-making.

Methods: A mapping study of twelve systematic reviews of TH interventions for COPD management was conducted. This was followed by an in-depth review of fourteen clinical trials performed in Europe extracted from the systematic reviews. Efficacy outcomes for COPD management were synthesized.

Results: The mapping study revealed that systematic reviews with a meta-analysis often report positive clinical outcomes. Despite this, we identified a lack of pragmatic trial design affecting the synthesis of reported outcomes. The in-depth review visualized outcomes for three TH categories, which revealed a plethora of heterogeneous outcomes. Suggestions for reporting within these three outcomes are synthesized as targets for future empirical research reporting.

Conclusion: The present study indicates the need for more standardized and updated systematic reviews. Policymakers should advocate for improved TH trial designs, focusing on the entire intervention's adoption process evaluation. One of the policymakers' priorities should be the harmonization of the outcome sets, which would be considered suitable for deciding about subsequent reimbursement. We propose possible outcome sets in three TH categories which could be used for discussion with stakeholders.

1. Background

Based on a recent Global Burden of Disease Study, by 2030, chronic obstructive pulmonary disease (COPD) will be the third leading cause of death worldwide [1]. COPD is a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms. These symptoms are the effect of significant exposure to noxious particles or gases resulting in airway and/or alveolar abnormalities that limit airflow [2]. Due to the increase in worldwide prevalence, and an aging population, COPD accounts for a substantial economic burden. It is evident that improved care services are necessary [3].

The World Health Organization describes telehealth (TH) as “the use of telecommunications and virtual technology to deliver healthcare outside of traditional healthcare facilities” [4]. TH interventions for COPD patient management have been introduced to help prevent acute COPD related exacerbations leading to hospital admission (AECOPD)

Abbreviations: COPD, chronic obstructive pulmonary disease; TH, telehealth; SR, Systematic review; AECOPD, acute COPD related exacerbations leading to hospital admission; PRO, patient-related outcomes; HUO, healthcare utilization outcomes; ERS, the European Respiratory Society; ATS, American Thoracic Society; GOLD, global initiative for chronic lung disease; HRQOL, health related quality of life

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through timely detection of health status deterioration [5]. Moreover, TH may help patients maintain better self-management [6], for instance, by supporting the training of a suitable physical activity regime [7]. Furthermore, TH is expected to be a cost-saving healthcare service alternative, enabling its introduction to Europe [8].

TH interventions as part of COPD care management have been the topic of various systematic reviews [5,7,9]. Systematic reviews (SRs) are considered to be the highest level of evidence synthesis and may be used to inform clinical practice and steer policy decisions [10]. In a SR, results of several individual clinical trials are amalgamated into a cohesive summary. Strict inclusion and exclusion criteria for trials are implemented to avoid bias and minimize random errors [11]. The SRs conducted in recent years have concluded that TH is promising as a component of continuous care management, and has a positive effect on physical activity and the education delivery level in COPD [7,12,13]. However, some SRs report only limited evidence with positive effects, prompting authors not to recommend implementation of TH for COPD management [9]. A positive effect, if present, may be obscured by limited trial design which inherently produces results with limited value [14]. Considering the diverse nature of TH interventions as well as recent calls to evaluate them as part of a complex intervention framework [15], more research is needed to improve our understanding of why particular interventions are or are not successful [16].

Despite the promise of TH, current European guidelines are reluctant to recommend them for COPD patient management primarily due to the conflicting results published in literature [2]. Only the UK adopted "The National Institute for Health and Care Excellence" (NICE) guidelines consider routine TH monitoring of physiological status as a potential part of COPD patient management plan. However, TH implementation in this setting has not been recommended [17]. Moreover, the NICE guidelines do not consider the possibility that other supporting interventions, such as short-term monitoring following hospital discharge, may be of benefit [17]. However, new TH trials considering COPD patient management are continually being published [18]. Regular review and reporting of TH trials remains of considerable interest to healthcare policymakers [19].

As available SRs to date cannot provide a comprehensive or consistent summary of TH benefits, a different approach is necessary to appraise the value of TH. The present study aimed to address this gap by following a two-phase approach to obtain an aggregate view of the TH interventions provision and efficacy in COPD management. Ultimately, the objectives are to provide policymakers with a systematic map of the different available TH interventions for COPD patients and an in-depth review of how TH influences outcomes for patients, as well as, healthcare utilization and cost in Europe.

2. Material and methods

In this study, a two-phase process was conducted to first systematically map empirical research followed by an in-depth synthesis of the relevant evidence. This methodological approach has been adopted from an Evidence for Policy and Practice Information and Coordinating Centre (EPPI-Centre) article [20]. Phase I consisted of conducting a search for SRs, selecting studies based on strict inclusion and exclusion criteria, and finally carrying out a critical appraisal for quality assessment. Phase II consisted of extraction of the clinical trials from the included SRs in phase I, then narrowing it down to a subset of trials based on inclusion criteria, and a synthesis of quantitative outcomes in a qualitative representation of TH efficacy.

Mapping reviews are a tool to offer policymakers, practitioners and researchers an explicit and transparent means of identifying narrower policy and practice-relevant review questions [21]. They are distinguishable from SRs as they do not follow guidelines provided by the Cochrane Collaboration [22]. The mapping review can be used as a methodological tool to narrow the focus of a research question and rationalize the most pragmatic approach for the next stage of the study, an in-depth review. An in-depth review shifts from the broader characterization of the SRs to a directed target for syntheses. However, the in-depth review does not intend to offer a meta-analyses as an interpretation of the available articles, rather a syntheses [21].

2.1. Phase I – systematic map

2.1.1. Search strategy and selection criteria

A search strategy was defined and developed by three authors (V. Gaveikaite, C. Grundstrom and I. Chouvarda). A systematic search was performed in the Cochrane Library, EBSCOHost CINAHL and Scopus on July 13th, 2018. The search was conducted in the Title, Abstract, and Keywords functions (keywords could not be searched in EBSCOHost CINAHL) using the Boolean phrase: ((“*chronic obstructive pulmonary disease*” OR “*COPD*”) AND (“*literature review*” OR “*systematic review*” OR “*systematic literature review*” OR “*SR*” or “*SLR*” or “*LR*”) AND “*tele**“)). After the search, all retrieved articles were screened by two authors individually (V. Gaveikaite and C. Grundstrom). Article inclusion conflicts were discussed until a consensus was reached. The inclusion criteria for SRs can be found in Appendix Table A.1.

2.2. Quality assessment and data extraction

Using a critical appraisal checklist to complement the research syntheses [23,24] two authors (V. Gaveikaite, C. Grundstrom) individually conducted a quality assessment. Article inclusion conflicts were discussed until a consensus was reached. The critical appraisal checklist included 10 quality questions with 4 possible responses: ‘met’ (score +1), ‘not met’ (score −1), ‘unclear’ (score −1), and ‘not applicable’ (score 0) [23]. The highest possible total score was a value of 10.By adhering to the structure of a passing score, only articles scoring 5/10 or higher were included. All assessed articles were included. The methodological quality assessment of the SRs is presented in Appendix Table A.2.

Descriptive data were extracted by one reviewer (V. Gaveikaite) using a standard form verified by a second reviewer (C. Grundstrom). Data collection included general characteristics of the review (country, year of publication, publication type, author, publication status, funding sources, and type of analysis), clinical characteristics, intervention features (functionality), results (number of primary studies included, review findings), conclusions, and recommendations for clinical practice. Characteristics of the SRs have been summarized descriptively (Table 1). An evidence table has been produced to synthesize the clinical findings, general characteristics of the review intervention, included reported population, intervention description, trial design, overall recommendations, and the presence of a meta-analysis.

2.3. Phase II – individual articles review

2.3.1. Selection criteria and data extraction

The structure of healthcare systems is different in Europe compared to other geographical regions. Moreover, standard care (SC), to which implementation of TH is compared, shows a significant variation in relation to the geographical region [25]. Therefore, with our goal to inform European policymakers in mind, we limited our evaluation to clinical trials performed in Europe. An exploration of the differences within Europe were beyond the scope of this review.

Phase II consisted of extracting individual clinical trials from SRs selected in Phase I. Inclusion criteria for the individual clinical trials were defined and are available in Appendix Table A.3. Two researchers (V.Gaveikaite and C.Grundstrom) individually assessed trials for inclusion, followed by a consensus meeting. Table 2 has been produced to synthesize the clinical outcomes, general characteristics of the individual trial, including sample size, study duration (months), severity of airflow limitation (FEV1 predicted), trial design, a definition of SC and TH feedback components (collection, frequency, prompted actions).

Table 1
Characteristics of systematic reviews.

First author; Reference, Year	Title	MA	Intervention purpose	Included study designs	COPD population description	Overall recommendation
Baroi [31] 2018	Advances in remote respiratory assessments for people with chronic obstructive pulmonary disease: A systematic review	–	Remote assessment of respiratory function for AECOPD	x	nCD	Daily remote assessment of respiratory function was feasible and well tolerated in most people with COPD.
Rush [13] 2018	The efficacy of telehealth delivered educational approaches for patients with chronic diseases: A systematic review	–	Education support	x	nCD*	Education, delivered through virtual modalities to chronic patients was comparable, or more, effective than SC.
Yang [12] 2017	Continuity of Care to Prevent Readmissions for Patients with Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis	+	Continuity of care support	RCT	CD	CNI and TH interventions have the evidence for reducing all-cause readmissions up to 6 months for patients with COPD.
Gregersen [32] 2016	Do telemedical interventions improve quality of life, in patients with COPD? A systematic review	–	Efficacy reported by HrQoL tool	x	nCD; EX	TH does not make a strong case for itself for QoL as an outcome. This does not rule out the possibility that TH is superior to SC.
Majothi [6] 2015	Supported self-management for patients with COPD who have recently been discharged from hospital: A systematic review and meta-analysis	+	SM support for patients recently discharged from the hospital	RCT	CD; moderate to severe COPD at discharge	The evidence is not currently adequate to support SM interventions for COPD patients after hospital discharge.
Pedone [9] 2015	Systematic review of telemonitoring in COPD: An update	–	Remote monitoring (stable patient)	RCT	CD	The evidence scarcity of TH in COPD does not allow to support it; most evidence suggests a positive effect of TH on HA and ER visits
Cruz [29] 2014	Home telemonitoring effectiveness in COPD: A systematic review	+	Remote monitoring (stable patient)	RCT NRCT	nCD; EX	TH have a positive effect in exacerbations and improving HRQOL, there is no clear indication that it reduces healthcare utilization and associated costs as only HA risk was reduced in the TH Findings on patients' HRQOL were inconsistent.
Lundell [7] 2014	Telehealthcare in COPD: A systematic review and meta-analysis on physical outcomes and dyspnoea	+	Physical activity and dyspnoea support	RCT	nCD	The results from the MA may imply that TH have an effect on physical activity, however this is the results from one study only and further studies are needed
Kamei [30] 2013	Systematic review and meta-analysis of studies involving telehome monitoring-based telenursing for patients with chronic obstructive pulmonary disease	+	Remote monitoring emphasizing nurse role	RCT, CCT	CD, GOLD II–IV COPD	TH decreased HA, ED visits, exacerbations, and duration of HBD in GOLD II–IV COPD patients. HA rates and ED visits were comparable between patients undergoing TH of different durations. TH had no effect on M.
McLean [16] 2012	Telehealthcare for chronic obstructive pulmonary disease: Cochrane Review and meta-analysis	+	Remote monitoring (stable patient)	RCT	CD	TH can significantly reduce the risk of ED attendance and HA, but has little effect on M.
Bolton [33] 2010	Insufficient evidence of benefit: A systematic review of home telemonitoring for COPD	–	Remote monitoring	CCT NRCT RCT	nCD; EX	Heterogeneity discussion. Some patients had an additional education before being monitored. The benefit of TH for COPD is not yet proven.
Polisena [5] 2010	Home telehealth for chronic obstructive pulmonary disease: A systematic review and meta-analysis	+	Remote monitoring	RCT NRCT	nCD; EX	Heterogeneity discussion. TH reduces HA and ED, while findings for HBD varied. The M was greater in the telephone-support group. TH were similar or better than SC for HrQoL and patient satisfaction.

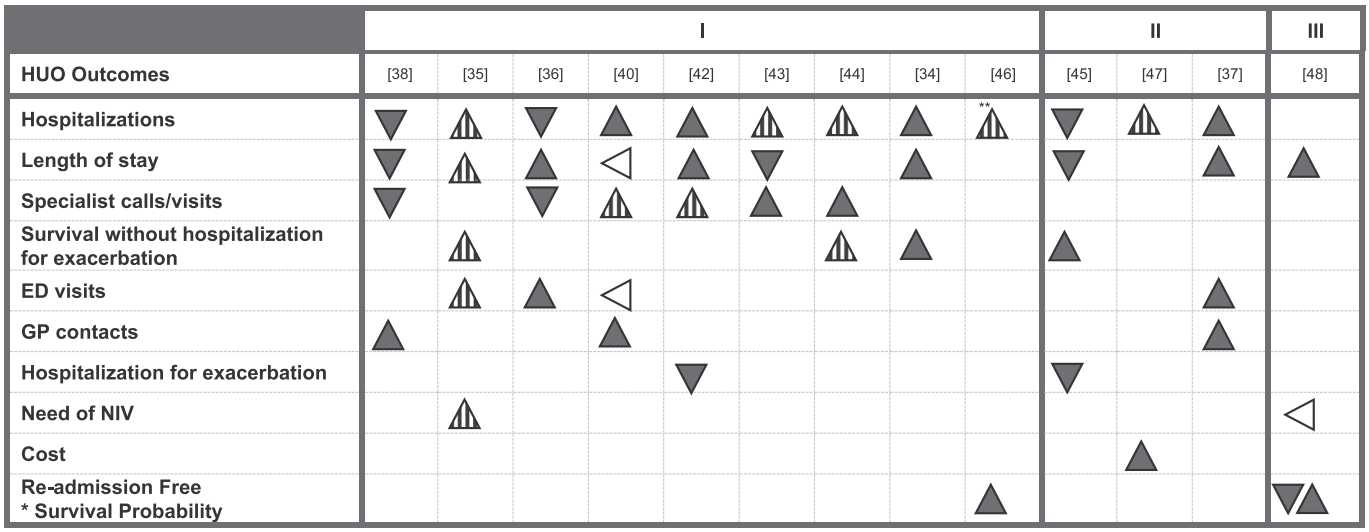
*X, not reported; MA, Meta-Analysis; CNI, Comprehensive nursing intervention; SM, self-management intervention; CD, clinically confirmed diagnosis; nCD, not explicitly stated that COPD was clinically confirmed; EX, excludes mixed population or outcomes not specific for COPD; M, mortality; HA, Hospital admission; HRQOL, health related quality of life; HBD, hospital bed days; SC, standard care; RCT, Randomized controlled trial; CCT, controlled clinical trial; NRCT, non-randomized controlled trial; *SR reported various outcomes for the chronic disease management, we retained just those reported for COPD.*

Table 2
Clinical trials in Europe.

Author, Year, Reference, Country	Sample size (I/C)	FEV% pred. (I/C)	Trial duration: months	Outcomes reporting		Telehealth category			Standard care definition	TH feedback components (Data Collection, Frequency of Collection, Prompted actions)
				PRO	HUO	I	II	III		
Berkhof, 2015 [38], Netherlands	52/49	40/41	6	HrQol; TEx	HBD; GP visits; Pulm. visits	x			Visit at baseline and after 6 months. Interim visits with a specialized nurse.	- Call by nurse (call center) - Once in 2 weeks - Escalation
Halpin, 2011 [39], England	40/39	48/54	4	HrQol; TEx		x			SC: Patients without health-risk forecast service	- Manual by patient (smartphone) - Every day once - Triage;escalation in two days
Jódar-Sánchez, 2013 [36], Spain	24/21	38/37	4	HrQol	HBD; Hospital admissions; Nb. ED visits; Pulm. visits	x			Patients received SC.	- Automatic (vital signs) - Every day once - Triage and escalation
Lewis,2010 [40], *Lewis,2010 [41], Wales	20/20	38/40	12	HrQol	HBD; Hospital admissions; Nb. ED visits; GP visits	x			SC, including continued care support of their clinical teams. They can contact GP, ED.	- Automatic and manual - Every day once - Triage and escalation
Ringbæk,2015 [42], Denmark	141/140	35/13	6	Total deaths; MEx	HBD; HBD (AECOPD); Hospital admissions; AECOPD; Nb. ED visits; Pulm.visits;	x			Managed according to national and international guidelines, including pulmonary rehabilitation.	- Automatic, manual and video call - First month : data transfer 3 times + 1 video call. - Other months: data transfer once a week and one call - Triage and escalation
Trappenburg, 2008 [43], Netherlands	59/56	42/39	6	HrQol; TEx	HBD; Hospital admissions Pulm. visits	x			Patients received SC	- Manual by patient - Every day once - Triage and escalation
Segrelles, 2014 [35], Spain	29/30	GOLD III-IV	7	x	HBD; HBD(AECOPD); Hospital admissions; Nb. ED visits	x			SC. Data relating to clinical activity obtained from the HULP information system and monthly calls	- Automatic (vital signs) - Every day once - Triage and escalation
Sorknæs, 2013 [34], Denmark	132/134	33/37	~7 days: active; 6,5 month passive	So	SwR; HBD; HBD (AECOPD); Hospital admissions; AECOPD	x			SC by GOLD guidelines.	- Automatic(vital signs) and video call (briefcase) - 7 days after discharge and then follow up call - During call decision was made
Casas, 2006 [44], Belgium,	65/90	43/41	12	Total deaths	SwR; Hospital admissions; Home visits	x			Visits were scheduled every 6 months.	- Call by nurse - Weekly for a first month, then after 3 and 9 months - Escalation after patients call
McDowell, 2015 [37], N. Ireland	55/55	46/43	6	HrQol; TEx	HBD; Hospital admissions; Nb. ED visits; GP visit		x		SC: home visits + education. Contact with respiratory team.	- Automatic (vital signs) and manual - Triage and escalation - Every day once
Pinnock, 2013 [45], Scotland	128/128	44/40	12	MA; Total deaths; HrQol	HBD; HBD(AECOPD); Hospital admission; AECOPD		x		SC.Education on SM of exacerbations was provided for all participants.	- Automatic (oximetry) and manual - Every day once - Triage and escalation
Pedone, 2013 [46], Italy	50/49	53/56	9	TEx	Hospital admission		x		SC (no definition). From the discussion: "the education provided to the patients …"	- Automatic (vital signs) (wristband) - Real-time - Triage and escalation
Dinesen, 2012 [47], Denmark	57/48	GOLD III-IV	10		Hospital admission; Cost of admission		x		Instructed on performing home exercises. In urgency, they can contact GP or ED.	- Automatic (vital signs) (wristband) - Not reported - Call once a month
Jakobsen, 2015 [48] *Schou, 2013 [49], Denmark	29/28 22/22	GOLD III-IV	6	So; Lung function; Oxygen satur.; HrQol; TEx	HBD; SwR			x	Hospitalized as usual, receiving SC for an exacerbation.	- Automatic (vital signs) and video call (briefcase) - Everyday until discharged - During the call decision was made

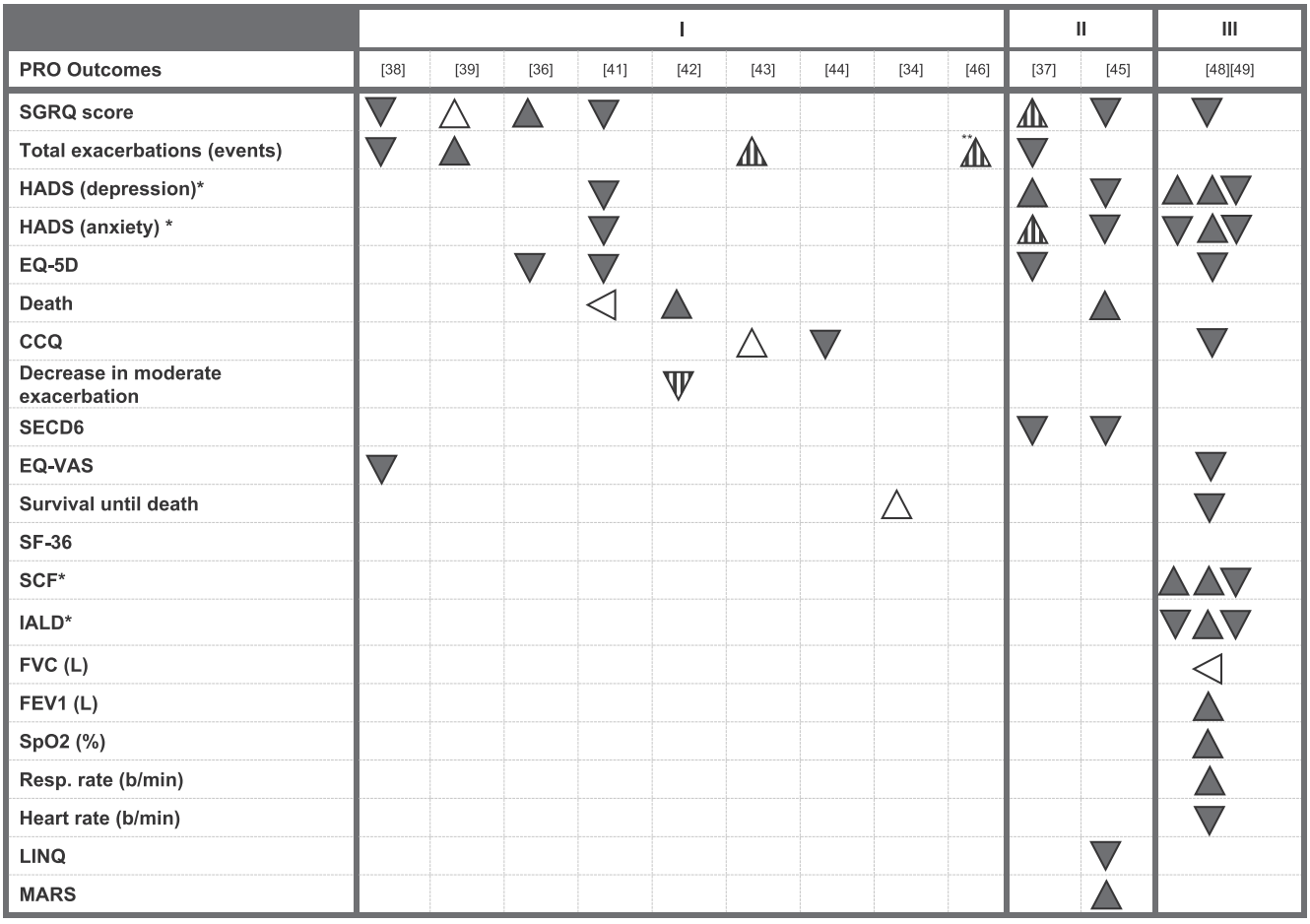
*I/C, number of patients included in the intervention (I) and control (C) groups; SC, standard care; FEV% pred. forced expiratory volume in one second as percentage of predicted value. I: Stable patients which receives the TH combined with SC without extra services. II: Stable patients which receives the TH combined with SC with other services. III: Patients experiencing the exacerbation during which they are discharged home and monitored when control group is experiencing hospital admission. HC, healthcare; HBD, duration of hospitalization; Tex, total exacerbations; Mex, moderate exacerbations; SwR, Survival without re-admission; So, Overall survival; *reporting on the same primary study; MA, medical adherence.*

Table 3a
HUO for COPD management by three TH categories.



Effect direction: up arrow: positive health impact, down arrow: negative health impact, left arrow: no change/conflicting findings. Statistical significance: vertical stripe $p < 0.05$; filled $p > 0.05$; no fill = no statistics/data reported.*Jabobsen/ Schou: used three time moments to measure their effects at: 3 days; 6 weeks or 3 months; ** outcome statistical significance was not reported, but derived by authors from the provided data.

Table 3b
PRO COPD management by three TH categories.



Effect direction: up arrow: positive health impact, down arrow: negative health impact, left arrow: no change/conflicting findings. Statistical significance: vertical stripe $p < 0.05$; filled $p > 0.05$; no fill: no statistics/data reported.
*Jakobsen: Re-admission-Free Survival Probabilities were measured at 30, 90, and 180 days after discharge; ** outcome statistical significance was not reported, but derived by authors from the provided data.

2.4. Data synthesis and visualization

During Phase II, quantitative outcomes were visualized using an effect direction plot [26]. This provides an analytical visualized summary of various intervention effects designed for policy makers [27].

In order to make this visualization more intuitive, the reporting of quantitative outcomes was divided into two types: patient-related outcomes (PRO) and healthcare utilization outcomes (HUO). PRO represents patient disease status (i.e., death, exacerbations), health-related quality of life (i.e., SGRQ tool), and physical functioning (i.e., IALD score, lung function). HUO represent consultations (i.e., any doctor visits, ED visits), all-cause hospitalizations, length of hospitalization, and costs. In this stage we retained trials which define TH as the ongoing and remote exchange of data between patients at home and healthcare professionals as part of disease management [28]. To facilitate the outcomes discussion, we classified TH intervention into three categories based on the COPD activity (stable versus exacerbated) and the control group components (SC with an extra service versus SC without an extra service). Extra service denotes services which relate to non-pharmacological patient management during the trial such as self-management training, disease education or pulmonary rehabilitation. It is essential to mention that the control group receives the same usual care as the intervention group. These TH categories are:

I: Stable patients who receive TH combined with SC without extra services.
II: Stable patients who receive TH combined with SC with other services.
III: Patients experiencing the exacerbation during which they are discharged home and monitored while the control group is experiencing hospital admission.

In the effect direction plot, results are displayed in two tables to represent HUO (Table 3a) and PRO (Table 3b) outcomes types. Each table was subsequently divided into three TH related categories. In each of these three categories, outcomes directionality (upward arrow: positive health impact, downward arrow: negative health impact, leftward arrow: no effect/not clear findings) was indicated by the arrows. The statistical significance of these outcomes is pattern-coded (Vertical Stripe $p < 0.05$; filled $p > 0.05$; no fill = no statistics reported or p-value not reported and not possible to calculate). After the effect directionality plots were drawn (Plot 3a and 3b), the outcomes sets were proposed. An outcome set is defined by the most reported statistically significant quantitative outcomes. It is proposed to be endorsed in future trials as well as initial discussion point with policy makers for subsequent reimbursement. If the category does not have positive outcomes, proposed outcome sets are based on the ERS/ATS recommendations. The rational for this proposal is to increase homogeneity for future meta-analyses, which requires sufficient data in the same format for the same intervention design and patient population [22].

Data for both the characteristics table and quantitative outcomes visualization were extracted by V. Gaveikaite and verified by R. Priori. Conflicts were discussed until a consensus was reached.

3. Results

3.1. Study flowchart

In Phase I, 84 SRs were retrieved from three database queries. After 16 duplicates were removed, the remaining 68 articles were filtered through the exclusion criteria and appraised for quality. In total, 12 SRs were included for systematic mapping. In Phase II, 156 individual trials were extracted from the 12 SRs in Phase I. After screening for eligibility criteria, 140 articles were excluded. 16 articles, referring to 14 individual trials, were included for the in-depth review (see Fig. 1).

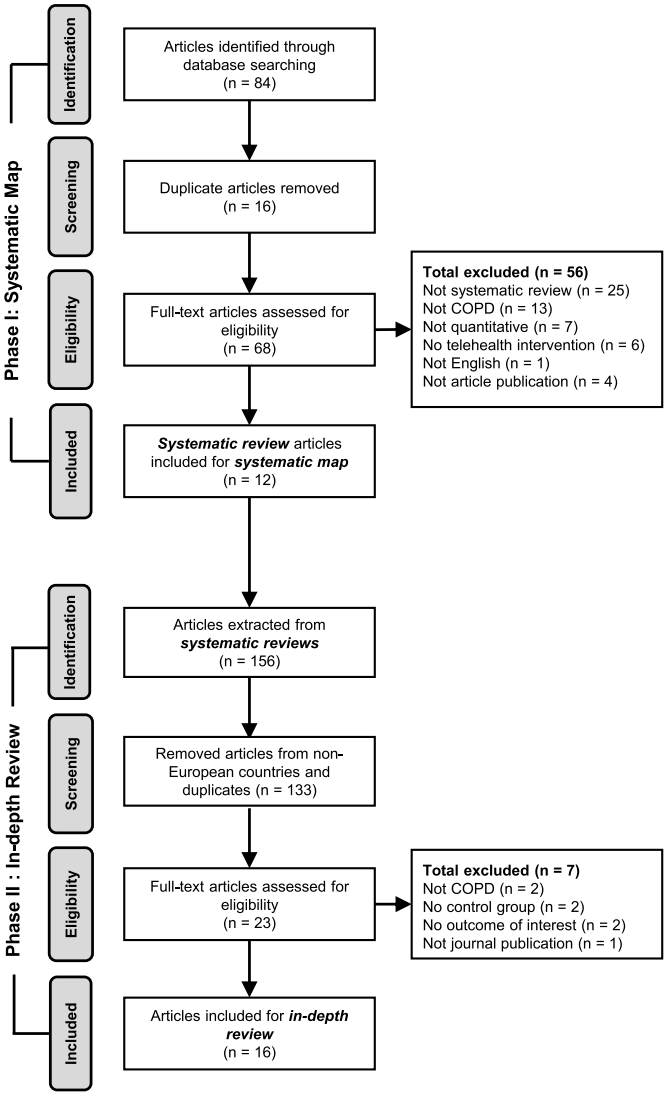


Fig. 1. Study flowchart.

3.2. Phase I quality assessment

A total of 11 out of the 12 reviews scored 7/10 or higher, with only one review scoring 5/10. Four reviews [6,7,29,30] met all criteria from the critical appraisal. The main problems identified by the quality assessment were lack of testing for publication bias, selection of sources for search strategy, criteria for study appraisal, and the number of reviewers appraising study quality. In contrast, all studies had a study question. However, we did not check for "PICO" components or recommendations for further research. The methodological quality assessment of the SRs is presented in Appendix Table A2 (after consensus between V.Gaveikaite and C.Grundstrom was reached).

3.3. Phase I characteristics of systematic reviews

12 SRs were included for the systematic map. All SRs were published between 2010 and 2018. Interventions varied considerably among the included SRs and are listed in terms of their primary focus, with seven reporting a meta-analysis, and nine having a randomization component in their study design. Considering the meta-analyses of the SRs: five showed a reduction in hospital admissions [5,12,16,29,30], three a reduction in visits to the emergency department [5,9], and two a significant decrease in the exacerbation rate [16,29,30]. One SR by Polisena et al. [5] reported a higher mortality rate in the telephone-

support group compared with SC.

Three SRs reported a significant improvement in the SGRQ total score [6,29,30]. One SR was unique as it focused on physical activity level, physical capacity, and dyspnea in patients with COPD [7]. While this SR reported a significant increase in physical activity level in the TH group, it was based on only one study. Another SR, without a meta-analysis [13], focused on the effect of virtual education delivery on patient outcomes in chronic diseases, including COPD. Only this SR supported virtual education implementation in clinical practice for the management of chronic diseases.

3.4. Phase II in-depth review trial descriptions

16 articles, referring to 14 individual trials, were included for the in-depth review and reported in Table 2. Articles from 9 different European countries were published between 2006 and 2015.The total patient sample size for all 16 articles is 923/929 for intervention and control groups respectively. No trial lasted longer than 12 months, with the shortest trial time being 7 days (active monitoring) [34]. Mostly, severe COPD patients were included in the trials. The individual clinical trials retrieved from the included SRs reported outcomes for PRO and HUO. As mentioned in the methodology section, we were using the TH category classification. I: Stable patients who receive TH combined with SC without extra services. II: Stable patients who receive the TH combined with SC with other services.III: Patients experiencing the exacerbation during which they are discharged home and monitored while the control group is experiencing hospital admission.I TH category was the most reported category (N = 10), followed by second (N = 4), and third (N = 2).Many trials reported patient [35–37] and healthcare professional [36] satisfaction with TH services. Reported satisfaction was comprehensively positive.

I/C, number of patients included in the intervention (I) and control (C) groups; SC, standard care; FEV% pred. forced expiratory volume in 1 s as percentage of predicted value. I: Stable patients which receives the TH combined with SC without extra services. II: Stable patients which receives the TH combined with SC with other services. III: Patients experiencing the exacerbation during which they are discharged home and monitored when control group is experiencing hospital admission. HC, healthcare; HBD, duration of hospitalization; Tex, total exacerbations; Mex, moderate exacerbations; SwR, Survival without re-admission; So, Overall survival; *reporting on the same primary study; MA, medical adherence.

3.5. Phase II – qualitative outcomes visualization included in the in-depth review

3.5.1. Stable patients receiving TH combined with SC without extra services

Two plots present reported outcomes in HUO and PRO categories (See Plot 3a and 3b). Authors most frequently used the exacerbations severity classification defined in the GOLD guidelines (this classification has not changed in the cited GOLD guidelines from 2012 to 2018) [2]. GOLD is classified in three areas: mild - increase in symptoms only, moderate - increase in symptoms requiring a change in medication, and severe - requiring hospitalization [2]. Three of the nine trials reported a significant reduction of hospital admission rates in the intervention group: two considered general hospital admission [35,43]. One trial reported increase in the moderate exacerbation rate in the control group [42]. A significant decrease in total exacerbation rate [43] and time to the first exacerbation [34,45] were exemplified in the TH group for two studies as well. Two trials reported a significant reduction in the number of contacts or visits to a pulmonary specialist [40,42]. No trials reported significant differences between intervention and control groups for mortality or survival, although results were consistently in the positive direction for the three reporting on mortality. Other stated outcomes, not significantly different between control and intervention groups, were general practitioner visits and HrQol (SGRQ, HADS (anxiety and depression sub-domains), CCQ, SF-36, EuroQoLEQ-5D, EQ- VAS, SECD6) between control and intervention groups, were general practitioner visits and HrQol (SGRQ, HADS (anxiety and depression sub-domains), CCQ, SF-36, EuroQoLEQ-5D, EQ- VAS, SECD6).

3.5.2. Stable patients receiving TH combined with SC with extra services

In this category, four trials were reported with a different focus: tele-rehabilitation [47], a home-based program with community support visits [37], endorsed education [46], endorsed self-management [45]. Two plots present reported outcomes in HUO and PRO categories (See Plot B.1 and B.2). Dinesen et al. [47] reported lower hospital re-admission rates, as did Pedone et al. [46] which also reported positive results for reduction of AECOPD and reduced moderate exacerbation frequency. McDowell et al. [37] reported a single positive significant change in the intervention group towards HrQoL reported by SGRQ and HADS scales.

3.5.3. Unstable patients receiving SC at home

In this category, two articles reported a single trial [48,49]. Two plots present reported outcomes in HUO and PRO categories (See Plot B.1 and B.2). None of the outcomes, reported at three days, six weeks and six months, were significant in the intervention g6roup.

4. Discussion

4.1. Phase I: systematic map

The systematic map from Phase I compiled the evidence from twelve SRs reporting on the effectiveness of TH interventions for COPD patient management. The two main contributions of the systematic map are a commentary on the quality of available empirical research, as well as the nature of that research, and what it means for future TH intervention trial design.

A quality assessment of the articles selected for inclusion was performed “to establish validity and to establish the risk of bias” [24]. Although the majority of the SRs scored high in the critical appraisal, many SRs lacked a precise definition of the COPD patient population, a description of the TH intervention and were vague about study design criteria [23]. In many of SRs, the reported outcomes are too heterogeneous to perform a meta-analysis. More adherence to standard methodology is needed in SRs to develop quality through rigor and transparency [50]. It is vital to perform SRs of high quality as the conclusions drawn in these articles may directly influence policymakers, clinicians or other healthcare stakeholders to change their practice [51,52].At the very least, future SRs should have a research question formulated according to the PICO framework to improve SR quality [53,54].

The majority of the SRs with a meta-analysis reported positive clinical outcomes. However, the evidence base from these SRs was not comprehensive enough to be directly used to suggest TH implementation into clinical practice for many different reasons. Those reasons were: trial design [9], limited compliance [6,29], complex interventions where TH connects with other intervention types [5,7], limited follow-up and sample size [30,55], and an absence of blinding to healthcare providers [30]. Therefore, policymakers should advocate for more pragmatic trial designs to accurately study the effect of TH in a complex chronic disease setting [56].

4.2. Phase II: in-depth review: impact of TH interventions on patient and healthcare utilization outcomes in Europe

In the discussion, we focus on the outcomes which improved in the intervention group. We discuss why TH may have led to an improvement in outcome, and what that means for policymakers and future research.

4.2.1. General in-depth review observations

If we consider the in-depth review as a synthesized ensemble, inconsistencies can be seen more easily. (See Plot B.1 and B.2) The average severity of COPD in the clinical trials was moderate to severe. This may be because mild patients rarely have exacerbations and have minimal healthcare needs when compared to patients with more severe COPD [57]. Moreover, considering that reducing exacerbations is one of the most desired outcomes in clinical trials for COPD, recruiting patients that have minimal exacerbations may be counterintuitive. However, it is important to consider including mild patients in the future. This may help prevent the progression of COPD to more severe grades by behavior change support using TH interventions with SM activities, inspired by the recently published clinical trial by Jolly et al. [58].

The heterogeneity in reporting between clinical trials is noteworthy for several reasons. The definition of SC varied greatly depending on the country and individual elements, such as patient-education. For instance, Pinnock et al. [45] followed the Lothian protocol as the standard of care, while another clinical trial by Halpin et al. [39] provided a vaguer description of SC. Illustrating a need for more consistent descriptions of SC within clinical trial reporting. The follow-up length of the trials varied greatly from one week to one year. Sorknæs et al. [34] is an exception with an active follow-up of one week (in total 6,5 months). She argues that the re-admittance of COPD patients due to exacerbations typically occurs within two weeks [34], indicating that future studies should perform more intensive follow-up in a shorter time window. This advice mirrors the gap in current research identified by our in-depth review. Finally, we would like to comment on the different measurement and outcome reporting details such as tools and units. A total of eight different tools are used to measure HrQoL. Units were also heterogeneous. For example, reporting of hospital re-admissions were described in four ways: number of people, average exacerbation quantity, rate of exacerbation, or days to the first exacerbation. While the current study cannot be used to determine the optimal tool or unit of measurement, it does enforce the idea that a lack of reporting standards requires the attention of policymakers. At the end of each category section below, we propose the outcome sets, which are based on the approach explained in the methodology section.

4.2.1.1. Category I: Stable patients receiving TH combined with SC without extra services. Category I was the most reported category (N = 9). Three trials reported a significant reduction in hospital admission rates in the intervention group [34,43,45]. It is worth to mention, that the Casas et al. [44] trial reports integrated care in their intervention group, and the control group, receives the SC. The authors hypothesized that the presence of this positive effect is due to the exceptionally high rates of adherence or levels of involvement by support staff. In other words, these trials were successful because key factors that fall outside standard clinical trial protocols were managed adequately. In trials that failed to demonstrate improved outcomes, low levels of adherence and involvement by support staff were often mentioned as limitations. We consider these factors to be pivotal points towards establishing a standard framework that shows the effects of TH accurately.

Category I resulted in significant exacerbation reduction in the intervention group, which is an important outcome when considering the health status of patients with COPD. The importance of using TH interventions to prevent, predict, or minimize exacerbations, is a critical component for reducing overall costs [59]. The study by Trappenburg et al. [43].had a decrease in the total exacerbation rate in the intervention group of the study. However, Ringbæk et al. [42] reported a significantly positive result in the control group which might be due to a heterogeneous control group. The control group included a significantly higher percentage of smokers, and there was a tendency towards lower levels of pulmonary rehabilitation participation. Moderate exacerbations are very important from a policy perspective as patients will be treated by increasing the number or dose of prescription drugs rates [60]. A recent publication emphasized the increase in COPD-related spending on prescription drugs [61].

There are striking resemblances between the functionality and purpose of TH interventions designed to predict, prevent, and intervene when necessary between the clinical trials of Trappenburg et al. [43], and Ringbæk et al. [42]. Interestingly, the success of the TH interventions differed between these two clinical trials. A homogenous patient population may be essential for the success of a trial. Active and ongoing monitoring of the TH intervention was present in the Trappenburg et al. [43] trial, whereas Ringbæk et al. [42] used a strategic intermittent reporting system on patient vitals. In summary, TH interventions which offer intensive vital-sign monitoring with feedback are promising.

Future implementation research should focus on clinical trials with a homogeneous patient population in terms of pulmonary rehabilitation participation and smoking habits. In the setting of TH category I, we propose future researchers, clinicians, and policymakers the following outcome set to serve as the bare minimum of reporting in empirical studies: all-cause hospital admission, survival without hospitalization for exacerbation (days), total exacerbations (events/patients), ED visits, pulmonary. specialist visits, length of stay, and all-cause mortality.

4.2.1.2. II: Stable patients receiving TH combined with SC with extra services. Finally, the II category has considerable overlap between pulmonary rehabilitation, integrated care, and case management which allows merging of these formats [6]. Advocacy, as well as empirical proof for using TH in conjunction with self-management (SM) is necessary activation and empowerment in chronic care [62]. However, the leap to apply SM to COPD is limited by the uncertainty of the role TH plays and remains mostly unexplored in clinical research [63]. In the in-depth review, four SM studies were synthesized. All of the studies reported at least one significant positive result, except one Pinnock et al. [45] reported the HrQoL score in the intervention group was significantly improved [37]. These findings resonate with the notion of patient-centered care through intensive monitoring, or contextual considerations such as seasonal depression.

If we consider the improved outcomes in the intervention group, two studies reported lower re-admission rates for hospitalization [46].The study by Pedone et al. [46] showed a significant reduction in moderate exacerbations in the intervention group. The TH intervention monitored patient vital signs and prompted clinical intervention when necessary. Early detection of exacerbations using TH was shown to allow for a timely response to prevent escalations of detected exacerbations and active patient management. These results are in line with a recent SR where “continuity of care is recognized as a potential improvement of health outcomes for patients with COPD” [12]. Therefore, SM is vital for chronic care as it helps balance the responsibility between clinical personel and patients. This may help redistribute the workload on healthcare professionals, while at the same time empower patients [19]. Further research is needed to consider recommendations about SM provision to COPD patient management, such as the influence on smoking cessation. In the setting of SM, we propose the introduction of the following minimal outcome set: HrQoL reported by SGRQ and HADS, and all cause-hospital admission rates and total exacerbations.

4.2.1.3. III: Unstable patients receiving SC at home. Our in-depth review revealed only one clinical trial, reported by two articles using TH for unstable patient management [48,49]. In this trial, AECOPD patients were either treated in the hospital with SC (control group) or were discharged to home with remote monitoring by healthcare professionals (intervention group). None of the reported outcomes showed a significant difference between the groups. The authors [48,49] suggest that patient recruitment barriers and subsequent low rates of patient participation may have negatively influenced the results. Therefore, they advise to duplicate this trial after strategies to remove patient recruitment barriers have been reconciled.

A recent ERS/ATS report conditionally supports a home-based management program for AECOPD patients who present to the emergency department or hospital [64]. However, this report does not consider TH to support early hospital discharge. According to this report, a particular combination of reported outcomes is critical for guiding treatment recommendations: all-cause mortality, hospital readmission and time to the first readmission [64]. Therefore, in conjunction with this finding, we advocate the need for more focused research on TH in category III while embracing the ERS/ATS recommendations. Also, we advise caution when including category III trials in a SR on TH as the control groups in such trials are very different from those used in the other TH categories. In the category of category III, we propose the following outcome set to allow homogeneous trial reporting: all-cause mortality, hospital re-admission, and time to first readmission outcomes.

4.3. Strengths and limitations

The main strength of this article is its comprehensive external validation approach. Two researchers independently performed the two-phase inclusion process and subsequent quality assessment while adhering to strict and predefined inclusion and exclusion criteria. Conducting a systematic map allowed the pooling of SR which have already done extensive work in ensuring quality and accuracy in their summaries. We believe that the transparency of our process is an important contribution to future studies.

The field of TH in COPD care management is relatively new, which means that the pool of our results is relatively shallow. Moreover, the systematic map approach can be used only to show connections and gaps. Separate studies with a different methodology are needed to study causality. While the scope of research with a focus on the European setting may be viewed as a limitation, we advocate that it is an important approach to European healthcare policy making by contextualization. In addition, our in-depth review is based on a subset of articles extracted from SRs. Relevant articles may therefore be missing as SRs are updated infrequently and article inclusion in these SRs is based on different selection criteria.

4.4. Future research

In the future, it is prudent to continue updating SRs with new trial findings and with a focus on more standardized SR reporting. Future clinical trials should include a cost analysis in their reporting to provide financial insights related to the implementation of the intervention. Moreover, different types of TH services, such as those where real-time data transfer occurs during the consultation with a feedback-loop, warrant an extensive study. Qualitative research would also be useful to explore factors otherwise not captured by traditional clinical trial reporting such as influencing patient activation, engagement, and wellness all while providing SC supported by TH services.

5. Conclusions

This article maps and synthesizes the available evidence on the efficacy of TH interventions for COPD management in Europe providing valuable information for policymakers In conclusion, despite the tendency of TH interventions to provide positive outcomes, the heterogeneity of clinical trials and SRs limit the extent to which the value of TH can be understood. Therefore regarding clinical trials, we strongly advice researchers to use outcome sets that can provide policymakers with the information necessary to evaluate, guide and facilitate the implementation of TH service into routine patient management and subsequent reimbursement. Regarding SRs, we advocate for comprehensive trial evaluation including both a quantitative and qualitative approach. In addition, we suggest that policymakers (including clinical guideline editors) should encourage and support initiatives to create and harmonize these outcome sets.

Declaration of competing interests

V. Gaveikaite, R. Priori are employees of Philips Research, the Netherlands. S. Winter is employee of Philips Research, Germany.

Authorship

V. Gaveikaite, C. Grundstrom, G, I. Chouvarda developed the concept and design of the study. V. Gaveikaite, C. Grundstrom, S. Winter, and R. Priori planned and executed the data extraction and representations. V. Gaveikaite, and C. Grundstrom drafted and revised the article. I. Chouvarda, N. Maglaveras, S. Winter, and R. Priori provided critical insight and feedback. All authors approved and contributed to the final written manuscript.

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Appendix

Appendix Table A.1
The inclusion criteria for systematic reviews

Exclusion Criteria	Description
1. Not a systematic review	An article was excluded if the review was not explicitly declared to be a systematic review, having a meta-analysis component was allowed.
2. Not COPD focused	An article was excluded if diseases among populations were mixed, or not clearly denoted as having differing disease. Example asthma and COPD.
3. Not quantitative	An article was excluded if the reported outcomes were only qualitative in nature.
4. No telehealth component	An article was excluded if telehealth interventions were not part of the systematic review aim.
5. Not English	An article was excluded if it was not published in English.
6. Not Article or Journal	An article was excluded if it was not published as an article or journal, no protocols or reports were included.

Appendix Table A.2
The methodological quality of the SRs after the consensus was reached

Criteria	1	2	3	4	5	6	7	8	9	10	11	12
Is the review question clearly and explicitly stated?	M	M	M	M	M	M	M	M	M	M	M	U
Were the inclusion criteria appropriate for the review question?	U	U	M	M	M	M	M	M	M	M	M	M
Was the search strategy appropriate?	M	M	U	M	M	U	M	M	M	M	M	M
Were the sources and resources used to search for studies adequate?	M	M	M	M	M	NM	M	M	M	M	M	M
Were the criteria for appraising studies appropriate?	M	M	M	NM	M	U	M	M	M	M	M	M
Was critical appraisal conducted by two or more reviewers independently?	U	M	M	NM	M	U	M	M	M	M	M	M
Were the methods used to combine studies appropriate?	M	M	M	M	M	M	M	M	M	M	U	M
Was the likelihood of publication bias assessed?	NM	U	M	NM	N/A	NM	M	M	M	NM	NM	N/A
Were recommendations for policy and/or practice supported by the reported data?	M	U	M	M	M	M	M	M	M	M	M	M
Were the specific directives for new research appropriate?	M	M	M	M	M	M	M	M	M	M	M	M
Total	7/10	7/10	9/10	7/10	10/10	5/10	10/10	10/10	10/10	9/10	8/10	9/10

M, criteria was met; U, criteria was unmet; NA, not applicable; U, unclear.

Appendix Table A.3
Inclusion criteria for the individual clinical trials

Inclusion of Trials from Included Systematic Reviews	Description
1. Europe or Schengen Country exclusively (no mixing)	The trial must be conducted within one of the 28 European Countries or a Schengen Country
2. Must have a control group with usual care (RCT or NRCT)	The trial must include a control group with usual care
3. FEV% or GOLD or a description of target population for recruitment	The trial must include a description of the target population, this could be either FEV%, GOLD classifications, or severity declaration
4. COPD patients (no mixing) clarifications	The trial must exclusively separate COPD patients from other diseases, no patient mixing

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