BMJ Open

Telehealthcare for patients suffering from COPD: Effects on health-related quality of life - Results from the Danish "TeleCare North" cluster-randomised trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014587
Article Type:	Research
Date Submitted by the Author:	05-Oct-2016
Complete List of Authors:	Lilholt, Pernille; Aalborg University, Faculty of Medicine, Department of Health Science and Technology Witt Udsen, Flemming; Aalborg University, Danish Center for Healthcare Improvements Ehlers, Lars; Aalborg University, Danish Centre for Healthcare Improvements, Faculty of Social Sciences and Faculty of Medicine Hejlesen, Ole; Aalborg University, Faculty of Medicine, Department of Health Science and Technology
Primary Subject Heading:	Health informatics
Secondary Subject Heading:	Health services research, Medical management
Keywords:	Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS, telehealth, COPD, Effectiveness, Quality of Life, Outcome Assessment (Health Care)

Telehealthcare for patients suffering from COPD: Effects on health-related quality of life - Results from the Danish "TeleCare North" cluster-randomised trial

Pernille Heyckendorff Lilholt, *PhD candidate*[a, 1], Flemming Witt Udsen, *PhD candidate*[b], Lars H. Ehlers, *Professor*[b] & Ole K. Hejlesen, *Professor*[a]

[a]Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Denmark

[b]Danish Centre for Healthcare Improvements, Faculty of Social Sciences and Faculty of Medicine, Aalborg University, Denmark

Correspondence[1]: Pernille Heyckendorff Lilholt, Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Denmark. Fredrik Bajers Vej 7C (C1-223), DK-9220 Aalborg Ø, Denmark (E-mail: phl@hst.aau.dk)

Word count (excluding title page, abstract, references, figures and tables): 4,240

Abstract

Objective: To assess the effect of telehealthcare compared with usual practice in patients with chronic obstructive pulmonary disease (COPD).

Design: This was a cluster-randomised trial. The intervention group received telehealthcare and usual practice; the control group received usual practice only. Telehealthcare involved exchanging data online between patients and healthcare personnel. Data on health-related quality of life (HRQoL) were collected at baseline and at 12-month follow-up; data were analysed using multilevel modelling.

Setting: 26 municipal districts in the North Denmark Region of Denmark.

Participants: Patients were recruited from 26 municipal districts between April and November 2013. A total of 1,225 patients were enrolled in the trial and randomised to the intervention group (n = 578) or the control group (n = 647). Included were patients who fulfilled the Global Initiative for COPD (GOLD) guidelines and one of the following criteria: COPD Assessment Test (CAT) score ≥ 10; or Medical Research Dyspnoea Council Scale (MRC) ≥ 3 or mModified Medical Research Dyspnoea Council Scale (MMRC) ≥ 2; or ≥ 2 exacerbations during the past 12 months. The exclusion criteria were no phone line, no GSM coverage, cognitive impairment, or inability to fill in the study questionnaires.

Main outcome measures: HRQoL assessed by the physical component summary (PCS) and mental component summary (MCS) scores of the Short Form 36-Item Health Survey, Version 2 (SF-36v2).

Results: The adjusted mean difference in PCS between groups at 12 months was 0.1399 (95% CI: -1.37; 1.65). The adjusted mean difference in MCS between groups at 12 months was 0.3603 (95% CI: -1.68; 2.40).

Conclusions: Compared with usual practice, the overall sample and certain intervention subgroups demonstrated no significant differences in their HRQoL.

Trial registration: ClinicalTrials.gov, NCT01984840, November 14, 2013.

Keywords: Effectiveness; COPD; Telemedicine; RCT; Denmark; Quality of Life; Telehealth; Telemonitoring; Outcome Assessment (Health Care)

Strengths and limitations of this study

- This is the first large-scale trial in Denmark established to remedy the lack of International evidence on HRQoL in patients with COPD who are receiving telehealthcare
- The study is a pragmatic, cluster-randomised, controlled trial with 12-month follow-up, which produces results applicable to clinical practice
- The trial succeeded in establishing a fruitful inter-sectoral and inter-institutional cooperation towards a common goal; the implementation of telehealthcare to improve COPD patients' HRQoL
- To avoid selection bias, it was decided to randomise clusters at a higher organisational level to avoid that the GPs could have any knowledge of the randomisation
- SF-36v2 was used as a QoL measure, but may be less sensitive to change related to telehealthcare. It would have been desirable to employ a combination of generic and disease-specific questionnaires in this study

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a significant cause of impaired quality of life (QoL), disability, morbidity, and mortality in industrialised countries. Moreover, it constitutes a considerable burden on the affected patients and places an important socio-economic burden on society due to the growing number of patients requiring care. COPD, and other chronic diseases, challenge the healthcare systems in ways that call for changes in management and delivery of patient care [1,2].

Telehealthcare facilitates timely transmission of clinical and physiological data and allows patients to be followed by clinicians more frequently and from a distance. It may therefore also facilitate early intervention and improve clinical and patient-related outcomes [3]. Systematic reviews conclude that there is, indeed, a potential for demonstrating that telehealthcare improves health-related outcomes or is at least as good as conventional treatment, but more research is needed [4,5]. Some reviews [4–7] raise concerns about the quality of the available evidence that is presented in heterogeneous pilot projects which are small, incomparable, and difficult to appraise in relation to QoL [4,6–17]. A recent systematic review [18] indicates only limited evidence for a positive effect of telehealth interventions on QoL in COPD. This situation has given rise to a demand for large-scale studies; but to our knowledge, only one large-scale study, The Whole System Demonstrator Project (WSD) conducted in the UK, has attempted to establish a robust evidence base for telehealth [19–23]. In the WSD, Cartwright and colleagues [24] concluded that the effect of telehealth was clinically insignificant as a supplement to usual care, and telehealth did not improve psychological outcomes and QoL in patients with COPD, heart failure, or diabetes [24]. In a recent

randomised controlled trial (RCT), a more extensive assessment of QoL and psychological outcomes was performed on the COPD cohort of the WSD [25]. The findings from the RCT [25] are consistent with the above conclusion made by Cartwright and colleagues [24]. However, the RCT found no reductions in patients' QoL in the longer term. In contrast, there was a trend towards improved QoL and mood in the telehealth group at longer-term follow-up, but not at the short term follow-up, as observed through disease-specific measures [25].

National strategy

In Denmark, the lack of evidence for telehealthcare was discussed among healthcare decision-makers who agreed to strengthen the evidence base by conducing a large-scale study as part of "The National Danish Action Plan for Dissemination of Telemedicine" [26]. In 2012, the Danish Government decided to launch the Action Plan to disseminate telemedicine nationally [26]. The action plan included, among others, the TeleCare North trial, the purpose of which was to contribute to the generation of valuable knowledge about the use of telehealthcare for COPD patients in the North Denmark Region. The TeleCare North trial was designed based on experiences from two Danish pilot studies; the TeleKat Study [27,28] and the Nursing Consultations Study [29,30], which had both demonstrated positive effects of tele-homecare and tele-consultations.

The present study is embedded in the Danish TeleCare North trial. Its objective was to assess the effect of telehealthcare compared with usual practice based on an assessment of HRQoL in COPD patients at the individual level. We hypothesised that adding telehealthcare to usual practice would significantly enhance patients' HRQoL [31].

2. Methods

2.1. Study design

This study was conducted in accordance with the study protocol for the TeleCare North trial [31], which we describe briefly in this section (see the published protocol for more detailed information).

The TeleCare North trial was a large-scale, pragmatic, two-level, cluster-randomised, controlled trial with 12-month follow-up. The trial was based on the collaborative efforts of the North Denmark Region, all municipalities in the Region, the Region's general practitioners (GPs), and Aalborg University. The municipalities were organised into 26 districts with 13 clusters in each arm.

2.2. Participants

The trial targeted all COPD patients in the North Denmark Region who fulfilled the inclusion criteria. All GPs from the Region recruited the COPD patients from a list of suitable patients attending their practices. The selection of participants followed identical guidelines and instructions at all practices. All patients who accepted to participate and were deemed suitable for participation were included. Assigned to the intervention or to usual practice were 1,225 (578 intervention, 647 controls) patients representing different COPD stages, GOLD I-IV (Global Initiative for Chronic Obstructive Lung Disease) [32].

2.2.1. Inclusion and exclusion criteria

All COPD patients who may benefit from telehealthcare were considered for inclusion. The following inclusion criteria were used: Patients were required to have COPD as their primary disease and be diagnosed by spirometry, and they should receive or be motivated for treatment corresponding to the GOLD guidelines [32]. One of the following criteria should also be met: A Medical Research Dyspnoea Council scale (MRC) score ≥ 3; or a modified Medical Research Dyspnoea Council scale (MMRC) score ≥ 2; or a COPD Assessment Test (CAT) score ≥ 10; or ≥ 2 exacerbations during the past 12 months.

In addition, on the basis of a health professional's qualified estimate and assessment, the patients should also have a telephone connection, have permanent residence, and be on the list of a GP in the North Denmark Region. Patients should also be able to speak Danish or they should be living with Danish-speaking relatives who were able to support them in their use of the telehealthcare system and to provide assistance in situations involving issues of comprehension of the Danish language.

Patients were excluded if they were cognitively impaired, had no phone line or GSM coverage, or were unable to understand Danish to the extent allowing them to complete the study questionnaires.

2.3. Intervention

The intervention of the TeleCare North trial was based on the concept and logic of the TeleKat study [28]. Its key concept and primary logic was empowerment achieved by engaging COPD patients in their illness and increasing their coping abilities through self-monitoring. The study introduced extended monitoring with store-and-forward data connected to healthcare providers to facilitate detection of exacerbations and rapidly initiate preventive antibiotic therapy.

2.3.1. Telehealthcare

Patients in the intervention group received telehealthcare in addition to usual practice. The telehealthcare system coined Telekit was used in the TeleCare North trial. It consists of a Samsung Galaxy Tab2 (10.1) with associated devices: a digital blood pressure monitor (UA-767, plus BT-C, Nonin Medical, Minnesota, USA), a

fingertip pulse oximeter (Nonin, Onyx II% SpO^2), and a health precision scale (UC-321PBT-C, A&D Medical, Tokyo, Japan). The devices can collect and wirelessly transmit relevant disease-specific data consisting of answers to questions related to COPD exacerbations, symptoms, and patients' vital signs: systolic and diastolic blood pressure, heart rate, weight, and oxygen saturation (Figure 1). The patients were instructed to measure their vital signs, which were then sent asynchronously to municipality healthcare personnel who subsequently established if these data deviated from the normal threshold values. The communication between the healthcare personnel and the patient was one-way only. The patients were contacted if there were adverse changes in their values and responses. Patients were also contacted if the measurements were not carried out as agreed or the measurements were not received as expected.

2.3.2. Usual practice

Patients in the control group received their existing usual practice. This involved treatment, monitoring, and care throughout the study period. The patients' GPs provided this treatment and monitoring, and the municipalities held responsibility for the practical help and care provided. The patients in the control group had not received any form of telehealthcare system; but at the end of the 12-months study period, they were offered the same Telekit system as the intervention group for ethical reasons.

2.4. Randomisation

On November 4, 2013, the municipality districts (n = 26) were randomised so that patients residing in the same district received the same type of care – either telehealthcare in addition to usual practice, or usual practice only. The municipality districts were matched two by two by the following variables: the total population size of the districts; the proportion of people with a higher education; the sum of the district's total income; unemployment; and the estimated number of patients with COPD [31]. The districts were distributed randomly by a blinded volunteer with no relation to the trial who performed the randomisation by throwing a dice. The volunteer had no knowledge of the distribution of districts on intervention or control group, respectively. The randomisation was recorded by the trial administration secretariat to ensure that the procedure was performed randomly.

2.5. Outcome measures

Upon inclusion at the GP, patients were handed a questionnaire comprising the Short Form 36-Item Health Survey version 2 (SF-36v2) [33] and questions concerning their baseline demographic characteristics such as gender, age, education, comorbidities, smoking status, marital status, and job status. The SF-36v2 consists of 36 questions and is one of the most commonly used generic, validated questionnaires for measuring general HRQoL. It captures patients' perceptions of physical, social, mental, and emotional domains, and

overall summary scores of physical (PCS) and mental components (MCS) are derived from domain scores using a norm-based scoring method. The scores are standardised to fall between 0 and 100 with a higher score indicating "better health" [33]. After 12 months, a similar patient questionnaire was sent to the included patients to compare baseline data with follow-up data.

The primary outcomes of this study were the patients' mean differences in HRQoL at baseline and at the 12-month follow-up assessed with SF-36v2 at the patient level. The primary outcome was adjusted mean changes in the intervention groups' and control groups' PCS and MCS scores from baseline to follow-up. Secondary outcomes included subgroup analyses at the clustered level of the mean differences in both summary scores, PCS, and MCS.

2.6. Sample size

The sample size calculation was based on the PCS outcome measure. A sample size of 350 patients from at least seven municipality districts (clusters) in each arm (α = 0.05, power = 80%) was needed to detect minimal, clinically important differences (change equal to 5) and intracluster correlation ((ICC) equal to 0.05)) between the intervention group and the control group [34]. The total required sample size was estimated to be around 800 patients with an expected lost-to-follow-up-rate of 10%.

2.7. Statistical analysis

The effectiveness analysis of the cluster-randomised trial was conducted as an intention-to-treat analysis for all outcomes. Data were analysed at baseline and at 12 months. The analysis was undertaken in STATA 12.1.

SF-36v2 standardised scores for each patient were produced using Software provided by QualityMetric Incorporated (http://www.sf-36.org/). Two separate linear mixed models for continuous outcomes were used to assess the mean differences in PCS and MCS scores between groups from baseline to the 12-month follow-up controlling for treatment arm, respective baseline score, age, gender, baseline forced expiratory volume in one second (FEV1%), marital status, diabetes status, cancer status, and clustering at the municipality district level. The clusters were assumed to be represented as random effects, and the models had robust covariance structures. ICC estimates of patient-reported outcome variables were calculated for measurement of the variability within and across the clusters.

Missing PCS and MCS scores and baseline characteristics were imputed using multiple imputation and were estimated separately by treatment group. Imputation models included PCS and MCS scores, predictors for these scores at both time points, predictors for missing observations in the individual variables, and all

baseline characteristics. The variables included were non-missing health-related quality-of-life (HRQoL) (PCS and MCS scores), measures of disease status (FEV1%, forced vital capacity (FVC%)), diastolic and systolic blood pressure), smoking status, duration of COPD, potential comorbidities (diabetes, cardiovascular disease, mental illness, musculoskeletal disorders, or cancer), and socio-demographic variables (age, gender, marital status, education, employment status). The imputation models involved the generation of 30 complete datasets combined by Rubin's rule.

3. Results

3.1. Descriptive characteristics

The CONSORT diagram is shown in Figure 2. Twenty-six municipal districts (13 intervention clusters; 13 control clusters) were randomised in 2013, and the TeleCare North trial was completed after the 12-month assessment in 2015. At baseline, 1,225 (578 intervention, 647 controls) patients were enrolled in the TeleCare North trial (Figure 2).

At baseline, we assessed socio-demographic factors (gender, age, marital status) and health characteristics (smoking status, duration of COPD, FEV1%, FVC%, comorbidities, SF-36). Statistical comparisons of the participants' baseline characteristics demonstrated that the two study groups were similar, except for statistically significant differences in FVC% ($p < 0.05$). The control group's mean FVC% (74.34%) was slightly higher than the intervention group's mean FVC% (70.38%) (Table 1).

Table 1: Baseline characteristics, at baseline and at 12 months follow-up.

Characteristics	All participants at baseline			Complete cases at 12 months follow-up#			Lost-to-follow-up at 12 months##			Incomplete cases at 12 months follow-up###		
	THC *n=578*	UP *n=647*	Diff *Raw*	THC *n=258*	UP *n=316*	Diff *Raw*	THC *n=210*	UP *n=177*	Diff *Raw*	THC *n=110*	UP *n=154*	Diff *Raw*
Age (years)§	69.55 (9.36)	70.33 (9.11)	-0.78	68.24 (8.84)	69.51 (9.08)	-1.27	70.46 (10.19)	71.82 (9.49)	-1.36	70.91 (8.54)	70.32 (8.55)	-0.59
Men (%)§	48.27 (n=279)	43.74 (n=283)	4.53	53.49 (n=138)	44.62 (n=141)	8.87*	45.24 (n=95)	45.76 (n=81)	-0.52	41.82 (n=46)	39.61 (n=61)	2.21
Marital status (%)												
Married/in a relationship	55.88 (n=323)	54.25 (n=351)	1.63	70.16 (n=181)	62.03 (n=196)	8.13	40.00 (n=84)	45.20 (n=80)	-5.20	52.73 (n=58)	48.70 (n=75)	4.03
Single	20.42 (n=118)	22.10 (n=143)	-1.68	17.44 (n=45)	22.15 (n=70)	-4.71	24.76 (n=52)	23.16 (n=41)	1.60	19.06 (n=21)	20.78 (n=32)	-1.69
Widow/widower	16.78 (n=97)	16.54 (n=107)	0.24	12.02 (n=31)	15.19 (n=48)	-3.17	22.86 (n=48)	19.21 (n=34)	3.65	16.36 (n=18)	16.23 (n=25)	0.10
Missing (%)	6.92	7.11	-0.19	0.39	0.63	-0.24	12.38	12.43	-0.05	11.82	14.29	-2.47

	(n=40)	(n=46)		(n=1)	(n=2)		(n=26)	(n=22)		(n=13)	(n=22)	
Smoking status (%)												
Non-smokers	59.34 (n=343)	63.06 (n=408)	-3.72	66.28 (n=171)	67.41 (n=213)	-1.13	50.95 (n=107)	61.02 (n=108)	-10.07	59.09 (n=65)	56.49 (n=87)	2.60
Smokers	33.91 (n=196)	29.21 (n=189)	4.70	32.95 (n=85)	31.01 (n=98)	1.94	36.76 (n=77)	26.55 (n=47)	10.12	30.91 (n=34)	28.57 (n=44)	2.34
Missing (%)	6.75 (n=39)	7.73 (n=50)	-0.98	0.78 (n=2)	1.58 (n=5)	-0.80	12.38 (n=26)	12.43 (n=22)	-0.05	10.00 (n=11)	14.94 (n=23)	-4.94
Duration of COPD (years)	7.80 (6.23)	7.70 (5.79)	0.10	7.58 (6.48)	7.47 (5.36)	0.11	7.99 (6.45)	8.37 (6.40)	-0.38	8.00 (5.13)	7.50 (6.04)	0.50
Missing (%)	14.01 (n=81)	15.14 (n=98)	-1.13	7.75 (n=20)	8.23 (n=26)	-0.48	21.43 (n=45)	22.03 (n=39)	-0.60	14.55 (n=16)	21.43 (n=33)	-6.88
FEV1 (%)	47.70 (18.05)	48.37 (18.94)	-0.67	48.87 (18.31)	50.26 (19.82)	-1.39	47.72 (18.94)	45.65 (17.92)	2.07	45.06 (15.62)	47.74 (17.91)	-2.68
Missing (%)	18.51 (n=107)	19.78 (n=128)	-1.27	18.22 (n=47)	19.94 (n=63)	-1.72	21.43 (n=45)	15.82 (n=28)	5.61	13.64 (n=15)	24.03 (n=37)	-10.39
FVC (%)	70.38 (20.02)	73.34 (22.33)	-3.96**	71.22 (19.13)	75.43 (21.73)	-3.71	70.63 (21.34)	73.22 (24.56)	-2.59	66.44 (19.41)	73.31 (20.83)	-6.87**
Missing (%)	34.43 (n=199)	39.41 (n=255)	-4.98	31.01 (n=80)	37.97 (n=120)	-6.96	37.14 (n=78)	38.42 (n=68)	-1.28	37.27 (n=41)	43.51 (n=67)	-6.24
Comorbidities (%)												
Diabetes	10.21 (n=59)	9.89 (n=64)	0.32	8.91 (n=23)	9.81 (n=31)	-0.90	10.48 (n=22)	8.47 (n=15)	2.01	12.73 (n=14)	11.69 (n=18)	1.04
Coronary heart disease	32.70 (n=189)	31.84 (n=206)	0.86	32.56 (n=84)	32.28 (n=102)	0.28	36.19 (n=76)	34.46 (n=61)	1.73	26.36 (n=29)	27.92 (n=43)	-1.56
Mental health problem	4.84 (n=28)	4.79 (n=31)	0.05	4.26 (n=11)	5.06 (n=16)	-0.80	7.14 (n=15)	5.08 (n=9)	2.06	1.81 (n=2)	3.90 (n=6)	-2.08
Musculoskeletal disorder	24.91 (n=144)	29.37 (n=190)	-4.46	27.91 (n=72)	29.11 (n=92)	-1.20	22.38 (n=47)	31.07 (n=55)	-8.69	22.73 (n=25)	27.92 (n=43)	-5.19
Cancer	6.06 (n=35)	4.79 (n=31)	1.27	5.81 (n=15)	4.43 (n=14)	1.38	5.71 (n=12)	5.65 (n=10)	0.06	7.27 (n=8)	4.55 (n=7)	2.72
Missing (%)	8.13 (n=47)	7.88 (n=51)	0.25	1.94 (n=5)	2.22 (n=7)	-0.28	13.81 (n=29)	12.43 (n=22)	1.38	11.81 (n=13)	14.29 (n=22)	-2.47
Baseline PCS	37.48 (9.21)	37.71 (8.93)	-0.23	38.24 (9.06)	38.21 (9.15)	0.03	36.04 (9.10)	36.21 (8.44)	-0.16	37.75 (10.11)	37.88 (8.39)	-0.13
Missing (%)	23.88 (n=138)	25.50 (n=165)	1.62	0.00 (n=0)	0.00 (n=0)	0.00	31.90 (n=67)	37.85 (n=67)	-5.95	64.55 (n=71)	63.64 (n=98)	0.91
Baseline MCS	48.48 (11.59)	48.91 (11.22)	-0.43	49.92 (11.03)	50.63 (10.76)	-0.71	45.98 (12.25)	45.05 (11.56)	0.92	48.13 (11.49)	46.80 (11.04)	1.33
Missing (%)	23.88 (n=138)	25.50 (n=165)	1.62	0.00 (n=0)	0.00 (n=0)	0.00	31.90 (n=67)	37.85 (n=67)	-5.95	64.55 (n=71)	63.64 (n=98)	0.91

Data are mean (standard deviation) or proportion (number of patients)
THC: telehealthcare; UP: usual practice; Diff: difference
COPD: chronic obstructive pulmonary disease; FEV1(%): forced expiratory volume in one second of predicted normal; FVC(%): forced vital capacity
#Complete case: a case that have nonmissing values on MCS and PCS score at baseline and follow-up
##Lost-to-follow-up: cases that died, withdrew consent or did not return any study questionnaires after baseline

###Incomplete case: a case that is not lost to follow-up but has missing values on items in either PCS and MCS at baseline or follow-up
§ Variable has no missing values
*Fischer's exact test for differences in proportions of patients in telehealth group and usual practice group (at baseline, complete cases, lost-to-follow-up and incomplete cases), P < 0.05
**Mann-Whitney's test for differences in mean in telehealth group and usual practice group (at baseline, complete cases, lost-to-follow-up and incomplete cases), P < 0.05

3.2. HRQoL outcomes

3.2.1. Unadjusted and adjusted primary outcomes

A comparison of the unadjusted statistically significant differences between the two groups' PCS and MCS scores indicated that both groups scored lower HRQoL from baseline to follow-up, with a mean difference in PCS score of -2.62, (95% CI, -1.9238464 to -3.317276) for the intervention and -2.83, (95% CI, -2.16342096; -3.494888704) for the control group, and a mean difference in MCS score of -4.69, (95% CI, -3.76360248; -5.61360952) for the intervention and -5.31, (95% CI, -4.44201504; -6.17870496) for the control group. The unadjusted mean difference scores for both groups combined were MCS: 0.3771, (95% CI, 1.7506; 2.5049) and PCS: 0.1813, (95% CI, 1.3848; 1.7474). The confidence intervals suggested that the unadjusted mean difference in scores between the intervention and the control group was not statistically significant (Table 2).

The adjusted mean differences in HRQoL from baseline to the 12-month follow-up were PCS: 0.1399 (95% CI, -1.3689; 1.6496) and MCS: 0.3603 (95% CI, -1.6788; 2.3994). The adjusted outcomes indicated no evidence of statistically significant differences between the groups (Table 2).

Table 2: Unadjusted and adjusted outcomes of the mean differences in HRQoL, PCS and MCS scores between treatment groups.

Effectiveness	
PCS (raw mean difference, 95% CI)*	0.1813 (-1.3848; 1.7474)
MCS (raw mean difference, 95% CI)*	0.3771 (-1.7506; 2.5049)
PCS (adjusted mean difference, 95% CI)	0.1399 (-1.3689; 1.6496)
MCS (adjusted mean difference, 95% CI)	0.3603 (-1.6788; 2.3994)

*Adjusted only for baseline utility (PCS or MCS score at baseline)

Tables 3 and 4 provide estimates of the intra-class correlation coefficients (ICC), 95% confidence intervals and p-values for the total sample and for subgroups. The ICC estimates for the total sample of the primary outcome variables from baseline to the 12-month follow-up were 0.0004 for PCS and 0.0031 for MCS.

3.2.2. Secondary outcomes

We also performed a posteriori-defined subgroup analyses which showed no statistically significant effect of the intervention in any of the defined subgroups. The ICC was in the 0.0000-0.0043 range, which indicated low variability between clusters (Table 3, Table 4).

Table 3: Primary outcome and subgroup analyses of the COPD patients' socio-demographic characteristics: difference from baseline to 12 months follow-up in PCS and MCS for total sample and subgroups, adjusted for baseline PCS or baseline MCS and age, gender, baseline FEV1, marital status, cancer and diabetes.

Socio-demographic characteristics								
Effectiveness	**PCS**	**PCS 95% CI**	**Wald test**	**ICC**	**MCS**	**MCS 95% CI**	**Wald test**	**ICC**
Total sample	0.1399	[-1.37;1.65]	**P value**	0.0004	0.3603	[-1.68;2.40]	**P value**	0.0031
Gender								
Female (54%)	-0.2660	[-1.61;1.08]	0.5586	0.0001	-0.4518	[-2.57;1.66]	0.3101	0.0031
Male (46%)	0.5435	[-2.07;3.15]			-1.3149	[-1.86;4.49]		
Age								
< 60 years (16%)	-0.4760	[-4.02;3.07]	0.6530	0.0000	-0.1045	[-4.34;4.13]	0.9149	0.0032
60-69 years (33%)	-1.1693	[-3.18;0.85]			-0.7012	[-3.74;2.33]		
70-79 years (38%)	0.9853	[-1.88;3.86]			0.7242	[-2.74;4.19]		
≥ 80 years (13%)	1.7020	[-3.61;7.02]			2.1474	[-5.00;9.29]		
Marital status								
Married/relationship (58%)	0.3116	[-1.81;2.43]	0.6957	0.0007	1.0233	[-2.18;4.23]	0.8035	0.0034
Single (23%)	-0.8846	[-3.79;2.03]			-0.6200	[-4.87;3.63]		
Widow/widower (19%)	0.8631	[-2.59;4.31]			-0.4505	[-4.88;3.98]		
Smoking status								
Non-smokers (66%)	0.4378	[-1.62;2.50]	0.6107	0.0003	1.3343	[-1.62;4.28]	0.2136	0.0028
Smoker (34%)	-0.4124	[-2.75;1.92]			-1.4751	[-4.31;1.36]		
Job status								
Full time job (5%)	-1.1569	[-6.14;3.83]	0.7947	0.0015	-5.9561	[-12.55;0.63]	0.1998	0.0039
Part time job (7%)	-0.8405	[-4.99;3.30]			0.8363	[-5.18;6.85]		
No job (88%)	0.3255	[-1.37;2.02]			0.7341	[-1.70;3.17]		
Education								
Elementary school, 7th-10th grade (48%)	0.1001	[-1.57;1.77]	0.9564	0.0006	0.7203	[-1.99;3.43]	0.6697	0.0042
High school (2%)	0.5550	[-7.91;9.02]			4.6747	[-8.01;17.36]		
Skilled worker (34%)	0.8233	[-1.76;3.41]			1.2315	[-2.48;4.94]		
Short-term education (2-3 years) (8%)	-1.5662	[-5.66;2.52]			-2.3868	[-8.12;3.34]		
Middle-term education (3-5 years) (7%)	-0.4868	[-6.43;5.45]			-4.2856	[-10.20;1.63]		
Long-term education (5-8 years) (1%)	-0.8342	[-18.73;17.06]			0.4059	[-22.59;23.40]		

PCS=physical component score; MCS=mental component score; Mean difference; 95% confidence intervals
Multilevel linear models controlling for baseline PCS or MCS score and age, gender, baseline FEV1, marital status, cancer and diabetes and intraclass correlation. Priori hypothesis was that adding telehealthcare to usual practice would improve patients' HRQoL relative to usual practice.

Table 4: Primary outcome and subgroup analyses of the COPD patients' health characteristics: difference from baseline to 12 months follow-up in PCS and MCS for total sample and subgroups, adjusted for baseline PCS or baseline MCS and age, gender, baseline FEV1, marital status, cancer and diabetes.

Health characteristics								
Effectiveness	**PCS**	**PCS 95% CI**	**Wald test**	**ICC**	**MCS**	**MCS 95% CI**	**Wald test**	**ICC**
Total sample	0.1399	[-1.37;1.65]	**P value**	0.0004	0.3603	[-1.68;2.40]	**P value**	0.0031
COPD severity (GOLD 1-4)								
Mild, 1 (6%)	1.7325	[-4.74;8.21]	0.7077	0.0004	0.6261	[-6.82;8.07]	0.8067	0.0034
Moderate, 2 (38%)	-0,7478	[-3.02;1.53]			-0.6984	[-3.77;2.37]		
Severe, 3 (39%)	1.0118	[-1.67;3.70]			1.4735	[-2.11;5.05]		
Very severe, 4 (17%)	-0.6391	[-4.75;3.47]			-0.1792	[-5.19;4.84]		
COPD duration								
< 3.5 years (25%)	-0.6746	[-2.91;1.56]	0.2569	0.0006	-0.9665	[-4.36;2.43]	0.1050	0.0036
3.5-6 years (26%)	-1.5877	[-4.60;1.42]			-2.0297	[-5.70;1.64]		
7-10 years (26%)	0.5339	[-2.77;3.84]			0.5210	[-3.64;4.68]		
> 10 years (23%)	2.4954	[-0.70;5.69]			4.0211	[-0.19;8.23]		
Diabetes								
No (89%)	0.3313	[-1.23;1.90]	0.3881	0.0001	0.3155	[-1.82;2.45]	0.8879	0.0036
Yes (11%)	-1.4397	[-5.31;2.43]			0.7416	[-4.94;6.43]		
Heart disease								
No (65%)	0.0605	[-1.49;1.61]	0.8846	0.0003	0.7216	[-1.74;3.18]	0.6245	0.0033
Yes (35%)	0.2948	[-2.62;3.21]			-0.2910	[-3.67;3.09]		
Mental health problem								
No (95%)	0.2914	[-1.26;1.85]	0.2505	0.0001	0.3114	[-1.79;2.41]	0.7688	0.0032
Yes (5%)	-3.1215	[-8.74;2.50]			1.4941	[-6.16;9.15]		
Musculoskeletal disease								
No (70%)	0.0508	[-1.72;1.83]	0.8902	0.0002	0.5206	[-1.55;2.59]	0.7174	0.0031
Yes (30%)	0.2440	[-2.02;2.51]			-0.0837	[-3.45;3.28]		
Cancer								
No (94%)	0.0182	[-1.42;1.46]	0.5346	0.0003	0.2151	[-1.85;2.28]	0.5557	0.0030
Yes (6%)	2.1000	[-4.69;8.89]			2.6599	[-5.37;10.69]		
Number of comorbidities								
Yes (33%)	0.2565	[-2.11;2.63]	0.1254	0.0001	0.3358	[-2.75;3.42]	0.7387	0.0031
No (41%)	1.3736	[-1.04;3.78]			1.0275	[-2.15;4.21]		
2 or more (26%)	-1.9658	[-4.88;0.95]			-0.6933	[-4.32;2.93]		
Hypertension								
Yes (71%)	0.5924	[-1.34;2.53]	0.2868	0.0007	0.3869	[-2.11;2.88]	0.9585	0.0031
No (29%)	-1.1443	[-3.68;1.39]			0.2711	[-3.33;3.87]		
Tachycardia								
Yes (70%)	0.2661	[-1.35;1.92]	0.7957	0.0001	0.1025	[-2.04;2.24]	0.6614	0.0029
No (30%)	-0.1756	[-3.31;2.95]			1.0238	[-2.83;4.87]		
BMI								
< 25 (44%)	0.3670	[-2.10;2.83]	0.9577	0.0003	0.4484	[-2.85;3.74]	0.9553	0.0040
25-30 (34%)	0.2003	[-2.49;2.89]			-0.1175	[-3.84;3.61]		

> 30 (22%)	-0.3849	[-4.50;3.63]			0.7782	[-4.03;5.59]		

PCS=physical component score; MCS=mental component score; Mean difference; 95% confidence intervals
Multilevel linear models controlling for baseline PCS or MCS score and age, gender, baseline FEV1, marital status, cancer and diabetes and intraclass correlation. Priori hypothesis was that adding telehealthcare to usual practice would improve patients' HRQoL relative to usual practice.

4. Discussion

The present study was the first Danish large-scale trial established to remedy the lack of International evidence on HRQoL in patients with COPD who are receiving telehealthcare. In contrast to the WSD [20,21,24,25], the present cluster-randomised trial compared the effects of telehealthcare with the effects of usual practice in COPD patients only. The design of the WSD was characterised by variability in terms of the employed technologies, the recruited sample, the type of intervention, and defined care pathways. Contrary to the WSD, the TeleCare North trial used a "clean" control group of COPD patients who received usual practice and no other forms of care [35]. We did intention-to-treat analyses to evaluate the effect of HRQoL and found no statistical quality-of-life differences between groups and subgroups. These results demonstrate a further lack of any improvements in QoL following implementation of telehealthcare in COPD.

4.1. Interpretation of findings

The present study hypothesised that adding telehealthcare to usual practice would significantly increase patients' HRQoL [31]. This hypothesis was rejected: despite the lower QoL in the control group, the adjusted mean differences of PCS and MCS measured from baseline to follow-up were not significantly different between the groups. However, despite the non-significant differences, the mean differences in PCS and MCS scores from baseline to the 12-month follow-up were larger for the control group than for the intervention group, which indicates a faster deterioration over time for the control group than for the intervention group. The largest mean difference was seen in MCS, which indicates that the mental health component changed more than the physical health component throughout the period. If this is the case, it might be explained by the difficulty associated with affecting the physical QoL compared with the mental QoL. The slower decline in MCS for the telehealth group may be interpreted as a psychological benefit derived from using the Telekit.

The subgroup analyses indicated no statistically significant effects of the intervention in any of the posteriorly defined subgroups. However, there was an indication of some positive effects on HRQoL within certain subgroups of the intervention group compared with usual practice.

4.2. Strengths and weaknesses

The TeleCare North trial is one of the biggest large-scale studies with this focus internationally and the first large-scale study in Denmark to assess the HRQoL effect of telehealthcare in COPD patients. A total of 1,225 participants from 26 municipality districts in the North Denmark Region were included in the analysis. The trial succeeded in establishing a fruitful cooperation between many stakeholders with different interests in the trial. The trial hence demonstrated the feasibility of intersectoral and interinstitutional collaboration towards a shared end, viz. the implementation of telehealthcare to improve COPD patients' HRQoL.

The TeleCare North trial was based on the same concept, which was studied in previous Danish pilot studies [27–30,36] namely to increase patient empowerment and to detect disease deterioration through self-monitoring. In the present study, we attended to clarify the mechanisms that were supposed to provide effects. Organisational initiatives to further this concept, for example ensuring that patients had functional telehealthcare equipment, instructing patients how to use this equipment, and by gearing the organisation to rapidly respond to reported measures to prevent COPD exacerbations. However, no significant effects of HRQoL were found; and the failure to demonstrate a statistically significant effect, therefore cannot be attributed to patients' lack of equipment, a lack of instructions, or inadequate operational equipment.

We cannot rule out the influence of non-specific effects like a Hawthorne effect [37] or "natural history effects" [38], both of which could have influenced the intervention and the control group to some extent. The potential presence of any such effects may explain why differences in HRQoL between the groups were difficult to detect.

Another possible explanation why we found no significant differences in HRQoL between groups could be related to the telehealthcare system, Telekit, itself. The Telekit may not be equally useful to all patient groups; and use of the system may have affected their quality of life differently. Moreover, we know little about different user groups' different needs for particular functionalities and for instruction in the use of the system. These issues clearly need to be further studied in future studies.

The baseline variables used in the TeleCare North trial were not exhaustive; nor were all relevant variables included. At baseline, the FVC% indicated that the patients in the intervention group were poorer than the patients of the control group. It is widely known that QoL deteriorates with increasing severity of COPD [39]. This may also contribute to explaining why no significant differences in HRQoL were found between the groups. It would have been desirable to supplement the baseline variables with other clinical characteristics such as the Medical Research Council (MRC) score and with activities-of-daily-living measures to determine if the groups differed from each other in relation to their state of health. The

number of selected baseline variables made it possible to classify the patients only according to the old GOLD classification (I-V). It would have been desirable to classify the patients according to the new GOLD classification (A-D) which is based on symptoms, airflow obstruction, and exacerbation history. Use of the new GOLD classification would probably have made it possible to establish more relevant subgroups [32].

The SF-36v2 was selected as an appropriate primary outcome measure because it is a useful, generic, and validated questionnaire for comparing differences between populations. It is possible, however, that generic questionnaires do not adequately measure the QoL issues that different groups of patients experience. It has been shown that the SF-36 is susceptible to ceiling and floor effects as it is applicable to a wide population of both healthy and sick individuals. It is possible that the SF-36v2 was not sufficiently sensitive to changes and to identifying outcome differences in patients with COPD [40]. This was also confirmed by Rixon et al. [25] who suggest that generic instruments are less sensitive to change related to telehealth than disease-specific instruments are. COPD is associated with symptoms that might have an impact on the patients' QoL, which makes it uncertain whether the generic questionnaires capture these aspects. Another alternative for measuring QoL could have been a more disease-specific questionnaire for COPD patients, such as the St. George' Respiratory Questionnaire (SGRQ) [41] and other QoL instruments such as the Chronic Respiratory Questionnaire (CRQ) [42]; the EQ-5D [43] or the Hospital Anxiety and Depression Scale (HAD) [44]. A study by Engström and colleagues [45] illustrated that a combination of generic and disease-specific questionnaires was the most suitable choice for measuring differences in COPD patients' HRQoL following an intervention. They argued that both disease-specific effects and the overall burden of the disease on everyday functioning and mental wellbeing should be considered. This was also confirmed in a review by Chen who recommended the use of both generic and disease-specific questionnaires in combination [40].

Another relevant consideration is whether QoL measures should be expected to change by implementation of telehealthcare. A recent systematic review [18] found that the impact of telehealth on QoL in patients with COPD is limited. However, the review suggested that active interventions may improve QoL outcomes in the telehealth group compared with usual care [18]. Based on this study's results and the literature [5,18,24,25], telehealthcare is not assumed to be convincing when looking at QoL as an isolated factor. However, QoL improvements may be expected over time [25] in active telehealthcare interventions where some kind of self-management skills training is an integrated part of the intervention [18].

4.3. Comparison with other studies

The WSD is the only large-scale study of telehealthcare in COPD that we have come across. The findings from the WSD study by Cartwright and colleagues [24] indicated no improvement in HRQoL from

telehealth, but some significant differences suggested that the telehealth group had a slower rate of deterioration over time compared with the control group. Similarly, no statistical differences in the Telescot study [46] or the "The Virtual Hospital" trial [47] were identified between the control and intervention groups. The results of our study are consistent with the findings from these studies.

The review and meta-analysis by McLean et al. [5] is also relevant to consider; their findings also indicated no improvement in COPD patients' QoL. Another recent review by Cruz et al. [6] indicated inconsistency in HRQoL findings with most of the studies reporting no significant changes in HRQoL. However, the studies included in the reviews used different HRQoL instruments; and it has therefore been recommended to use similar HRQoL instruments in future studies to enable comparisons [5,6].

Nevertheless, the benefits in relation to QoL may be debated although telehealthcare seems unlikely to reduce QoL. One of our previous findings from the TeleCare North trial indicated that the intervention patients experienced enhanced control, freedom, security, and greater awareness of their COPD symptoms when using the telehealthcare system [48]. These benefits are not underpinned by the present study's findings on HRQoL.

4.4. Implications for practice

Our findings indicate that adding telehealthcare to usual practice does not improve HRQoL in patients with COPD. We did not succeed in achieving the HRQoL effects we had hoped for, and the reduced HRQoL in both groups means that it is doubtful whether telehealthcare benefits patients' QoL. Therefore, policymakers and healthcare professionals should consider whether telehealthcare should be implemented to achieve other objectives than improving patients' HRQoL, i.e. saving costs, reducing mortality, affecting other outcome variables, etc.

Furthermore, it is relevant to explore other domains such as physical activity, psychological symptoms and different modes of telehealth application and interventions, which may be important in improving Qol. In addition, more research should be considered within more specific subgroups of COPD patients to assess whether telehealthcare has a particularly beneficial effect on QoL in some groups. It is possible that patients' QoL varies between subgroups. Knowledge of such variation is useful and may inform future implementation of telehealthcare allowing for targeting of specific patient subgroups.

4.5. Future directions

In the future, more research is needed into the underlying mechanisms behind this lack of an identifiable effect. More qualitative research is required to gain a deeper understanding of the mechanism and preconditions needed to improve patients' HRQoL by use of telehealthcare. A greater effort should be dedicated to studying the specific subgroups instead of the population as whole because telehealthcare

systems likely fit some patients better than others. Furthermore, the COPD patients in the present trial were recruited from different municipalities, some of which might have been better at organizing telehealthcare than others. Large-scale studies are therefore not recommended until these underlying mechanisms have been further investigated.

Future studies should recognise telehealthcare as a complex intervention. Such studies should therefore be designed as a mix of randomised controlled trials and other research designs to fully assess complex interventions. It is possible that we have jumped too quickly to large-scale operational trials, and that we should instead have worked more on the initial stages. Furthermore, research on the causal relationship between QoL and patients' socio-demographic and health characteristics is limited, indicating that a number of exploratory studies need to be performed within the TeleCare North trial in the future.

In conclusion, the findings of the present study indicate that the potential of telehealthcare for improving COPD patients' HRQoL is limited. However, it is assumed on the basis of these results that telehealthcare as an additional service alongside the existing clinical care does not lead to poorer QoL.

Acknowledgements

The participation of the Trial Administration Office, the general practitioners, hospitals, healthcare providers and patients in the North Denmark Region is acknowledged. Without their commitment to the implementation of the TeleCare North trial, it would not have been possible to do this study.

Declarations

Detailed description of intervention and comparator: The study protocol is freely available and can be downloaded from: http://www.trialsjournal.com/content/15/1/178.

Details of contributors: PHL, FWU, OKH, and LHE conceived and designed the study and were responsible for its conduct. PHL and FWU managed the study and the data collection. The trial's Administration Office provided administrative support. FWU undertook the data analysis. PHL, FWU, OKH, and LHE interpreted the data. PHL prepared the first draft of the manuscript. OKH, FWU, and LHE revised and contributed to the manuscript. All authors read and approved the final manuscript.

Funding: This paper was funded by the North Denmark Region, the 11 municipalities in the North Denmark Region and by The Obel Family Foundation, the Danish Agency for Digitalization Policy and Strategy and the European Social Fund. The funding agencies had no influence on the design of the study, the analysis, or the shaping of the article. The article is based on the authors' views and not those of the sponsors.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work other than those detailed above; no financial relationships with any organisations that might have any interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethics approval: The trial was presented to the Danish Ethics Committee for Medical Research in the North Denmark Region and no ethical approval was needed. The trial has also been accepted by the Danish Data Protection Agency. All patients gave written informed consent for participation in this study and provided their approval for use of their data for research.

Data sharing: No additional data available.

Figure legends:

Figure 1: The Telekit system consists of a tablet, a blood pressure monitor, a fingertip pulse oximeter and a health precision scale

Figure 2: CONSORT diagram of the TeleCare North trial

References

1 Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. *Lancet* 2007;**370**:765–73. doi:10.1016/S0140-6736(07)61380-4

2 Halbert RJ, Natoli JL, Gano A, *et al.* Global burden of COPD: systematic review and meta-analysis. *Eur Respir J* 2006;**28**:523–32. doi:10.1183/09031936.06.00124605

3 Annandale J, Lewis KE. Can telehealth help patients with COPD? *Nurs Times* 2005;**107**:12–4.http://www.ncbi.nlm.nih.gov/pubmed/21661486

4 Bowles KH, Baugh AC. Applying research evidence to optimize telehomecare. *J Cardiovasc Nurs* 2007;**22**:5–15.http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2874189&tool=pmcentrez&rendertype=abstract

5 McLean S, Nurmatov U, Liu JL, *et al.* Telehealthcare for chronic obstructive pulmonary disease: Cochrane Review and meta-analysis. *Br J Gen Pract* 2012;**62**:739–49. doi:10.3399/bjgp12X658269

6 Cruz J, Brooks D, Marques A. Home telemonitoring effectiveness in COPD: a systematic review. *Int J Clin Pract* 2014;**68**:369–78. doi:10.1111/ijcp.12345

7 Bolton CE, Waters CS, Peirce S, *et al.* Insufficient evidence of benefit: a systematic review of home telemonitoring for COPD. *J Eval Clin Pract* 2011;**17**:1216–22. doi:10.1111/j.1365-2753.2010.01536.x

8 Polisena J, Tran K, Cimon K, *et al.* Home telehealth for chronic obstructive pulmonary disease: a systematic review and meta-analysis. *J Telemed Telecare* 2010;**16**:120–7.

doi:10.1258/jtt.2009.090812

9 Polisena J, Coyle D, Coyle K, *et al.* Home telehealth for chronic disease management: A systematic review and an analysis of economic evaluations. *Int J Technol Assess Health Care* 2009;**25**:339. doi:10.1017/S0266462309990201

10 Franek J. Home telehealth for patients with chronic obstructive pulmonary disease (COPD): an evidence-based analysis. *Ont Health Technol Assess Ser* 2012;**12**:1–58.http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3384362&tool=pmcentrez&rendertype=abstract

11 Jakobsen A, Laursen LC, Ostergaard B, *et al.* Hospital-admitted COPD patients treated at home using telemedicine technology in The Virtual Hospital Trial: methods of a randomized effectiveness trial. *Trials* 2013;**14**:280. doi:10.1186/1745-6215-14-280

12 Kitsiou S, Paré G, Jaana M. Systematic reviews and meta-analyses of home telemonitoring interventions for patients with chronic diseases: a critical assessment of their methodological quality. *J Med Internet Res* 2013;**15**:e150. doi:10.2196/jmir.2770

13 Ekeland AG, Bowes A, Flottorp S. Effectiveness of telemedicine: A systematic review of reviews. *Int J Med Inform* 2010;**79**:736–71. doi:10.1016/j.ijmedinf.2010.08.006

14 Brettle, A J et al. Telehealth - The effects on clinical outcomes, cost effectivness and the patient experience: a systematic overview of the litterature. 2013.

15 Botsis T, Hartvigsen G. Current status and future perspectives in telecare for elderly people suffering from chronic diseases. *J Telemed Telecare* 2008;**14**:195–203. doi:10.1258/jtt.2008.070905

16 Mclean S, Nurmatov U, Jly L, *et al.* Telehealthcare for chronic obstructive pulmonary disease (Review). *Cochrane Libr* 2012;:1–52.

17 Pedone C, Lelli D. Systematic review of telemonitoring in copd: An update. *Pneumonol Alergol Pol* 2015;**83**:476–84. doi:10.5603/PiAP.2015.0077

18 Ulrik CS, Lomholt Gregersen T, Green A, *et al.* Do telemedical interventions improve quality of life in patients with COPD? A systematic review. *Int J Chron Obstruct Pulmon Dis* 2016;**Volume 11**:809. doi:10.2147/COPD.S96079

19 Bower P, Cartwright M, Hirani SP, *et al.* A comprehensive evaluation of the impact of telemonitoring in patients with long-term conditions and social care needs: protocol for the whole systems demonstrator cluster randomised trial. *BMC Health Serv Res* 2011;**11**:184. doi:10.1186/1472-6963-11-184

20 Hirani SP, Beynon M, Cartwright M, *et al.* The effect of telecare on the quality of life and psychological well-being of elderly recipients of social care over a 12-month period: the Whole Systems Demonstrator cluster randomised trial. *Age Ageing* 2014;**43**:334–41. doi:10.1093/ageing/aft185

21 Steventon A, Bardsley M, Billings J, *et al.* Effect of telecare on use of health and social care services: findings from the Whole Systems Demonstrator cluster randomised trial. *Age Ageing* 2013;**42**:501–8. doi:10.1093/ageing/aft008

22 Steventon A, Bardsley M, Billings J, *et al.* Effect of telehealth on use of secondary care and mortality: findings from the Whole System Demonstrator cluster randomised trial. *BMJ* 2012;**344**:e3874–e3874. doi:10.1136/bmj.e3874

23 Henderson C, Knapp M, Fernandez J-L, *et al.* Cost effectiveness of telehealth for patients with long

term conditions (Whole Systems Demonstrator telehealth questionnaire study): nested economic evaluation in a pragmatic, cluster randomised controlled trial. *BMJ* 2013;**346**:f1035–f1035. doi:10.1136/bmj.f1035

24 Cartwright M, Hirani SP, Rixon L, *et al.* Effect of telehealth on quality of life and psychological outcomes over 12 months (Whole Systems Demonstrator telehealth questionnaire study): nested study of patient reported outcomes in a pragmatic, cluster randomised controlled trial. *BMJ* 2013;**346**:f653. doi:10.1136/bmj.f653

25 Rixon L, Hirani SP, Cartwright M, *et al.* A RCT of telehealth for COPD patient's quality of life: the whole system demonstrator evaluation. *Clin Respir J* 2015;:2–25. doi:10.1111/crj.12359

26 Fonden for Velfærdsteknologi. National handlingsplan for udbredelse af telemedicin. 2012. http://www.digst.dk/Digital-velfaerd/~/media/Files/Velfærdsteknologi/Telemedicinsk handlingsplan/Telemedicinsk handlingsplan-web.pdf

27 Haesum LKE, Soerensen N, Dinesen B, *et al.* Cost-utility analysis of a telerehabilitation program: a case study of COPD patients. *Telemed J E Health* 2012;**18**:688–92. doi:10.1089/tmj.2011.0250

28 Huniche L, Dinesen B, Grann O, *et al.* Empowering Patients with COPD using Tele-Homecare Technology. 2010;:48–54. doi:10.3233/978-1-60750-563-1-48

29 Sorknæs AD, Madsen H, Hallas J, *et al.* Nurse tele-consultations with discharged COPD patients reduce early readmissions - an interventional study. *Clin Respir J* 2011;**5**:26–34. doi:10.1111/j.1752-699X.2010.00187.x

30 Sorknaes AD, Bech M, Madsen H, *et al.* The effect of real-time teleconsultations between hospital-based nurses and patients with severe COPD discharged after an exacerbation. *J Telemed Telecare* 2013;**19**:466–74. doi:10.1177/1357633X13512067

31 Udsen FW, Lilholt PH, Hejlesen O, *et al.* Effectiveness and cost-effectiveness of telehealthcare for chronic obstructive pulmonary disease: study protocol for a cluster randomized controlled trial. *Trials* 2014;**15**:178. doi:10.1186/1745-6215-15-178

32 GOLD: Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, And Prevention of Chronic Obstructive Pulmonary Disease. 2015. www.goldcopd.org

33 Davenport TE, Stevens SR, Baroni K, *et al.* Reliability and validity of Short Form 36 Version 2 to measure health perceptions in a sub-group of individuals with fatigue. *Disabil Rehabil* 2011;**33**:2596–604. doi:10.3109/09638288.2011.582925

34 Bentsen SB, Rokne B, Wahl AK. Comparison of health-related quality of life between patients with chronic obstructive pulmonary disease and the general population. *Scand J Caring Sci* 2013;**27**:905–12. doi:10.1111/scs.12002

35 Ellis Tim. The Whole System Demonstrator Programme. York UK: 2009.

36 Dinesen B, Bajersvej F, Seeman J, *et al.* Development of a program for tele-rehabilitation of COPD patients across sectors : co-innovation in a network Presentation of the Telekat case study. 2011;**11**.

37 Konstantinou GN. Pragmatic trials: how to adjust for the 'Hawthorne effect'? *Thorax* 2012;**67**:562–562. doi:10.1136/thoraxjnl-2011-200657

38 Bouchet C, Guillemin F, Briançon S. Nonspecific effects in longitudinal studies: impact on quality of life measures. *J Clin Epidemiol* 1996;**49**:15–20. doi:10.1016/0895-4356(95)00540-4

39 Zamzam M, Azab N, Wahsh R El, *et al.* Quality of life in COPD patients. *Egypt J Chest Dis Tuberc*

2013;**5**:36–40. doi:10.1016/j.ejcdt.2012.08.012

40 Chen T, Li L, Kochen MM. A systematic review: How to choose appropriate health-related quality of life (HRQOL) measures in routine general practice? *J Zhejiang Univ Sci* 2005;**6B**:936–40. doi:10.1631/jzus.2005.B0936

41 Swigris JJ, Brown KK, Behr J, *et al.* The SF-36 and SGRQ: Validity and first look at minimum important differences in IPF. *Respir Med* 2010;**104**:296–304. doi:10.1016/j.rmed.2009.09.006

42 Guyatt GH, Berman LB, Townsend M, *et al.* A measure of quality of life for clinical trials in chronic lung disease. *Thorax* 1987;**42**:773–8. doi:10.1136/thx.42.10.773

43 The EuroQol Group. A New Facility for the Measurement of Health-Related Quality of Life. *Health Policy (New York)* 1990;**16**:199–208.

44 Aylard PR, Gooding JH, McKenna PJ, *et al.* A validation study of three anxiety and depression self-assessment scales. *J Psychosom Res* 1987;**31**:261–8. doi:10.1016/0022-3999(87)90083-3

45 Engström CP, Persson LO, Larsson S, *et al.* Health-related quality of life in COPD: why both disease-specific and generic measures should be used. *Eur Respir J* 2001;**18**:69–76.http://www.ncbi.nlm.nih.gov/pubmed/11510808

46 Pinnock H, Hanley J, McCloughan L, *et al.* Effectiveness of telemonitoring integrated into existing clinical services on hospital admission for exacerbation of chronic obstructive pulmonary disease: researcher blind, multicentre, randomised controlled trial. *Bmj* 2013;**347**:f6070. doi:10.1136/bmj.f6070

47 Jakobsen AS, Laursen LC, Rydahl-Hansen S, *et al.* Home-based telehealth hospitalization for exacerbation of chronic obstructive pulmonary disease: findings from 'the virtual hospital' trial. *Telemed J E Health* 2015;**21**:364–73. doi:10.1089/tmj.2014.0098

48 Lilholt PH, Korsbakke L, Hæsum E. Exploring User Experience of a Telehealth System for the Danish TeleCare North Trial. 2015;:301–5. doi:10.3233/978-1-61499-512-8-301

Figure 1: The Telekit system consists of a tablet, a blood pressure monitor, a fingertip pulse oximeter and a health precision scale.

53x50mm (300 x 300 DPI)

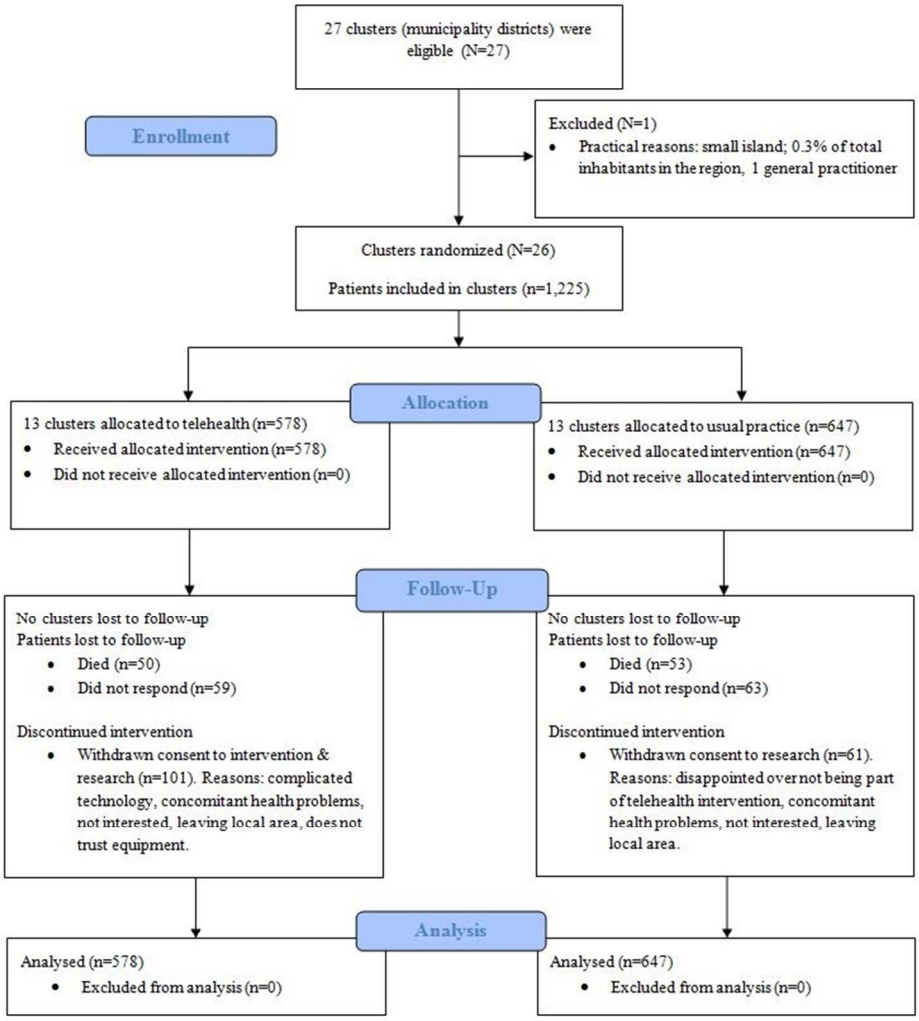

Figure 2: CONSORT diagram of the TeleCare North trial.

66x70mm (300 x 300 DPI)

Table 1: CONSORT 2010 checklist of information to include when reporting a cluster randomised trial

Section/Topic	Item No	Standard Checklist item	Extension for cluster designs	Page No *
Title and abstract				
	1a	Identification as a randomised trial in the title	Identification as a cluster randomised trial in the title	Page 1 in manus
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)[1,2]	See table 2	Page 2 in manus
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	Rationale for using a cluster design	Pages 3-4 in manus
	2b	Specific objectives or hypotheses	Whether objectives pertain to the the cluster level, the individual participant level or both	Page 3-4 in manus Page 4 in protocol
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Definition of cluster and description of how the design features apply to the clusters	Page 4 in manus Page 2-3 in protocol
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		
Participants	4a	Eligibility criteria for participants	Eligibility criteria for clusters	Page 4 in manus Page 2-3 in protocol
	4b	Settings and locations where the data were collected		Page 5 in manus Page 3 in

				protocol
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Whether interventions pertain to the cluster level, the individual participant level or both	Page 5 in manus Page 4-5 in protocol
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Whether outcome measures pertain to the cluster level, the individual participant level or both	Page 6 in manus Page 5 in protocol
	6b	Any changes to trial outcomes after the trial commenced, with reasons		
Sample size	7a	How sample size was determined	Method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a coefficient of intracluster correlation (ICC or *k*), and an indication of its uncertainty	Page 6 in manus Page 5 in protocol
	7b	When applicable, explanation of any interim analyses and stopping guidelines		
Randomisation:				
Sequence generation	8a	Method used to generate the random allocation sequence		Page 5 in manus Page 3 in protocol
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Details of stratification or matching if used	Page 5 in manus Page 3 in protocol
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level or both	Page 5 in manus Page 3 in protocol

Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Replace by 10a, 10b and 10c	
	10a		Who generated the random allocation sequence, who enrolled clusters, and who assigned clusters to interventions	Page 2-3 in protocol
	10b		Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete enumeration, random sampling)	Page 2-3 in protocol
	10c		From whom consent was sought (representatives of the cluster, or individual cluster members, or both), and whether consent was sought before or after randomisation	Page 3 in protocol
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how		
	11b	If relevant, description of the similarity of interventions		Page 7 in manus
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	How clustering was taken into account	Page 6 in manus Page 5 in protocol
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		Page 6 in manus Page 5 in protocol
Results				
Participant flow (a diagram is strongly	13a	For each group, the numbers of participants who were	For each group, the numbers of clusters that were randomly	Figure 1 in

recommended)		randomly assigned, received intended treatment, and were analysed for the primary outcome	assigned, received intended treatment, and were analysed for the primary outcome	manus
	13b	For each group, losses and exclusions after randomisation, together with reasons	For each group, losses and exclusions for both clusters and individual cluster members	Figure 2 in manus
Recruitment	14a	Dates defining the periods of recruitment and follow-up		Page 2 in protocol Page 7 in manus
	14b	Why the trial ended or was stopped		
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Baseline characteristics for the individual and cluster levels as applicable for each group	Table 1 in manus
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	For each group, number of clusters included in each analysis	Page 3 in protocol Page 7 in manus
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or k) for each primary outcome	Page 7-8 in manus
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory		Page 8 in manus
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms[3])		

Discussion				
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses		Page 9 in manus
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Generalisability to clusters and/or individual participants (as relevant)	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence		Page 9 in manus
Other information				
Registration	23	Registration number and name of trial registry		Page 2 in manus
Protocol	24	Where the full trial protocol can be accessed, if available		Page 4 in manus
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders		Page 16 in manus

** Note: page numbers optional depending on journal requirements*

Table 2: Extension of CONSORT for abstracts[1,2] to reports of cluster randomised trials

Item	Standard Checklist item	Extension for cluster trials
Title	Identification of study as randomised	**Identification of study as cluster randomised**
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	**Eligibility criteria for clusters**
Interventions	Interventions intended for each group	
Objective	Specific objective or hypothesis	**Whether objective or hypothesis pertains to the cluster level, the individual participant level or both**
Outcome	Clearly defined primary outcome for this report	**Whether the primary outcome pertains to the cluster level, the individual participant level or both**
Randomization	How participants were allocated to interventions	**How clusters were allocated to interventions**
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	
Results		
Numbers randomized	Number of participants randomized to each group	**Number of clusters randomized to each group**
Recruitment	Trial status[1]	
Numbers analysed	Number of participants analysed in each group	**Number of clusters analysed in each group**
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	**Results at the cluster or individual participant level as applicable for each primary outcome**
Harms	Important adverse events or side effects	
Conclusions	General interpretation of the results	
Trial registration	Registration number and name of trial register	
Funding	Source of funding	

[1] Relevant to Conference Abstracts

REFERENCES

1 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomised trials in journal and conference abstracts. *Lancet* 2008, 371:281-283

2 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG at al (2008) CONSORT for reporting randomized controlled trials in journal and conference abstracts: explanation and elaboration. *PLoS Med* 5(1): e20

3 Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, Moher D. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004; 141(10):781-788.

BMJ Open

Telehealthcare for patients suffering from COPD: Effects on health-related quality of life - Results from the Danish "TeleCare North" cluster-randomised trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014587.R1
Article Type:	Research
Date Submitted by the Author:	21-Dec-2016
Complete List of Authors:	Lilholt, Pernille; Aalborg University, Faculty of Medicine, Department of Health Science and Technology Witt Udsen, Flemming; Aalborg University, Danish Center for Healthcare Improvements Ehlers, Lars; Aalborg University, Danish Centre for Healthcare Improvements, Faculty of Social Sciences and Faculty of Medicine Hejlesen, Ole; Aalborg University, Faculty of Medicine, Department of Health Science and Technology
Primary Subject Heading:	Health informatics
Secondary Subject Heading:	Health services research, Medical management, Evidence based practice
Keywords:	Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS, telehealth, COPD, Effectiveness, Quality of Life, Outcome Assessment (Health Care)

Telehealthcare for patients suffering from COPD: Effects on health-related quality of life - Results from the Danish "TeleCare North" cluster-randomised trial

Pernille Heyckendorff Lilholt, *PhD candidate*[a, 1], Flemming Witt Udsen, *PhD candidate*[b], Lars H. Ehlers, *Professor*[b] & Ole K. Hejlesen, *Professor*[a]

[a]Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Denmark

[b]Danish Centre for Healthcare Improvements, Faculty of Social Sciences and Faculty of Medicine, Aalborg University, Denmark

Correspondence[1]: Pernille Heyckendorff Lilholt, Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Denmark. Fredrik Bajers Vej 7C (C1-223), DK-9220 Aalborg Ø, Denmark (E-mail: phl@hst.aau.dk)

Word count (excluding title page, abstract, references, figures and tables): 4,747

Abstract

Objective: To assess the effect of telehealthcare compared with usual practice in patients with chronic obstructive pulmonary disease (COPD).

Design: This was a cluster-randomised trial with 26 municipal districts that were randomly assigned either to an intervention group whose members received telehealthcare in addition to usual practice or to a control group whose members received usual practice only (13 district in each arm).

Setting: 26 municipal districts in the North Denmark Region of Denmark.

Participants: Patients who fulfilled the Global Initiative for COPD (GOLD) guidelines and one of the following criteria: COPD Assessment Test (CAT) score ≥ 10; or Medical Research Dyspnoea Council Scale (MRC) ≥ 3 or mModified Medical Research Dyspnoea Council Scale (MMRC) ≥ 2; or ≥ 2 exacerbations during the past 12 months.

Main outcome measures: Health-related quality of life (HRQoL) assessed by the physical component summary (PCS) and mental component summary (MCS) scores of the Short Form 36-Item Health Survey, Version 2 (SF-36v2). Data were collected at baseline and at 12-month follow-up and analysed according to the intention-to-treat principle with complete cases, n=574 (258 intervention; 316 controls) and imputed data, n=1,225 (578 intervention, 647 controls) using multilevel modelling.

Results: The raw mean difference in PCS score from baseline to 12-month follow-up was -2.62 (SD: 12.41) in the telehealthcare group and -2.83 (SD: 11.89) in the usual practice group. The raw mean difference in MCS scores in the same period were -4.69 (SD: 16.52) and -5.31 (SD: 15.51) for telehealthcare and usual practice, respectively. The adjusted mean difference in PCS between groups at 12 months was 0.14 (95% CI: -1.37; 1.65). The adjusted mean difference in MCS between groups at 12 months was 0.36 (95% CI: -1.68; 2.40).

Conclusions: The overall sample and all subgroups demonstrated no statistically significant differences in HRQoL between telehealthcare and usual practice.

Trial registration: ClinicalTrials.gov, NCT01984840, November 14, 2013.

Keywords: Effectiveness; COPD; Telemedicine; RCT; Denmark; Quality of Life; Telehealth; Telemonitoring; Outcome Assessment (Health Care)

Strengths and limitations of this study

- This is the first large-scale trial in Denmark established to remedy the lack of international evidence on HRQoL in patients with COPD who are receiving telehealthcare
- The study is a large-scale, pragmatic, two-level, cluster-randomised trial with 12-month follow-up, which produces results applicable to clinical practice
- The trial succeeded in establishing a fruitful inter-sectoral and inter-institutional cooperation towards a common goal; the implementation of telehealthcare to improve COPD patients' HRQoL
- SF-36v2 was used as a quality-of-life instrument, but may be less sensitive to change related to telehealthcare. It would have been desirable to employ a combination of generic and disease-specific questionnaires in this study
- A considerable high attrition rate (651/1,225 patients being incomplete cases or lost-to-follow-up) was present, which could have introduced bias and affected the strength of the trial's findings

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a significant cause of impaired quality of life (QoL), disability, morbidity, and mortality in industrialised countries [1,2]. Moreover, it constitutes a considerable burden on the affected patients and places an important socio-economic burden on society due to the growing number of patients requiring care. COPD, and other chronic diseases, challenge the healthcare systems in ways that call for changes in management and delivery of patient care [3,4].

Telehealthcare has the potential to facilitate timely transmission of clinical and physiological data and allows patients to be followed by clinicians more frequently and from a distance [5]. It may therefore also facilitate early intervention and improve clinical and patient-related outcomes [6]. Systematic reviews conclude that there is a potential for demonstrating that telehealthcare improves health-related outcomes or is at least as good as conventional treatment, but more research is needed [7–9]. Some reviews [10–12] raise concerns about the quality of the available evidence that is presented in heterogeneous pilot projects which are small, incomparable, and difficult to appraise in relation to QoL [13–17]. A recent systematic review [18] indicates only limited evidence for a positive effect of telehealth interventions on QoL in COPD. This situation has given rise to a demand for large-scale studies; and a large-scale study, The Whole System Demonstrator Project (WSD) conducted in the UK, has attempted to establish a robust evidence base for telehealth [19–23]. In the WSD, Cartwright and colleagues [24] concluded that the effect of telehealth was clinically insignificant as a supplement to usual care, and telehealth did not improve psychological outcomes and QoL in patients with COPD, heart failure, or diabetes [24]. In a recent randomised controlled

trial (RCT), a more extensive assessment of QoL and psychological outcomes was performed on the COPD cohort of the WSD [25]. The findings from the RCT [25] are consistent with the above conclusion made by Cartwright and colleagues [24]. However, the RCT found no reductions in patients' QoL in the longer term. In contrast, there was a trend towards improved QoL and mood in the telehealth group at longer-term follow-up, but not at the short term follow-up, as observed through disease-specific measures [25].

In Denmark, the lack of evidence for telehealthcare was discussed among healthcare decision-makers who agreed to strengthen the evidence base by conducing a large-scale study as part of "The National Danish Action Plan for Dissemination of Telemedicine" [26]. In 2012, the Danish Government decided to launch the Action Plan to disseminate telemedicine nationally [26]. The action plan included, among others, the TeleCare North trial, the purpose of which was to contribute to the generation of valuable knowledge about the use of telehealthcare for COPD patients in the North Denmark Region. The TeleCare North trial was designed based on experiences from two Danish pilot studies; the TeleKat Study [27,28] and the Nursing Consultations Study [29,30], which had both demonstrated positive effects of telehomecare and teleconsultations.

The present study is embedded in the Danish TeleCare North trial. Its objective was to assess the effectiveness of telehealthcare compared with usual practice based on an assessment of HRQoL in COPD patients. It was hypothesised that adding telehealthcare to usual practice would significantly enhance patients' HRQoL [31].

2. Methods

2.1. Study design

This study was conducted in accordance with the study protocol for the TeleCare North trial [31], which we describe briefly in this section.

The TeleCare North trial was a large-scale, pragmatic, two-level, cluster-randomised trial with 12-month follow-up. The trial was based on the collaborative efforts of the North Denmark Region, all municipalities in the Region, the Region's general practitioners (GPs), and Aalborg University. The municipalities were organised into 26 districts with 13 clusters in each arm.

2.2. Participants

The trial targeted all COPD patients in the North Denmark Region who fulfilled the inclusion criteria. All GPs from the Region recruited the COPD patients from a list of suitable patients attending their practices. The

selection of participants followed identical guidelines and instructions at all practices. All patients who accepted to participate and were deemed suitable for participation were included. The identification and recruitment of patients took place prior to random allocation of clusters in order to minimise biased recruitment. Assigned to the intervention or to usual practice were 1,225 (578 intervention, 647 controls) patients representing different COPD stages, GOLD I-IV (Global Initiative for Chronic Obstructive Lung Disease) [32].

2.2.1. Inclusion and exclusion criteria

All COPD patients who may benefit from telehealthcare were considered for inclusion. The following inclusion criteria were used: Patients were required to have COPD as their primary disease and be diagnosed by spirometry, and they should receive or be motivated for treatment corresponding to the GOLD guidelines [32]. One of the following criteria should also be met: A Medical Research Dyspnoea Council scale (MRC) score ≥ 3; or a modified Medical Research Dyspnoea Council scale (MMRC) score ≥ 2; or a COPD Assessment Test (CAT) score ≥ 10; or ≥ 2 exacerbations during the past 12 months.

In addition, on the basis of a health professional's qualified estimate and assessment, the patients should also have a telephone connection, have permanent residence, and be on the list of a GP in the North Denmark Region. Patients should also be able to speak Danish or they should be living with Danish-speaking relatives who were able to support them in their use of the telehealthcare system and to provide assistance in situations involving issues of comprehension of the Danish language.

Patients were excluded if they were cognitively impaired, had no phone line or GSM coverage, or were unable to understand Danish to the extent allowing them to complete the study questionnaires.

2.3. Intervention

The intervention of the TeleCare North trial was based on the concept and logic of the TeleKat study [28]. Its key concept and primary logic was empowerment achieved by engaging COPD patients in their illness and increasing their coping abilities through self-monitoring. The study introduced extended monitoring with store-and-forward data connected to healthcare providers to facilitate detection of exacerbations and rapidly initiate preventive antibiotic therapy.

2.3.1. Telehealthcare

Patients in the intervention group received telehealthcare in addition to usual practice. The telehealthcare system coined "Telekit" was used in the TeleCare North trial. It consists of a Samsung Galaxy Tab2 (10.1) with associated devices: a digital blood pressure monitor (UA-767, plus BT-C, Nonin Medical, Minnesota, USA), a fingertip pulse oximeter (Nonin, Onyx II% SpO^2), and a health precision scale (UC-321PBT-C, A&D

Medical, Tokyo, Japan). The devices can collect and wirelessly transmit relevant disease-specific data consisting of answers to questions related to COPD exacerbations, symptoms, and patients' vital signs: systolic and diastolic blood pressure, heart rate, weight, and oxygen saturation (Figure 1). The patients were instructed to measure their vital signs, which were then sent asynchronously to municipality healthcare personnel who subsequently established if these data deviated from the normal threshold values. The communication between the healthcare personnel and the patient was one-way only. The patients were contacted if there were adverse changes in their values and responses. Patients were also contacted if the measurements were not carried out as agreed or the measurements were not received as expected.

2.3.2. Usual practice

Patients in the control group received their existing usual practice. This involved treatment, monitoring, and care throughout the study period. The patients' GPs provided this treatment and monitoring, and the municipalities held responsibility for the practical help and care provided. The patients in the control group had not received any form of telehealthcare system; but at the end of the 12-months study period, they were offered the same Telekit system as the intervention group for ethical reasons.

2.4. Randomisation

On November 4, 2013, the municipality districts (n = 26) were randomised so that patients residing in the same district received the same type of care – either telehealthcare in addition to usual practice, or usual practice only. The municipality districts were matched 1:1 by the following variables: the total population size of the districts; the proportion of people with a higher education; the sum of the district's total income; unemployment; and the estimated number of patients with COPD [31]. The districts were distributed randomly by a blinded volunteer with no relation to the trial who performed the randomisation by throwing a dice. The volunteer had no knowledge of the distribution of districts on intervention or control group, respectively. The randomisation was recorded by the trial administration secretariat to ensure that the procedure was performed randomly.

2.5. Outcome measures

Upon inclusion at the GP's office, patients were handed a questionnaire comprising the Short Form 36-Item Health Survey version 2 (SF-36v2) [33] and questions concerning their baseline demographic characteristics such as gender, age, education, comorbidities, smoking status, marital status, and job status. The SF-36v2 consists of 36 questions and is one of the most commonly used generic, validated questionnaires for measuring general HRQoL. It captures patients' perceptions of physical, social, mental, and emotional

domains, and overall summary scores of physical (PCS) and mental components (MCS) are derived from domain scores using a norm-based scoring method [34]. The scores are standardised to fall between 0 and 100 with a higher score indicating "better health" [33]. After 12 months, a similar patient questionnaire was sent to the included patients to compare baseline data with follow-up data. The outcomes of this study were the patients' mean differences in HRQoL at baseline and at the 12-month follow-up assessed with SF-36v2. The primary outcome measure was the adjusted mean differences in PCS summary scores between treatment groups at 12 month follow-up.

2.6. Sample size

The sample size calculation was based on the study protocol's [31] primary outcome measure, PCS. Based on results from a previous Norwegian study [35], it was estimated that eligible COPD patients had a mean baseline PCS score of 38 with a standard deviation of 10. The average cluster size was assumed to be 50 with a coefficient of variation of 0.5. A sample size of 350 patients from at least seven municipality districts (clusters) in each arm (two-sided significance level, $\alpha = 0.05$, power = 80%) was needed to detect minimal, clinically important differences (change equal to 5) and intracluster correlation ((ICC) equal to 0.05)) between the intervention group and the control group [35]. The total required sample size was estimated to be around 800 patients with an expected lost-to-follow-up-rate of 10%.

2.7. Statistical analysis

All analyses of the cluster-randomised trial were conducted according to the intention-to-treat principle. A post hoc subgroup analysis was also performed as a secondary analysis. The analyses were undertaken in STATA 12.1.

SF-36v2 standardised scores for each patient were produced using Software provided by QualityMetric Incorporated (http://www.sf-36.org/), which converts all scores to a single metric (Norm-based scoring) based on 2009 US general population norms [34]. An ANCOVA analysis strategy was applied [36]. Two separate linear mixed models for continuous outcomes were used to assess PCS and MCS scores at 12-month follow-up controlling for treatment arm, respective baseline score, age, gender, baseline forced expiratory volume in one second (FEV1%), marital status, diabetes status, cancer status, and clustering at the municipality district level. The clusters were assumed to be represented as random effects, and the models had robust covariance structures. ICC estimates of patient-reported outcome variables were calculated for measurement of the variability within and across the clusters. The subgroup analyses applied the same statistical models and covariates as above, but with added treatment-by-covariate interaction for each subgroup.

Missing data were assumed missing at random and were handled in coordination with the health economic evaluation of the same trial as described in the trial protocol [31] and followed good practices for handling missing data in cost-effectiveness research [37]. Missing PCS and MCS scores and baseline characteristics were imputed using multiple imputation and were estimated separately by treatment group to allow for differential covariance structures in treatment group means. Imputation models included PCS and MCS scores, predictors for these scores at both time points, predictors for missing observations in the individual variables, and all baseline characteristics. Continuous variables were imputed by predictive mean matching and categorical variables by multinominal logistic or logistic regression. The variables included were non-missing health-related quality-of-life (HRQoL) (PCS and MCS scores), measures of disease status (FEV1%, forced vital capacity (FVC%)), diastolic and systolic blood pressure), smoking status, duration of COPD, potential comorbidities (diabetes, cardiovascular disease, mental illness, musculoskeletal disorders, or cancer), socio-demographic variables (age, gender, marital status, education, employment status) and clustering. The imputation models involved the generation of 30 complete datasets combined by Rubin's rule. Imputations were not performed on subjects that died during the 12 months but their summary scores were assigned values of 0 [38].

The primary analysis and subgroup analysis were based on imputed data, but a complete case analysis was also included as a sensitivity analysis to check the robustness of the main trial findings.

3. Results

3.1. Descriptive characteristics

The CONSORT diagram is shown in Figure 2. Twenty-six municipal districts (13 intervention clusters; 13 control clusters) were randomised in 2013, and the TeleCare North trial was completed after the 12-month assessment in 2015. At baseline, 1,225 (578 intervention, 647 controls) patients were enrolled in the TeleCare North trial. At 12 months, 109 (18.86%) intervention patients were lost to follow-up (50 were dead, 59 did not respond on questionnaires) and 116 (17.93%) control patients (53 were dead, 63 did not respond on questionnaires after baseline). 101 (17.47%) patients in the intervention group and 61 (9.43%) patients in the control group withdrew their consent. Reasons for withdrawing from the TeleCare North trial included: complicated technology; concomitant health problems; not interested; leaving local geographical area; does not trust the equipment; or disappointed over not being a part of the telehealth intervention. None of the twenty-six clusters were lost to follow-up. At 12 months, 264 (110 intervention, 154 controls) patients had incomplete data (patients that were not lost-to-follow-up but had missing values on items in either PCS or MCS at baseline or follow-up). Complete data (patients with nonmissing values on

MCS and PCS score at baseline and follow-up) were available for 574 (258 intervention; 316 controls) of the 1,225 patients at 12 month follow-up, giving an attrition rate of 53% (Figure 2).

At baseline, we assessed socio-demographic factors (gender, age, marital status) and health characteristics (smoking status, duration of COPD, FEV1%, FVC%, comorbidities, SF-36). Statistical comparisons of the participants' baseline characteristics demonstrated that the two study groups were similar, except for statistically significant differences in FVC% ($p < 0.05$). The control group's mean FVC% (74.34%) was slightly higher than the intervention group's mean FVC% (70.38%) (Table 1).

Table 1: Baseline characteristics, at baseline and at 12-month follow-up.

Characteristics	All participants at baseline			Complete cases at 12 months follow-up#			Lost-to-follow-up at 12 months##			Incomplete cases at 12 months follow-up###		
	THC *n=578*	UP *n=647*	Diff *Raw*	THC *n=258*	UP *n=316*	Diff *Raw*	THC *n=210*	UP *n=177*	Diff *Raw*	THC *n=110*	UP *n=154*	Diff *Raw*
Age (years)§	69.55 (9.36)	70.33 (9.11)	-0.78	68.24 (8.84)	69.51 (9.08)	-1.27	70.46 (10.19)	71.82 (9.49)	-1.36	70.91 (8.54)	70.32 (8.55)	-0.59
Men (%)§	48.27 (n=279)	43.74 (n=283)	4.53	53.49 (n=138)	44.62 (n=141)	8.87*	45.24 (n=95)	45.76 (n=81)	-0.52	41.82 (n=46)	39.61 (n=61)	2.21
Marital status (%)												
Married/in a relationship	55.88 (n=323)	54.25 (n=351)	1.63	70.16 (n=181)	62.03 (n=196)	8.13	40.00 (n=84)	45.20 (n=80)	-5.20	52.73 (n=58)	48.70 (n=75)	4.03
Single	20.42 (n=118)	22.10 (n=143)	-1.68	17.44 (n=45)	22.15 (n=70)	-4.71	24.76 (n=52)	23.16 (n=41)	1.60	19.06 (n=21)	20.78 (n=32)	-1.69
Widow/widower	16.78 (n=97)	16.54 (n=107)	0.24	12.02 (n=31)	15.19 (n=48)	-3.17	22.86 (n=48)	19.21 (n=34)	3.65	16.36 (n=18)	16.23 (n=25)	0.10
Missing (%)	6.92 (n=40)	7.11 (n=46)	-0.19	0.39 (n=1)	0.63 (n=2)	-0.24	12.38 (n=26)	12.43 (n=22)	-0.05	11.82 (n=13)	14.29 (n=22)	-2.47
Smoking status (%)												
Non-smokers	59.34 (n=343)	63.06 (n=408)	-3.72	66.28 (n=171)	67.41 (n=213)	-1.13	50.95 (n=107)	61.02 (n=108)	-10.07	59.09 (n=65)	56.49 (n=87)	2.60
Smokers	33.91 (n=196)	29.21 (n=189)	4.70	32.95 (n=85)	31.01 (n=98)	1.94	36.76 (n=77)	26.55 (n=47)	10.12	30.91 (n=34)	28.57 (n=44)	2.34
Missing (%)	6.75 (n=39)	7.73 (n=50)	-0.98	0.78 (n=2)	1.58 (n=5)	-0.80	12.38 (n=26)	12.43 (n=22)	-0.05	10.00 (n=11)	14.94 (n=23)	-4.94
Duration of COPD (years)	7.80 (6.23)	7.70 (5.79)	0.10	7.58 (6.48)	7.47 (5.36)	0.11	7.99 (6.45)	8.37 (6.40)	-0.38	8.00 (5.13)	7.50 (6.04)	0.50
Missing (%)	14.01 (n=81)	15.14 (n=98)	-1.13	7.75 (n=20)	8.23 (n=26)	-0.48	21.43 (n=45)	22.03 (n=39)	-0.60	14.55 (n=16)	21.43 (n=33)	-6.88
FEV1 (%)	47.70 (18.05)	48.37 (18.94)	-0.67	48.87 (18.31)	50.26 (19.82)	-1.39	47.72 (18.94)	45.65 (17.92)	2.07	45.06 (15.62)	47.74 (17.91)	-2.68
Missing (%)	18.51 (n=107)	19.78 (n=128)	-1.27	18.22 (n=47)	19.94 (n=63)	-1.72	21.43 (n=45)	15.82 (n=28)	5.61	13.64 (n=15)	24.03 (n=37)	-10.39

FVC (%)	70.38 (20.02)	73.34 (22.33)	-3.96**	71.22 (19.13)	75.43 (21.73)	-3.71	70.63 (21.34)	73.22 (24.56)	-2.59	66.44 (19.41)	73.31 (20.83)	-6.87**
Missing (%)	34.43 (n=199)	39.41 (n=255)	-4.98	31.01 (n=80)	37.97 (n=120)	-6.96	37.14 (n=78)	38.42 (n=68)	-1.28	37.27 (n=41)	43.51 (n=67)	-6.24
Comorbidities (%)												
Diabetes	10.21 (n=59)	9.89 (n=64)	0.32	8.91 (n=23)	9.81 (n=31)	-0.90	10.48 (n=22)	8.47 (n=15)	2.01	12.73 (n=14)	11.69 (n=18)	1.04
Coronary heart disease	32.70 (n=189)	31.84 (n=206)	0.86	32.56 (n=84)	32.28 (n=102)	0.28	36.19 (n=76)	34.46 (n=61)	1.73	26.36 (n=29)	27.92 (n=43)	-1.56
Mental health problem	4.84 (n=28)	4.79 (n=31)	0.05	4.26 (n=11)	5.06 (n=16)	-0.80	7.14 (n=15)	5.08 (n=9)	2.06	1.81 (n=2)	3.90 (n=6)	-2.08
Musculoskeletal disorder	24.91 (n=144)	29.37 (n=190)	-4.46	27.91 (n=72)	29.11 (n=92)	-1.20	22.38 (n=47)	31.07 (n=55)	-8.69	22.73 (n=25)	27.92 (n=43)	-5.19
Cancer	6.06 (n=35)	4.79 (n=31)	1.27	5.81 (n=15)	4.43 (n=14)	1.38	5.71 (n=12)	5.65 (n=10)	0.06	7.27 (n=8)	4.55 (n=7)	2.72
Missing (%)	8.13 (n=47)	7.88 (n=51)	0.25	1.94 (n=5)	2.22 (n=7)	-0.28	13.81 (n=29)	12.43 (n=22)	1.38	11.81 (n=13)	14.29 (n=22)	-2.47
Baseline PCS	37.48 (9.21)	37.71 (8.93)	-0.23	38.24 (9.06)	38.21 (9.15)	0.03	36.04 (9.10)	36.21 (8.44)	-0.16	37.75 (10.11)	37.88 (8.39)	-0.13
Missing (%)	23.88 (n=138)	25.50 (n=165)	1.62	0.00 (n=0)	0.00 (n=0)	0.00	31.90 (n=67)	37.85 (n=67)	-5.95	64.55 (n=71)	63.64 (n=98)	0.91
Baseline MCS	48.48 (11.59)	48.91 (11.22)	-0.43	49.92 (11.03)	50.63 (10.76)	-0.71	45.98 (12.25)	45.05 (11.56)	0.92	48.13 (11.49)	46.80 (11.04)	1.33
Missing (%)	23.88 (n=138)	25.50 (n=165)	1.62	0.00 (n=0)	0.00 (n=0)	0.00	31.90 (n=67)	37.85 (n=67)	-5.95	64.55 (n=71)	63.64 (n=98)	0.91

Data are mean (standard deviation) or proportion (number of patients)
All data is based on norms based scoring
THC: telehealthcare; UP: usual practice; Diff: difference
COPD: chronic obstructive pulmonary disease; FEV1(%): forced expiratory volume in one second of predicted normal; FVC(%): forced vital capacity
#Complete case: a case that have nonmissing values on MCS and PCS score at baseline and follow-up
##Lost-to-follow-up: cases that died, withdrew consent or did not return any study questionnaires after baseline
###Incomplete case: a case that is not lost to follow-up but has missing values on items in either PCS and MCS at baseline or follow-up
§ Variable has no missing values
*Fischer's exact test for differences in proportions of patients in telehealth group and usual practice group (at baseline, complete cases, lost-to-follow-up and incomplete cases), P < 0.05
**Mann-Whitney's test for differences in mean in telehealth group and usual practice group (at baseline, complete cases, lost-to-follow-up and incomplete cases), P < 0.05

3.1.1. Preliminary descriptive analysis of PCS and MCS summary scores

Table 2 presents descriptive statistics of PCS and MCS scores over time for the two analysis cohorts, complete cases (n=574) and available cases (n=1,225) in each treatment arm.

Table 2: Descriptive analysis of PCS and MCS summary scores.

	Primary analysis (n=1,225)#		Complete case analysis (n=574)	
	THC	UP	THC	UP
PCS at follow-up	34.63 (13.93)	34.73 (13.76)	38.27 (9.60)	38.12 (9.60)
MCS at follow-up	43.37 (17.20)	43.54 (17.28)	48.39 (11.15)	48.60 (11.42)
Difference in PCS scores from baseline to follow-up*	-2.62 (12.41)	-2.83 (11.89)	0.03 (7.12)	-0.09 (6.66)

Difference in MCS scores from baseline to follow-up*	-4.69 (16.52)	-5.31 (15.51)	-1.52 (10.62)	-2.03 (8.73)

Data are Mean (SD)
All data in based on norms-based scoring
PCS=physical component score; MCS=mental component score
THC: telehealthcare; UP: usual practice
*Follow-up score minus baseline score
#Primary analysis has imputed missing PCS and MCS summary scores

At follow-up, lower scores of mean PCS and MCS were represented in the primary analysis (n=1,225) compared with the complete case analysis (n=574). In the primary analysis, the raw mean difference in PCS scores from baseline to follow up was -2.62 (SD: 12.41) in the telehealthcare group and -2.83 (SD: 11.89) in the usual practice group. The raw mean difference in MCS scores in the same period were -4.69 (SD: 16.52) and -5.31 (SD: 15.51) for telehealthcare and usual practice, respectively (Table 2).

In the complete case analysis, the raw mean difference in PCS scores over time was 0.03 (SD: 7.12) in the telehealthcare group and -0.09 (SD: 6.66) in the usual practice group. The raw difference in MCS scores were -1.52 (SD: 10.62) and -2.03 (SD: 8.73) for telehealthcare and usual practice, respectively. A comparison of the raw differences in PCS and MCS scores between the two analysis cohorts' indicated that both complete cases and available cases scored lower HRQoL from baseline to follow-up, except for the telehealthcare group's PCS score from the complete case analysis, which score increased from baseline to follow-up (Table 2).

3.2. Primary analysis and complete case analysis

3.2.1. Adjusted outcomes

Table 3 presents adjusted mean difference in summary scores between treatment groups at 12-month follow-up for each analysis cohort.

Table 3: Adjusted mean difference in PCS and MCS summary scores between groups, 12-month follow-up.

	Primary analysis (n=1,225)#	ICC	Complete case analysis (n=574)	ICC
PCS (adjusted mean difference)*	0.14 (-1.37; 1.65)	0.00	0.17 (-0.93; 1.28)	0.00
MCS (adjusted mean difference)*	0.36 (-1.68; 2.40)	0.00	0.38 (-0.98; 1.73)	0.00

Data are Mean (95% CI)
All data is based on norms based scoring
Primary analysis have imputed missing PCS and MCS summary scores
*Adjusted mean differences are based on multilevel models controlling for all mentioned covariates and clustering.
Differences can be interpreted as the observed extra effect of telehealthcare compared to usual practice when all mentioned covariates and clustering are taken into account.
PCS=physical component score; MCS=mental component score; ICC=Intra-class coefficient

In the primary analysis (n=1,225), the adjusted mean differences in summary scores at 12-month follow-up were, PCS: 0.14 (95% CI, -1.37; 1.65) and MCS: 0.36 (95% CI, -1.68; 2.40). The overlapping confidence intervals indicated that differences between groups at 12-month follow-up were non-significant (Table 3).

In the complete case analysis (n=574), the adjusted mean differences in summary scores at 12-month follow-up were, PCS: 0.17 (95% CI, -0.93; 1.28) and MCS: 0.38 (95% CI, -0.98; 1.73). The adjusted outcomes indicated no evidence of statistically significant differences between groups at 12-month follow-up (all confidence intervals crossed 0) (Table 3).

3.2.2. Secondary analysis

We also performed a posteriori-defined subgroup analysis which showed no statistically significant effect of the intervention in any of the defined subgroups. Tables 4 and 5 provide estimates of both adjusted mean differences in PCS and MCS summary scores, 95% confidence intervals and p-values for the total sample and for subgroups (Table 4, Table 5).

Table 4: Primary outcome and subgroup analyses of the COPD patients' socio-demographic characteristics: Adjusted mean differences in PCS and MCS summary scores for the total sample and subgroups, adjusted for respective baseline PCS or baseline MCS scores and age, gender, baseline FEV1, marital status, cancer and diabetes.

Socio-demographic characteristics								
Effectiveness	**PCS**	**PCS 95% CI**	**Wald test**	**ICC**	**MCS**	**MCS 95% CI**	**Wald test**	**ICC**
Total sample	0.14	[-1.37;1.65]	**P value**	0.00	0.36	[-1.68;2.40]	**P value**	0.00
Gender								
Female (54%)	-0.27	[-1.61;1.08]	0.56	0.00	-0.45	[-2.57;1.66]	0.31	0.00
Male (46%)	0.54	[-2.07;3.15]			-1.31	[-1.86;4.49]		
Age								
< 60 years (16%)	-0.48	[-4.02;3.07]	0.65	0.00	-0.10	[-4.34;4.13]	0.91	0.00
60-69 years (33%)	-1.17	[-3.18;0.85]			-0.70	[-3.74;2.33]		
70-79 years (38%)	0.99	[-1.88;3.86]			0.72	[-2.74;4.19]		
≥ 80 years (13%)	1.70	[-3.61;7.02]			2.15	[-5.00;9.29]		
Marital status								
Married/relationship (58%)	0.31	[-1.81;2.43]	0.70	0.00	1.02	[-2.18;4.23]	0.80	0.00
Single (23%)	-0.88	[-3.79;2.03]			-0.62	[-4.87;3.63]		
Widow/widower (19%)	0.86	[-2.59;4.31]			-0.45	[-4.88;3.98]		
Smoking status								
Non-smokers (66%)	0.44	[-1.62;2.50]	0.61	0.00	1.33	[-1.62;4.28]	0.21	0.00
Smoker (34%)	-0.41	[-2.75;1.92]			-1.48	[-4.31;1.36]		
Job status								
Full time job (5%)	-1.16	[-6.14;3.83]	0.79	0.00	-5.96	[-12.55;0.63]	0.20	0.00
Part time job (7%)	-0.84	[-4.99;3.30]			0.84	[-5.18;6.85]		
No job (88%)	0.33	[-1.37;2.02]			0.73	[-1.70;3.17]		
Education								

Elementary school, 7th-10th grade (48%)	0.10	[-1.57;1.77]	0.96	0.00	0.72	[-1.99;3.43]	0.67	0.00
High school (2%)	0.56	[-7.91;9.02]			4.67	[-8.01;17.36]		
Skilled worker (34%)	0.82	[-1.76;3.41]			1.23	[-2.48;4.94]		
Short-term education (2-3 years) (8%)	-1.57	[-5.66;2.52]			-2.39	[-8.12;3.34]		
Middle-term education (3-5 years) (7%)	-0.49	[-6.43;5.45]			-4.29	[-10.20;1.63]		
Long-term education (5-8 years) (1%)	-0.83	[-18.73;17.06]			0.41	[-22.59;23.40]		

PCS=physical component score; MCS=mental component score; Mean difference; 95% confidence intervals
All data in based on norms-based scoring
Multilevel linear models controlling for baseline PCS or MCS score and age, gender, baseline FEV1, marital status, cancer and diabetes and clustering. Priori hypothesis was that adding telehealthcare to usual practice would improve patients' HRQoL relative to usual practice.

Table 5: Primary outcome and subgroup analyses of the COPD patients' health characteristics: Adjusted mean differences in PCS and MCS summary scores for the total sample and subgroups, adjusted for respective baseline PCS or baseline MCS and age, gender, baseline FEV1, marital status, cancer and diabetes.

Health characteristics								
Effectiveness	**PCS**	**PCS 95% CI**	**Wald test**	**ICC**	**MCS**	**MCS 95% CI**	**Wald test**	**ICC**
Total sample	0.14	[-1.37;1.65]	**P value**	0.00	0.36	[-1.68;2.40]	**P value**	0.00
COPD severity (GOLD 1-4)								
Mild, 1 (6%)	1.73	[-4.74;8.21]	0.71	0.00	0.63	[-6.82;8.07]	0.81	0.00
Moderate, 2 (38%)	-0,74	[-3.02;1.53]			-0.70	[-3.77;2.37]		
Severe, 3 (39%)	1.01	[-1.67;3.70]			1.47	[-2.11;5.05]		
Very severe, 4 (17%)	-0.64	[-4.75;3.47]			-0.18	[-5.19;4.84]		
COPD duration								
< 3.5 years (25%)	-0.67	[-2.91;1.56]	0.26	0.00	-0.97	[-4.36;2.43]	0.11	0.00
3.5-6 years (26%)	-1.59	[-4.60;1.42]			-2.03	[-5.70;1.64]		
7-10 years (26%)	0.53	[-2.77;3.84]			0.52	[-3.64;4.68]		
> 10 years (23%)	2.50	[-0.70;5.69]			4.02	[-0.19;8.23]		
Diabetes								
No (89%)	0.33	[-1.23;1.90]	0.39	0.00	0.32	[-1.82;2.45]	0.89	0.00
Yes (11%)	-1.44	[-5.31;2.43]			0.74	[-4.94;6.43]		
Heart disease								
No (65%)	0.06	[-1.49;1.61]	0.88	0.00	0.72	[-1.74;3.18]	0.62	0.00
Yes (35%)	0.29	[-2.62;3.21]			-0.29	[-3.67;3.09]		
Mental health problem								
No (95%)	0.29	[-1.26;1.85]	0.25	0.00	0.31	[-1.79;2.41]	0.77	0.00
Yes (5%)	-3.12	[-8.74;2.50]			1.49	[-6.16;9.15]		
Musculoskeletal disease								
No (70%)	0.05	[-1.72;1.83]	0.89	0.00	0.52	[-1.55;2.59]	0.71	0.00
Yes (30%)	0.24	[-2.02;2.51]			-0.08	[-3.45;3.28]		
Cancer								
No (94%)	0.02	[-1.42;1.46]	0.53	0.00	0.22	[-1.85;2.28]	0.56	0.00
Yes (6%)	2.10	[-4.69;8.89]			2.66	[-5.37;10.69]		
Number of comorbidities								

Yes (33%)	0.26	[-2.11;2.63]	0.13	0.00	0.34	[-2.75;3.42]	0.74	0.00
No (41%)	1.37	[-1.04;3.78]			1.03	[-2.15;4.21]		
2 or more (26%)	-1.97	[-4.88;0.95]			-0.69	[-4.32;2.93]		
Hypertension								
Yes (71%)	0.59	[-1.34;2.53]	0.29	0.00	0.39	[-2.11;2.88]	0.96	0.00
No (29%)	-1.14	[-3.68;1.39]			0.27	[-3.33;3.87]		
Tachycardia								
Yes (70%)	0.27	[-1.35;1.92]	0.80	0.00	0.10	[-2.04;2.24]	0.66	0.00
No (30%)	-0.18	[-3.31;2.95]			1.02	[-2.83;4.87]		
BMI								
< 25 (44%)	0.37	[-2.10;2.83]	0.96	0.00	0.45	[-2.85;3.74]	0.96	0.00
25-30 (34%)	0.20	[-2.49;2.89]			-0.12	[-3.84;3.61]		
> 30 (22%)	-0.38	[-4.50;3.63]			0.78	[-4.03;5.59]		

PCS=physical component score; MCS=mental component score; Mean difference; 95% confidence intervals
All data in based on norms-based scoring
Multilevel linear models controlling for baseline PCS or MCS score and age, gender, baseline FEV1, marital status, cancer and diabetes and clustering. Priori hypothesis was that adding telehealthcare to usual practice would improve patients' HRQoL relative to usual practice.

4. Discussion

The present study hypothesised that adding telehealthcare to usual practice would significantly increase patients' HRQoL [31]. This hypothesis was rejected. We found not statistical quality-of-life differences between groups in either the primary analysis, the complete case analysis or in any of the subgroups.

4.1. Interpretation of findings

Despite the non-significant differences, the mean differences in PCS and MCS scores at 12-month follow-up were larger for the control group than for the intervention group, which could indicate a faster deterioration over time for the controls than for the intervention patients. The largest mean difference was seen in MCS. If this is the case, it might be explained by the difficulty associated with affecting the physical QoL compared with the mental QoL. The slower decline in MCS for the telehealthcare group may be interpreted as a psychological benefit derived from using the Telekit.

Although the subgroup analysis indicated no statistically significant effects of the intervention in any of the posteriorly defined subgroups there was an indication of some positive effects on HRQoL within certain subgroups of the intervention group compared with usual practice. These trends towards positive effects on HRQoL should be further investigated.

4.2. Strengths and weaknesses

The present study was the first Danish large-scale trial established to remedy the lack of international evidence on HRQoL in patients with COPD who are receiving telehealthcare. A total of 1,225 participants from 26 municipality districts in the North Denmark Region were included in the analysis. The trial succeeded in establishing a fruitful cooperation between many stakeholders with different interests in the trial. The trial hence demonstrated the feasibility of intersectoral and interinstitutional collaboration towards a shared end, viz. the implementation of telehealthcare to improve COPD patients' HRQoL.

In contrast to the WSD [22–25], the TeleCare North trial compared the effects of telehealthcare with the effects of usual practice in COPD patients only. The design of the WSD was characterised by variability in terms of the employed technologies, the recruited sample, the type of intervention, and defined care pathways. Contrary to the WSD [39], the TeleCare North trial used a "clean" control group of COPD patients who received usual practice and no other forms of care.

The TeleCare North trial was based on the same concept as in previous Danish pilot studies [27–30,40] namely to increase patient empowerment and to detect disease deterioration through self-monitoring. In the present study, we attended to clarify the mechanisms that were supposed to provide effects. Organisational initiatives to further this concept, for example ensuring that patients had functional telehealthcare equipment, instructing patients how to use this equipment, and by gearing the organisation to rapidly respond to reported measures to prevent COPD exacerbations. That no significant effects of HRQoL were found, therefore cannot be attributed to patients' lack of equipment, a lack of instructions, or inadequate operational equipment.

In the trial, we found a considerable high attrition rate of 53% among participants with over half of the sample not providing follow-up data due to incomplete cases with missing data or loss to follow-up. Conducting a sensitivity analysis as a complete case analysis was therefore relevant in order to explore differences among complete and available cases. The high attrition rate may be attributed to disease progression and may have affected the findings of the trial. However, the consistency of results indicates that conclusions on findings are robust in spite of the high attrition rate. Further research is required to find explanations for high attrition rate among COPD patients.

The subgroup analysis was not pre-specified at the outset of the trial but was undertaken after the data collection of the trial. Because of the limitation noted, the findings of the post hoc subgroup analysis should be interpreted with caution irrespective of their significance.

We cannot rule out the influence of non-specific effects like a Hawthorne effect [41] or "natural history effects" [42], both of which could have influenced the intervention and the control group to some extent.

The potential presence of any such effects may explain why differences in HRQoL between the groups were difficult to detect.

The baseline variables used in the TeleCare North trial were not exhaustive; nor were all relevant variables included. At baseline, the FVC% indicated that the patients in the intervention group were poorer than the patients of the control group. It is widely known that QoL deteriorates with increasing severity of COPD [43]. This may also contribute to explaining why no significant differences in HRQoL were found between the groups. It would have been desirable to supplement the baseline variables with other clinical characteristics such as the Medical Research Council (MRC) dyspnoea score and with activities-of-daily-living measures to determine if the groups differed from each other in relation to their state of health. The number of selected baseline variables made it possible to classify the patients only according to the old GOLD classification (I-V). It would have been desirable to classify the patients according to the new GOLD classification (A-D) which is based on symptoms, airflow obstruction, and exacerbation history. Use of the new GOLD classification would probably have made it possible to establish more relevant subgroups [32].

The SF-36v2 was selected as an appropriate outcome measure because it is a useful, generic, and validated questionnaire for comparing differences between populations. It is possible, however, that generic questionnaires do not adequately measure the QoL issues that different groups of patients experience. It has been shown that the SF-36 is susceptible to ceiling and floor effects as it is applicable to a wide population of both healthy and sick individuals. It is possible that the SF-36v2 was not sufficiently sensitive to changes and to identifying outcome differences in patients with COPD [44]. This was also confirmed by Rixon et al. [25] who suggest that generic instruments are less sensitive to change related to telehealth than disease-specific instruments are. COPD is associated with symptoms that might have an impact on the patients' QoL, which makes it uncertain whether the generic questionnaires capture these aspects. Another alternative for measuring QoL could have been a more disease-specific questionnaire for COPD patients, such as the St. George' Respiratory Questionnaire (SGRQ) [45] and other QoL instruments such as the Chronic Respiratory Questionnaire (CRQ) [46]; the EQ-5D [47] or the Hospital Anxiety and Depression Scale (HAD) [48]. A study by Engström and colleagues [49] illustrated that a combination of generic and disease-specific questionnaires was the most suitable choice for measuring differences in COPD patients' HRQoL following an intervention. They argued that both disease-specific effects and the overall burden of the disease on everyday functioning and mental wellbeing should be considered. This was also confirmed in a review by Chen who recommended the use of both generic and disease-specific questionnaires in combination [44].

Another relevant consideration is whether QoL measures should be expected to change by implementation of telehealthcare. Two recent systematic reviews [18,50] found that the impact of telehealth on QoL in

patients with COPD is limited. However, the review suggested that active interventions may improve QoL outcomes in the telehealth group compared with usual care [18]. Based on this study's results and the literature [7,18,24,25], telehealthcare is not assumed to be convincing when looking at QoL as an isolated factor. However, QoL improvements may be expected over time [25] in active telehealthcare interventions where some kind of self-management skills training is an integrated part of the intervention [18].

4.3. Comparison with other studies

Our results demonstrate a further lack of any improvements in QoL following implementation of telehealthcare in COPD. The WSD is the only large-scale study of telehealthcare in COPD that we have come across. The findings from the WSD study by Cartwright and colleagues [24] indicated no improvement in HRQoL from telehealth, but some significant differences suggested that the telehealth group had a slower rate of deterioration over time compared with the control group.

Similarly, no statistical differences in the Telescot study [51] or the "The Virtual Hospital" trial [52] were identified between the control and intervention groups. The results of our study are consistent with the findings from these studies.

The review and meta-analysis by McLean et al. [7] is also relevant to consider; in contrast, their findings indicated possible impact of COPD patients' QoL. Another recent review by Cruz et al. [10] indicated inconsistency in HRQoL findings with most of the studies reporting no significant changes in HRQoL. However, the studies included in the reviews used different HRQoL instruments; and it has therefore been recommended to use similar HRQoL instruments in future studies to enable comparisons [7,10].

Nevertheless, the benefits in relation to QoL may be debated although telehealthcare seems unlikely to reduce QoL. One of our previous findings from the TeleCare North trial indicated that the intervention patients experienced enhanced control, freedom, security, and greater awareness of their COPD symptoms when using the telehealthcare system [53]. These benefits are not underpinned by the present study's findings on HRQoL.

4.4. Implications for practice

Our findings indicate that adding telehealthcare to usual practice does not improve HRQoL in patients with COPD. We did not succeed in achieving the HRQoL effects we had hoped for, and the reduced HRQoL in both groups means that it is doubtful whether telehealthcare benefits patients' QoL. Therefore, policymakers and healthcare professionals should consider whether telehealthcare should be implemented to achieve other objectives than improving patients' HRQoL, i.e. saving costs, reducing mortality, affecting other outcome variables, etc.

Furthermore, it is relevant to explore other domains such as physical activity, psychological symptoms and different modes of telehealth application and interventions, which may be important in improving QoL. In addition, more research should be considered within more specific subgroups of COPD patients to assess whether telehealthcare has a particularly beneficial effect on QoL in some groups. It is possible that patients' QoL varies between subgroups. Knowledge of such variation is useful and may inform future implementation of telehealthcare allowing for targeting of specific patient subgroups.

4.5. Future directions

In the future, more research is needed into the underlying mechanisms behind this lack of an identifiable effect. More qualitative research is required to gain a deeper understanding of the mechanism and preconditions needed to improve patients' HRQoL by use of telehealthcare. A greater effort should be dedicated to studying the specific subgroups instead of the population as whole because telehealthcare systems likely fit some patients better than others. Furthermore, the COPD patients in the present trial were recruited from different municipalities, some of which might have been better at organizing telehealthcare than others. Large-scale studies are therefore not recommended until these underlying mechanisms have been further investigated.

Future studies should recognize telehealthcare as a complex intervention. Such studies should therefore be designed as a mix of randomised controlled trials and other research designs to fully assess complex interventions. It is possible that we have jumped too quickly to large-scale operational trials. Furthermore, research on the causal relationship between QoL and patients' socio-demographic and health characteristics is limited, indicating that a number of exploratory studies need to be performed within the TeleCare North trial in the future.

In conclusion, the findings of the present study indicate that the potential of telehealthcare for improving COPD patients' HRQoL is limited. However, it is assumed on the basis of these results that telehealthcare as an additional service alongside the existing clinical care does not lead to poorer QoL.

Acknowledgements

The participation of the Trial Administration Office, the general practitioners, hospitals, healthcare providers and patients in the North Denmark Region is acknowledged. Without their commitment to the implementation of the TeleCare North trial, it would not have been possible to do this study.

Declarations

Detailed description of intervention and comparator: The study protocol is freely available and can be downloaded from: http://www.trialsjournal.com/content/15/1/178.

Details of contributors: PHL, FWU, OKH, and LHE conceived and designed the study and were responsible for its conduct. PHL and FWU managed the study and the data collection. The trial's Administration Office provided administrative support. FWU undertook the data analysis. PHL, FWU, OKH, and LHE interpreted the data. PHL prepared the first draft of the manuscript. OKH, FWU, and LHE revised and contributed to the manuscript. All authors read and approved the final manuscript.

Funding: This paper was funded by the North Denmark Region, the 11 municipalities in the North Denmark Region and by The Obel Family Foundation, the Danish Agency for Digitalization Policy and Strategy and the European Social Fund. The funding agencies had no influence on the design of the study, the analysis, or the shaping of the article. The article is based on the authors' views and not those of the sponsors.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work other than those detailed above; no financial relationships with any organisations that might have any interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethics approval: The trial was presented to the Danish Ethics Committee for Medical Research in the North Denmark Region and no ethical approval was needed. The trial has also been accepted by the Danish Data Protection Agency. All patients gave written informed consent for participation in this study and provided their approval for use of their data for research.

Data sharing: No additional data available.

Figure legends:

Figure 1: The Telekit system consists of a tablet, a blood pressure monitor, a fingertip pulse oximeter and a health precision scale

Figure 2: CONSORT diagram of the TeleCare North trial

References

1 Fletcher M, Upton J, Taylor-Fishwick J, *et al.* COPD uncovered: an international survey on the impact of chronic obstructive pulmonary disease [COPD] on a working age population. *BMC Public Health* 2011;**11**:1–13. doi:10.1186/1471-2458-11-612

2 Lõpez-Campos JL, Tan W, Soriano JB. Global burden of COPD. *Respirology* 2016;**21**:14–23. doi:10.1111/resp.12660

3 Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. *Lancet* 2007;**370**:765–73. doi:10.1016/S0140-6736(07)61380-4

4 Adeloye D, Chua S, Lee C, *et al.* Global and regional estimates of COPD prevalence: Systematic review and meta–analysis. *J Glob Health* 2015;**5**:1–17. doi:10.7189/jogh.05-020415

5 Goodridge D, Marciniuk D. Rural and remote care: Overcoming the challenges of distance. *Chron Respir Dis* 2016;**21**:21. doi:http://dx.doi.org/10.1177/1479972316633414

6 Annandale J, Lewis KE. Can telehealth help patients with COPD? *Nurs Times* 2005;**107**:12–4.http://www.ncbi.nlm.nih.gov/pubmed/21661486

7 McLean S, Nurmatov U, Liu JL, *et al.* Telehealthcare for chronic obstructive pulmonary disease: Cochrane Review and meta-analysis. *Br J Gen Pract* 2012;**62**:739–49. doi:10.3399/bjgp12X658269

8 Lundell S, Holmner Å, Rehn B, *et al.* Telehealthcare in COPD: A systematic review and meta-analysis on physical outcomes and dyspnea. *Respir Med* 2015;**109**:11–26. doi:10.1016/j.rmed.2014.10.008

9 Calvo GS, Hernández AS, Padilla DL, *et al.* Clinical Outcomes of Home Telemonitoring in Severe COPD. *iMedPub Journals* 2016;**1**:1–7.

10 Cruz J, Brooks D, Marques A. Home telemonitoring effectiveness in COPD: a systematic review. *Int J Clin Pract* 2014;**68**:369–78. doi:10.1111/ijcp.12345

11 Bolton CE, Waters CS, Peirce S, *et al.* Insufficient evidence of benefit: a systematic review of home telemonitoring for COPD. *J Eval Clin Pract* 2011;**17**:1216–22. doi:10.1111/j.1365-2753.2010.01536.x

12 Bowles KH, Baugh AC. Applying research evidence to optimize telehomecare. *J Cardiovasc Nurs* 2007;**22**:5–15.http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2874189&tool=pmcentrez&rendertype=abstract

13 Polisena J, Tran K, Cimon K, *et al.* Home telehealth for chronic obstructive pulmonary disease: a systematic review and meta-analysis. *J Telemed Telecare* 2010;**16**:120–7. doi:10.1258/jtt.2009.090812

14 Franek J. Home telehealth for patients with chronic obstructive pulmonary disease (COPD): an evidence-based analysis. *Ont Health Technol Assess Ser* 2012;**12**:1–58.http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3384362&tool=pmcentrez&rendertype=abstract

15 Kitsiou S, Paré G, Jaana M. Systematic reviews and meta-analyses of home telemonitoring interventions for patients with chronic diseases: a critical assessment of their methodological quality. *J Med Internet Res* 2013;**15**:e150. doi:10.2196/jmir.2770

16 Ekeland AG, Bowes A, Flottorp S. Effectiveness of telemedicine: A systematic review of reviews. *Int J Med Inform* 2010;**79**:736–71. doi:10.1016/j.ijmedinf.2010.08.006

17 Pedone C, Lelli D. Systematic review of telemonitoring in copd: An update. *Pneumonol Alergol Pol* 2015;**83**:476–84. doi:10.5603/PiAP.2015.0077

18 Ulrik CS, Lomholt Gregersen T, Green A, *et al.* Do telemedical interventions improve quality of life in patients with COPD? A systematic review. *Int J Chron Obstruct Pulmon Dis* 2016;**Volume 11**:809. doi:10.2147/COPD.S96079

19 Bower P, Cartwright M, Hirani SP, *et al.* A comprehensive evaluation of the impact of telemonitoring in patients with long-term conditions and social care needs: protocol for the whole systems demonstrator cluster randomised trial. *BMC Health Serv Res* 2011;**11**:184. doi:10.1186/1472-6963-11-184

20 Hirani SP, Beynon M, Cartwright M, *et al.* The effect of telecare on the quality of life and psychological well-being of elderly recipients of social care over a 12-month period: the Whole Systems Demonstrator cluster randomised trial. *Age Ageing* 2014;**43**:334–41. doi:10.1093/ageing/aft185

21 Steventon A, Bardsley M, Billings J, *et al.* Effect of telecare on use of health and social care services: findings from the Whole Systems Demonstrator cluster randomised trial. *Age Ageing* 2013;**42**:501–8. doi:10.1093/ageing/aft008

22 Steventon A, Bardsley M, Billings J, *et al.* Effect of telehealth on use of secondary care and mortality: findings from the Whole System Demonstrator cluster randomised trial. *BMJ* 2012;**344**:e3874–e3874. doi:10.1136/bmj.e3874

23 Henderson C, Knapp M, Fernandez J-L, *et al.* Cost effectiveness of telehealth for patients with long term conditions (Whole Systems Demonstrator telehealth questionnaire study): nested economic evaluation in a pragmatic, cluster randomised controlled trial. *BMJ* 2013;**346**:f1035–f1035. doi:10.1136/bmj.f1035

24 Cartwright M, Hirani SP, Rixon L, *et al.* Effect of telehealth on quality of life and psychological outcomes over 12 months (Whole Systems Demonstrator telehealth questionnaire study): nested study of patient reported outcomes in a pragmatic, cluster randomised controlled trial. *BMJ* 2013;**346**:f653. doi:10.1136/bmj.f653

25 Rixon L, Hirani SP, Cartwright M, *et al.* A RCT of telehealth for COPD patient's quality of life: the whole system demonstrator evaluation. *Clin Respir J* 2015;:2–25. doi:10.1111/crj.12359

26 Fonden for Velfærdsteknologi. National handlingsplan for udbredelse af telemedicin. 2012. http://www.digst.dk/Digital-velfaerd/~/media/Files/Velfærdsteknologi/Telemedicinsk handlingsplan/Telemedicinsk handlingsplan-web.pdf

27 Haesum LKE, Soerensen N, Dinesen B, *et al.* Cost-utility analysis of a telerehabilitation program: a case study of COPD patients. *Telemed J E Health* 2012;**18**:688–92. doi:10.1089/tmj.2011.0250

28 Huniche L, Dinesen B, Grann O, *et al.* Empowering Patients with COPD using Tele-Homecare Technology. 2010;:48–54. doi:10.3233/978-1-60750-563-1-48

29 Sorknæs AD, Madsen H, Hallas J, *et al.* Nurse tele-consultations with discharged COPD patients reduce early readmissions - an interventional study. *Clin Respir J* 2011;**5**:26–34. doi:10.1111/j.1752-699X.2010.00187.x

30 Sorknaes AD, Bech M, Madsen H, *et al.* The effect of real-time teleconsultations between hospital-based nurses and patients with severe COPD discharged after an exacerbation. *J Telemed Telecare* 2013;**19**:466–74. doi:10.1177/1357633X13512067

31 Udsen FW, Lilholt PH, Hejlesen O, *et al.* Effectiveness and cost-effectiveness of telehealthcare for chronic obstructive pulmonary disease: study protocol for a cluster randomized controlled trial. *Trials* 2014;**15**:178. doi:10.1186/1745-6215-15-178

32 GOLD: Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, And Prevention of Chronic Obstructive Pulmonary Disease. 2015. www.goldcopd.org

33 Davenport TE, Stevens SR, Baroni K, *et al.* Reliability and validity of Short Form 36 Version 2 to measure health perceptions in a sub-group of individuals with fatigue. *Disabil Rehabil* 2011;**33**:2596–604. doi:10.3109/09638288.2011.582925

34 Kosinski M, Dewy J. *How to Score Version Two of the SF-36 Health Survey.* 3rd ed. Quality Metric

2001.

35 Bentsen SB, Rokne B, Wahl AK. Comparison of health-related quality of life between patients with chronic obstructive pulmonary disease and the general population. *Scand J Caring Sci* 2013;**27**:905–12. doi:10.1111/scs.12002

36 Vickers AJ, Altman DG. Statistics notes: Analysing controlled trials with baseline and follow up measurements. *BMJ* 2001;**323**:1123–4. doi:10.1136/bmj.323.7321.1123

37 Faria R, Gomes M, Epstein D, *et al.* A Guide to Handling Missing Data in Cost-Effectiveness Analysis Conducted Within Randomised Controlled Trials. *Pharmacoeconomics* 2014;**32**:1157–70. doi:10.1007/s40273-014-0193-3

38 Ware J, Bayliss M, Rogers W, *et al.* Differences in 4-Year Health Outcomes for Elderly and Poor, Chronically III Patients Treated in HMO and Fee-for-Service Systems: Results from the Medical Outcomes Study. *J Am Med Assoc* 1996;**276**:1039–47. doi:doi:10.1001/jama.1996.03540130037027

39 Ellis Tim. The Whole System Demonstrator Programme. York UK: 2009.

40 Dinesen B, Seeman J, Gustafsson J. Development of a program for tele-rehabilitation of COPD patients across sectors : co-innovation in a network Presentation of the Telekat case study. 2011;**11**.

41 Konstantinou GN. Pragmatic trials: how to adjust for the 'Hawthorne effect'? *Thorax* 2012;**67**:562–562. doi:10.1136/thoraxjnl-2011-200657

42 Bouchet C, Guillemin F, Briançon S. Nonspecific effects in longitudinal studies: impact on quality of life measures. *J Clin Epidemiol* 1996;**49**:15–20. doi:10.1016/0895-4356(95)00540-4

43 Zamzam M, Azab N, Wahsh R El, *et al.* Quality of life in COPD patients. *Egypt J Chest Dis Tuberc* 2013;**5**:36–40. doi:10.1016/j.ejcdt.2012.08.012

44 Chen T, Li L, Kochen MM. A systematic review: How to choose appropriate health-related quality of life (HRQOL) measures in routine general practice? *J Zhejiang Univ Sci* 2005;**6B**:936–40. doi:10.1631/jzus.2005.B0936

45 Swigris JJ, Brown KK, Behr J, *et al.* The SF-36 and SGRQ: Validity and first look at minimum important differences in IPF. *Respir Med* 2010;**104**:296–304. doi:10.1016/j.rmed.2009.09.006

46 Guyatt GH, Berman LB, Townsend M, *et al.* A measure of quality of life for clinical trials in chronic lung disease. *Thorax* 1987;**42**:773–8. doi:10.1136/thx.42.10.773

47 The EuroQol Group. A New Facility for the Measurement of Health-Related Quality of Life. *Health Policy (New York)* 1990;**16**:199–208.

48 Aylard PR, Gooding JH, McKenna PJ, *et al.* A validation study of three anxiety and depression self-assessment scales. *J Psychosom Res* 1987;**31**:261–8. doi:10.1016/0022-3999(87)90083-3

49 Engström CP, Persson LO, Larsson S, *et al.* Health-related quality of life in COPD: why both disease-specific and generic measures should be used. *Eur Respir J* 2001;**18**:69–76.http://www.ncbi.nlm.nih.gov/pubmed/11510808

50 Liu L, Stroulia E, Nikolaidis I, *et al.* Smart homes and home health monitoring technologies for older adults: A systematic review. *Int J Med Inform* 2016;**91**:44–59. doi:10.1016/j.ijmedinf.2016.04.007

51 Pinnock H, Hanley J, McCloughan L, *et al.* Effectiveness of telemonitoring integrated into existing clinical services on hospital admission for exacerbation of chronic obstructive pulmonary disease: researcher blind, multicentre, randomised controlled trial. *Bmj* 2013;**347**:f6070. doi:10.1136/bmj.f6070

52 Jakobsen AS, Laursen LC, Rydahl-Hansen S, *et al.* Home-based telehealth hospitalization for exacerbation of chronic obstructive pulmonary disease: findings from 'the virtual hospital' trial. *Telemed J E Health* 2015;**21**:364–73. doi:10.1089/tmj.2014.0098

53 Lilholt PH, Korsbakke L, Hæsum E. Exploring User Experience of a Telehealth System for the Danish TeleCare North Trial. 2015;:301–5. doi:10.3233/978-1-61499-512-8-301

Figure 2: Consort Flow Diagram

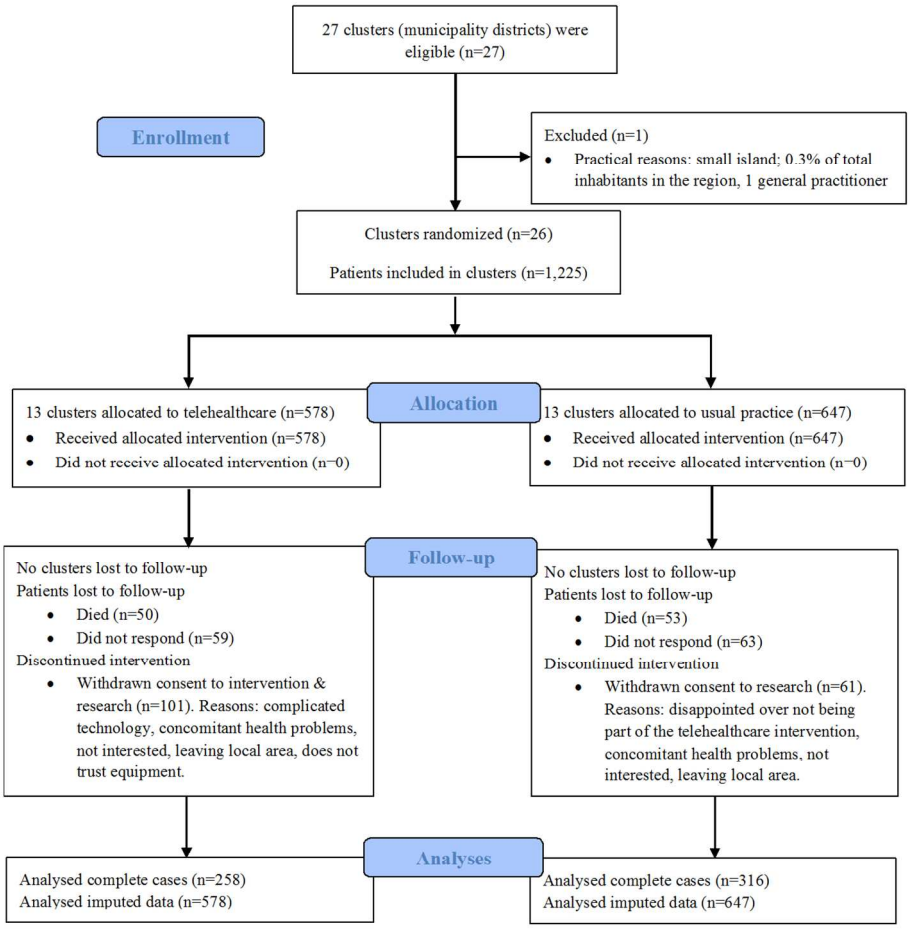

Figure 2: CONSORT Flow Diagram of the TeleCare North trial

310x369mm (120 x 120 DPI)

Figure 1: The Telekit system consists of a tablet, a blood pressure monitor, a fingertip pulse oximeter and a health precision scale

133x125mm (120 x 120 DPI)

Table 1: CONSORT 2010 checklist of information to include when reporting a cluster randomised trial

Section/Topic	Item No	Standard Checklist item	Extension for cluster designs	Page No *
Title and abstract				
	1a	Identification as a randomised trial in the title	Identification as a cluster randomised trial in the title	Page 1 in manus
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)[1,2]	See table 2	Page 2 in manus
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	Rationale for using a cluster design	Pages 3-4 in manus
	2b	Specific objectives or hypotheses	Whether objectives pertain to the the cluster level, the individual participant level or both	Page 3-4 in manus Page 4 in protocol
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Definition of cluster and description of how the design features apply to the clusters	Page 4 in manus Page 2-3 in protocol
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		
Participants	4a	Eligibility criteria for participants	Eligibility criteria for clusters	Page 4 in manus Page 2-3 in protocol
	4b	Settings and locations where the data were collected		Page 5 in manus Page 3 in

				protocol
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Whether interventions pertain to the cluster level, the individual participant level or both	Page 5 in manus Page 4-5 in protocol
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Whether outcome measures pertain to the cluster level, the individual participant level or both	Page 6 in manus Page 5 in protocol
	6b	Any changes to trial outcomes after the trial commenced, with reasons		
Sample size	7a	How sample size was determined	Method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a coefficient of intracluster correlation (ICC or *k*), and an indication of its uncertainty	Page 6 in manus Page 5 in protocol
	7b	When applicable, explanation of any interim analyses and stopping guidelines		
Randomisation:				
Sequence generation	8a	Method used to generate the random allocation sequence		Page 5 in manus Page 3 in protocol
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Details of stratification or matching if used	Page 5 in manus Page 3 in protocol
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level or both	Page 5 in manus Page 3 in protocol

Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Replace by 10a, 10b and 10c	
	10a		Who generated the random allocation sequence, who enrolled clusters, and who assigned clusters to interventions	Page 2-3 in protocol
	10b		Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete enumeration, random sampling)	Page 2-3 in protocol
	10c		From whom consent was sought (representatives of the cluster, or individual cluster members, or both), and whether consent was sought before or after randomisation	Page 3 in protocol
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how		
	11b	If relevant, description of the similarity of interventions		Page 7 in manus
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	How clustering was taken into account	Page 6 in manus Page 5 in protocol
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		Page 6 in manus Page 5 in protocol
Results				
Participant flow (a diagram is strongly	13a	For each group, the numbers of participants who were	For each group, the numbers of clusters that were randomly	Figure 1 in

recommended)		randomly assigned, received intended treatment, and were analysed for the primary outcome	assigned, received intended treatment, and were analysed for the primary outcome	manus
	13b	For each group, losses and exclusions after randomisation, together with reasons	For each group, losses and exclusions for both clusters and individual cluster members	Figure 2 in manus
Recruitment	14a	Dates defining the periods of recruitment and follow-up		Page 2 in protocol Page 7 in manus
	14b	Why the trial ended or was stopped		
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Baseline characteristics for the individual and cluster levels as applicable for each group	Table 1 in manus
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	For each group, number of clusters included in each analysis	Page 3 in protocol Page 7 in manus
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or k) for each primary outcome	Page 7-8 in manus
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory		Page 8 in manus
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms[3])		

Discussion				
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses		Page 9 in manus
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Generalisability to clusters and/or individual participants (as relevant)	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence		Page 9 in manus
Other information				
Registration	23	Registration number and name of trial registry		Page 2 in manus
Protocol	24	Where the full trial protocol can be accessed, if available		Page 4 in manus
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders		Page 16 in manus

** Note: page numbers optional depending on journal requirements*

Table 2: Extension of CONSORT for abstracts[1,2] to reports of cluster randomised trials

Item	Standard Checklist item	Extension for cluster trials
Title	Identification of study as randomised	**Identification of study as cluster randomised**
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	**Eligibility criteria for clusters**
Interventions	Interventions intended for each group	
Objective	Specific objective or hypothesis	**Whether objective or hypothesis pertains to the cluster level, the individual participant level or both**
Outcome	Clearly defined primary outcome for this report	**Whether the primary outcome pertains to the cluster level, the individual participant level or both**
Randomization	How participants were allocated to interventions	**How clusters were allocated to interventions**
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	
Results		
Numbers randomized	Number of participants randomized to each group	**Number of clusters randomized to each group**
Recruitment	Trial status[1]	
Numbers analysed	Number of participants analysed in each group	**Number of clusters analysed in each group**
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	**Results at the cluster or individual participant level as applicable for each primary outcome**
Harms	Important adverse events or side effects	
Conclusions	General interpretation of the results	
Trial registration	Registration number and name of trial register	
Funding	Source of funding	

[1] Relevant to Conference Abstracts

REFERENCES

1 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomised trials in journal and conference abstracts. *Lancet* 2008, 371:281-283

2 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG at al (2008) CONSORT for reporting randomized controlled trials in journal and conference abstracts: explanation and elaboration. *PLoS Med* 5(1): e20

3 Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, Moher D. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004; 141(10):781-788.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	p. 1 in protocol/p. 2 in manuscript
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	p. 1 in protocol/p. 2 in manuscript
	2b	All items from the World Health Organization Trial Registration Data Set	Clinicaltrials.gov
Protocol version	3	Date and version identifier	Original protocol
Funding	4	Sources and types of financial, material, and other support	p. 7 in protocol/p. 19 in manuscript
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	p. 7 in protocol/p. 19 in manuscript
	5b	Name and contact information for the trial sponsor	Clinicaltrials.gov, p. 19 in manuscript
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Not relevant

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Clinicaltrials.gov
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	p. 1-2 in protocol/p. 3-4 in manuscript
	6b	Explanation for choice of comparators	p. 4 in protocol, p. 6 in manuscript
Objectives	7	Specific objectives or hypotheses	p. 2/5 in protocol, p. 4 in manuscript
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	p. 2 in protocol/p. 4-5 in manuscript
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	p. 2-3 in protocol/p. 2 in manuscript
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	p. 2-3 in protocol/p. 5 in manuscript
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	p. 3-5 in protocol/p. 5-6 in manuscript
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Not relevant

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	p. 3-5 in protocol/ p. 6 in manuscript
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	p. 4 in protocol/p. 6 in manuscript
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	p. 5 in protocol/p. 7 in manuscript
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	p. 2-5 in protocol
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	p. 5 in protocol/p. 7 in manuscript
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	p. 3 in protocol/p. 5 in manuscript
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	p. 3-4 in protocol/p. 6 in manuscript
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	p. 3-4 in protocol/p. 6 in manuscript
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	p. 2-4 in protocol/ p. 5-6 in manuscript

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	p. 3-4 in protocol
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not relevant
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	p. 5 in protocol/p.7-8 in manuscript Clinicaltrials.gov
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	p. 5 in protocol Clinicaltrials.gov
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Clinicaltrials.gov
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	p. 5-6 in protocol/p. 7 in manuscript
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	p. 7 in manuscript
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	p. 5 in protocol/p. 7 in manuscript
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Clinicaltrials.gov

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Not relevant
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Not relevant
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	www.telecarenord.dk
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	p. 6 in protocol/ p. 20 in manuscript
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Not relevant
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	p. 3 in protocol/p. 5 in manuscript
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not relevant
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	www.telecarenord.dk
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	p. 7 in protocol/p. 19 in manuscript
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	p. 20 in manuscript
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not relevant

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	www.telecarenord.dk
	31b	Authorship eligibility guidelines and any intended use of professional writers	www.telecarenord.dk
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	The original protocol is open assess published
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	www.telecarenord.dk
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not relevant

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

Telehealthcare for patients suffering from chronic obstructive pulmonary disease: Effects on health-related quality of life - Results from the Danish "TeleCare North" cluster-randomised trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014587.R2
Article Type:	Research
Date Submitted by the Author:	31-Jan-2017
Complete List of Authors:	Lilholt, Pernille; Aalborg University, Faculty of Medicine, Department of Health Science and Technology Witt Udsen, Flemming; Aalborg University, Danish Center for Healthcare Improvements Ehlers, Lars; Aalborg University, Danish Centre for Healthcare Improvements, Faculty of Social Sciences and Faculty of Medicine Hejlesen, Ole; Aalborg University, Faculty of Medicine, Department of Health Science and Technology
Primary Subject Heading:	Health informatics
Secondary Subject Heading:	Health services research, Medical management, Evidence based practice
Keywords:	Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS, telehealth, COPD, Effectiveness, Quality of Life, Outcome Assessment (Health Care)

Telehealthcare for patients suffering from chronic obstructive pulmonary disease: Effects on health-related quality of life - Results from the Danish "TeleCare North" cluster-randomised trial

Pernille Heyckendorff Lilholt, *PhD*[a, 1], Flemming Witt Udsen, *PhD candidate*[b], Lars H. Ehlers, *Professor*[b] & Ole K. Hejlesen, *Professor*[a]

[a]Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Denmark

[b]Danish Centre for Healthcare Improvements, Faculty of Social Sciences and Faculty of Medicine, Aalborg University, Denmark

Correspondence[1]: Pernille Heyckendorff Lilholt, Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Denmark. Fredrik Bajers Vej 7C (C1-223), DK-9220 Aalborg Ø, Denmark (E-mail: phl@hst.aau.dk)

Word count (excluding title page, abstract, references, figures and tables): 5,022

Abstract

Objective: To assess the effect of telehealthcare compared with usual practice in patients with chronic obstructive pulmonary disease (COPD).

Design: A cluster-randomised trial with 26 municipal districts that were randomly assigned either to an intervention group whose members received telehealthcare in addition to usual practice or to a control group whose members received usual practice only (13 district in each arm).

Setting: 26 municipal districts in the North Denmark Region of Denmark.

Participants: Patients who fulfilled the Global Initiative for COPD (GOLD) guidelines and one of the following criteria: COPD Assessment Test (CAT) score ≥ 10; or Medical Research Dyspnoea Council Scale (MRC) ≥ 3 or mModified Medical Research Dyspnoea Council Scale (MMRC) ≥ 2; or ≥ 2 exacerbations during the past 12 months.

Main outcome measures: Health-related quality of life (HRQoL) assessed by the physical component summary (PCS) and mental component summary (MCS) scores of the Short Form 36-Item Health Survey, Version 2 (SF-36v2). Data were collected at baseline and at 12-month follow-up and analysed according to the intention-to-treat principle with complete cases, n=574 (258 intervention; 316 controls) and imputed data, n=1,225 (578 intervention, 647 controls) using multilevel modelling.

Results: In the intention-to-treat analysis (n=1,225), the raw mean difference in PCS from baseline to 12-month follow-up was -2.6 (SD: 12.4) in the telehealthcare group and -2.8 (SD: 11.9) in the usual practice group. The raw mean difference in MCS scores in the same period were -4.7 (SD: 16.5) and -5.3 (SD: 15.5) for telehealthcare and usual practice, respectively. The adjusted mean difference in PCS and MCS between groups at 12 months was 0.1 (95% CI: -1.4; 1.7) and 0.4 (95% CI: -1.7; 2.4), respectively.

Conclusions: The overall sample and all subgroups demonstrated no statistically significant differences in HRQoL between telehealthcare and usual practice.

Trial registration: ClinicalTrials.gov, NCT01984840, November 14, 2013; Results.

Keywords: Effectiveness; COPD; Telemedicine; RCT; Denmark; Quality of Life; Telehealth; Telemonitoring; Outcome Assessment (Health Care)

Strengths and limitations of this study

- This is the first large-scale trial in Denmark established to remedy the lack of international evidence on HRQoL in patients with COPD who are receiving telehealthcare
- The study is a large-scale, pragmatic, two-level, cluster-randomised trial with 12-month follow-up, which produces results applicable to clinical practice
- The trial succeeded in establishing a fruitful inter-sectoral and inter-institutional cooperation towards a common goal; the implementation of telehealthcare to improve COPD patients' HRQoL
- SF-36v2 was used as a quality-of-life instrument, but may be less sensitive to change related to telehealthcare. It would have been desirable to employ a combination of generic and disease-specific questionnaires in this study
- A considerable high attrition rate (651/1,225, (53%)) patients being incomplete cases or lost-to-follow-up) was present, which could have introduced bias and affected the strength of the trial's findings

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a significant cause of impaired quality of life (QoL), disability, morbidity, and mortality in industrialised countries [1,2]. Moreover, it constitutes a considerable burden on the affected patients and places an important socio-economic burden on society due to the growing number of patients requiring care. COPD, and other chronic diseases, challenge the healthcare systems in ways that call for changes in management and delivery of patient care [3,4].

Telehealthcare has the potential to facilitate timely transmission of clinical and physiological data and allows patients to be followed by clinicians more frequently and from a distance [5]. It may therefore also facilitate early intervention and improve clinical and patient-related outcomes [6]. Systematic reviews conclude that there is a potential for demonstrating that telehealthcare improves health-related outcomes or is at least as good as conventional treatment, but more research is needed [7–9]. Some reviews [10–12] raise concerns about the quality of the available evidence that is presented in heterogeneous pilot projects which are small, incomparable, and difficult to appraise in relation to QoL [13–17]. A recent systematic review [18] indicates only limited evidence for a positive effect of telehealth interventions on QoL in COPD. This situation has given rise to a demand for large-scale studies; and a large-scale study, The Whole System Demonstrator Project (WSD) conducted in the UK, has attempted to establish a robust evidence base for telehealth [19–23]. In the WSD, Cartwright and colleagues [24] concluded that the effect of telehealth was clinically insignificant as a supplement to usual care, and telehealth did not improve psychological outcomes and QoL in patients with COPD, heart failure, or diabetes [24]. In a recent randomised controlled

trial (RCT), a more extensive assessment of QoL and psychological outcomes was performed on the COPD cohort of the WSD [25]. The findings from the RCT [25] are consistent with the above conclusion made by Cartwright and colleagues [24]. However, the RCT found no reductions in patients' QoL in the longer term. In contrast, there was a trend towards improved QoL and mood in the telehealth group at longer-term follow-up, but not at the short term follow-up, as observed through disease-specific measures [25].

In Denmark, the lack of evidence for telehealthcare was discussed among healthcare decision-makers who agreed to strengthen the evidence base by conducing a large-scale study as part of "The National Danish Action Plan for Dissemination of Telemedicine" [26]. In 2012, the Danish Government decided to launch the Action Plan to disseminate telemedicine nationally [26]. The action plan included, among others, the TeleCare North trial, the purpose of which was to contribute to the generation of valuable knowledge about the use of telehealthcare for COPD patients in the North Denmark Region. The TeleCare North trial was designed based on experiences from two Danish pilot studies; the TeleKat Study [27,28] and the Nursing Consultations Study [29,30], which had both demonstrated positive effects of telehomecare and teleconsultations.

The present study is embedded in the Danish TeleCare North trial. Its objective was to assess the effectiveness of telehealthcare compared with usual practice based on an assessment of HRQoL in COPD patients. It was hypothesised that adding telehealthcare to usual practice would significantly enhance patients' HRQoL [31].

2. Methods

2.1. Study design

This study was conducted in accordance with the study protocol for the TeleCare North trial [31], which we describe briefly in this section.

The TeleCare North trial was a large-scale, pragmatic, two-level, cluster-randomised trial with 12-month follow-up. The trial was based on the collaborative efforts of the North Denmark Region, all municipalities in the Region, the Region's general practitioners (GPs), and Aalborg University. The municipalities were organised into 26 districts with 13 clusters in each arm.

2.2. Participants

The trial targeted all COPD patients in the North Denmark Region who fulfilled the inclusion criteria. All GPs from the Region recruited the COPD patients from a list of suitable patients attending their practices. The selection of participants followed identical guidelines and instructions at all practices. All patients who accepted to participate and were deemed suitable for participation were included. The identification and

recruitment of patients took place prior to random allocation of clusters in order to minimise biased recruitment. Assigned to the intervention or to usual practice were 1,225 (578 intervention, 647 controls) patients representing different COPD stages, GOLD I-IV (Global Initiative for Chronic Obstructive Lung Disease) [32].

2.2.1. Inclusion and exclusion criteria

All COPD patients who may benefit from telehealthcare were considered for inclusion. The following inclusion criteria were used: Patients were required to have COPD as their primary disease and be diagnosed by spirometry, and they should receive or be motivated for treatment corresponding to the GOLD guidelines [32]. One of the following criteria should also be met: A Medical Research Dyspnoea Council scale (MRC) score ≥ 3; or a modified Medical Research Dyspnoea Council scale (MMRC) score ≥ 2; or a COPD Assessment Test (CAT) score ≥ 10; or ≥ 2 exacerbations during the past 12 months.

In addition, on the basis of a health professional's qualified estimate and assessment, the patients should also have a telephone connection, have permanent residence, and be on the list of a GP in the North Denmark Region. Patients should also be able to speak Danish or they should be living with Danish-speaking relatives who were able to support them in their use of the telehealthcare system and to provide assistance in situations involving issues of comprehension of the Danish language.

Patients were excluded if they were cognitively impaired, had no phone line or GSM coverage, or were unable to understand Danish to the extent allowing them to complete the study questionnaires.

2.3. Intervention

The intervention of the TeleCare North trial was based on the concept and logic of the TeleKat study [28]. Its key concept and primary logic was empowerment achieved by engaging COPD patients in their illness and increasing their coping abilities through self-monitoring. The study introduced extended monitoring with store-and-forward data connected to healthcare providers to facilitate detection of exacerbations and rapidly initiate preventive antibiotic therapy.

2.3.1. Intervention arm: Telehealthcare

Patients in the intervention group received telehealthcare in addition to usual practice. The telehealthcare system coined "Telekit" was used in the TeleCare North trial. It consists of a Samsung Galaxy Tab2 (10.1) with associated devices: a digital blood pressure monitor (UA-767, plus BT-C, Nonin Medical, Minnesota, USA), a fingertip pulse oximeter (Nonin, Onyx II% SpO^2), and a health precision scale (UC-321PBT-C, A&D Medical, Tokyo, Japan). The devices can collect and wirelessly transmit relevant disease-specific data

consisting of answers to questions related to COPD exacerbations, symptoms, and patients' vital signs: systolic and diastolic blood pressure, heart rate, weight, and oxygen saturation (Figure 1). The patients were instructed to measure their vital signs, which were then sent asynchronously to municipality healthcare personnel who subsequently established if these data deviated from the normal threshold values. The communication between the healthcare personnel and the patient was one-way only. The patients were contacted if there were adverse changes in their values and responses. Patients were also contacted if the measurements were not carried out as agreed or the measurements were not received as expected.

2.3.2. Comparative arm: Usual practice

Patients in the control group received their existing usual practice. This involved treatment, monitoring, and care throughout the study period. The patients' GPs provided this treatment and monitoring, and the municipalities held responsibility for the practical help and care provided. The patients in the control group had not received any form of telehealthcare system; but at the end of the 12-months study period, they were offered the same Telekit system as the intervention group for ethical reasons.

2.4. Randomisation

On November 4, 2013, the municipality districts (n = 26) were randomised so that patients residing in the same district received the same type of care – either telehealthcare in addition to usual practice, or usual practice only. The municipality districts were matched 1:1 by the following variables: the total population size of the districts; the proportion of people with a higher education; the sum of the district's total income; unemployment; and the estimated number of patients with COPD [31]. The districts were distributed randomly by a blinded volunteer with no relation to the trial, who performed the randomisation by throwing a dice. The volunteer had no knowledge of the distribution of districts on intervention or control group, respectively. The randomisation was recorded by the trial administration secretariat to ensure that the procedure was performed randomly.

2.5. Outcome measures

Upon inclusion at the GP's office, patients were handed a questionnaire comprising the Short Form 36-Item Health Survey version 2 (SF-36v2) [33] and questions concerning their baseline demographic characteristics such as gender, age, education, comorbidities, smoking status, marital status, and job status. The SF-36v2 consists of 36 questions and is one of the most commonly used generic, validated questionnaires for measuring general HRQoL. It captures patients' perceptions of physical, social, mental, and emotional

domains, and overall summary scores of physical (PCS) and mental components (MCS) are derived from domain scores using a norm-based scoring method [34]. The scores are standardised to fall between 0 and 100 with a higher score indicating "better health" [33]. After 12 months, a similar patient questionnaire was sent to the included patients to compare baseline data with follow-up data. The outcomes of this study were the patients' mean differences in HRQoL at baseline and at the 12-month follow-up assessed with SF-36v2. The primary outcome measure was the adjusted mean differences in PCS summary scores between treatment groups at 12 month follow-up.

2.6. Sample size

The sample size calculation was based on the study protocol's [31] primary outcome measure, PCS. Based on results from a previous Norwegian study [35], it was estimated that eligible COPD patients had a mean baseline PCS score of 38 with a standard deviation of 10. The average cluster size was assumed to be 50 with a coefficient of variation of 0.5. A sample size of 350 patients from at least seven municipality districts (clusters) in each arm (two-sided significance level, $\alpha = 0.05$, power = 80%) was needed to detect minimal, clinically important differences (change equal to 5) and intracluster correlation ((ICC) equal to 0.05)) between the intervention group and the control group [35]. The total required sample size was estimated to be around 800 patients with an expected lost-to-follow-up-rate of 10%.

2.7. Statistical analysis

All analyses of the cluster-randomised trial were conducted according to the intention-to-treat principle. A post hoc subgroup analysis was also performed as a secondary analysis. The analyses were undertaken in STATA 12.1.

SF-36v2 standardised scores for each patient were produced using Software provided by QualityMetric Incorporated (http://www.sf-36.org/), which converts all scores to a single metric (Norm-based scoring) based on 2009 US general population norms [34]. An ANCOVA analysis strategy was applied [36]. Two separate linear mixed models for continuous outcomes were used to assess PCS and MCS scores at 12-month follow-up controlling for treatment arm, respective baseline score, age, gender, baseline forced expiratory volume in one second (FEV1%), marital status, diabetes status, cancer status, and clustering at the municipality district level. The clusters were assumed to be represented as random effects, and the models had robust covariance structures. ICC estimates of patient-reported outcome variables were calculated for measurement of the variability within and across the clusters. The subgroup analyses applied the same statistical models and covariates as above, but with added treatment-by-covariate interaction for each subgroup.

Missing data were assumed missing at random and were handled in coordination with the health economic evaluation of the same trial as described in the trial protocol [31] and followed good practices for handling missing data in cost-effectiveness research [37]. Missing PCS and MCS scores and baseline characteristics were imputed using multiple imputation and were estimated separately by treatment group to allow for differential covariance structures in treatment group means. Imputation models included PCS and MCS scores, predictors for these scores at both time points, predictors for missing observations in the individual variables, and all baseline characteristics. Continuous variables were imputed by predictive mean matching and categorical variables by multinominal logistic or logistic regression. The variables included were non-missing health-related quality-of-life (HRQoL) (PCS and MCS scores), measures of disease status (FEV1%, forced vital capacity (FVC%)), diastolic and systolic blood pressure), smoking status, duration of COPD, potential comorbidities (diabetes, cardiovascular disease, mental illness, musculoskeletal disorders, or cancer), socio-demographic variables (age, gender, marital status, education, employment status) and clustering. The imputation models involved the generation of 30 complete datasets combined by Rubin's rule. Single Imputation was performed on subjects that died during the 12 months by assigning their summary scores values of 0 [38,39].

The primary analysis and subgroup analysis were based on imputed data, but a complete case analysis was also included as a sensitivity analysis to check the robustness of the main trial findings.

3. Results

3.1. Descriptive characteristics

The CONSORT diagram is shown in Figure 2. Twenty-six municipal districts (13 intervention clusters; 13 control clusters) were randomised in 2013, and the TeleCare North trial was completed after the 12-month assessment in 2015. At baseline, 1,225 (578 intervention, 647 controls) patients were enrolled in the TeleCare North trial. At 12 months, 109 (18.86%) intervention patients were lost to follow-up (50 were dead, 59 did not respond on questionnaires) and 116 (17.93%) control patients (53 were dead, 63 did not respond on questionnaires after baseline). 101 (17.47%) patients in the intervention group and 61 (9.43%) patients in the control group withdrew their consent. Reasons for withdrawing from the TeleCare North trial included: complicated technology; concomitant health problems; not interested; leaving local geographical area; does not trust the equipment; or disappointed over not being a part of the telehealth intervention. None of the twenty-six clusters were lost to follow-up. At 12 months, 264 (110 intervention, 154 controls) patients had incomplete data (patients that were not lost-to-follow-up but had missing values on items in either PCS or MCS at baseline or follow-up). Complete data (patients with nonmissing values on

MCS and PCS score at baseline and follow-up) were available for 574 (258 intervention; 316 controls) of the 1,225 patients at 12 month follow-up, giving an attrition rate of 53% (Figure 2).

At baseline, we assessed socio-demographic factors (gender, age, marital status) and health characteristics (smoking status, duration of COPD, FEV1%, FVC%, comorbidities, SF-36). Statistical comparisons of the participants' baseline characteristics demonstrated that the two study groups were similar, except for statistically significant differences in FVC% ($p < 0.05$). The control group's mean FVC% (74.34%) was slightly higher than the intervention group's mean FVC% (70.38%) (Table 1).

Table 1: Baseline characteristics, at baseline and at 12-month follow-up.

Characteristics	All participants at baseline			Complete cases at 12 months follow-up#			Lost-to-follow-up at 12 months##			Incomplete cases at 12 months follow-up###		
	THC *n=578*	UP *n=647*	Diff *Raw*	THC *n=258*	UP *n=316*	Diff *Raw*	THC *n=210*	UP *n=177*	Diff *Raw*	THC *n=110*	UP *n=154*	Diff *Raw*
Age (years)§	69.6 (9.4)	70.3 (9.1)	-0.8	68.2 (8.8)	69.5 (9.1)	-1.3	70.5 (10.2)	71.8 (9.5)	-1.4	70.9 (8.5)	70.3 (8.6)	-0.6
Men (%)§	48.3 (n=279)	43.7 (n=283)	4.5	53.5 (n=138)	44.6 (n=141)	8.9*	45.2 (n=95)	45.8 (n=81)	-0.5	41.8 (n=46)	39.6 (n=61)	2.2
Marital status (%)												
Married/in a relationship	55.9 (n=323)	54.3 (n=351)	1.6	70.2 (n=181)	62.0 (n=196)	8.1	40.0 (n=84)	45.2 (n=80)	-5.2	52.7 (n=58)	48.7 (n=75)	4.0
Single	20.4 (n=118)	22.1 (n=143)	-1.7	17.4 (n=45)	22.2 (n=70)	-4.7	24.8 (n=52)	23.2 (n=41)	1.6	19.1 (n=21)	20.8 (n=32)	-1.7
Widow/widower	16.8 (n=97)	16.5 (n=107)	0.2	12.0 (n=31)	15.2 (n=48)	-3.2	22.9 (n=48)	19.2 (n=34)	3.7	16.4 (n=18)	16.2 (n=25)	0.1
Missing (%)	6.9 (n=40)	7.1 (n=46)	-0.2	0.4 (n=1)	0.6 (n=2)	-0.2	12.4 (n=26)	12.4 (n=22)	-0.1	11.8 (n=13)	14.3 (n=22)	-2.5
Smoking status (%)												
Non-smokers	59.3 (n=343)	63.1 (n=408)	-3.7	66.3 (n=171)	67.4 (n=213)	-1.1	51.0 (n=107)	61.0 (n=108)	-10.1	59.1 (n=65)	56.5 (n=87)	2.6
Smokers	33.9 (n=196)	29.2 (n=189)	4.7	3.0 (n=85)	31.0 (n=98)	1.9	36.8 (n=77)	26.6 (n=47)	10.1	30.9 (n=34)	28.6 (n=44)	2.3
Missing (%)	6.8 (n=39)	7.7 (n=50)	-1.0	0.8 (n=2)	1.6 (n=5)	-0.8	12.4 (n=26)	12.4 (n=22)	-0.1	10.0 (n=11)	14.9 (n=23)	-4.9
Duration of COPD (years)	7.8 (6.2)	7.7 (5.8)	0.1	7.6 (6.5)	7.5 (5.4)	0.1	8.0 (6.5)	8.4 (6.4)	-0.4	8.0 (5.1)	7.5 (6.0)	0.5
Missing (%)	14.0 (n=81)	15.1 (n=98)	-1.1	7.8 (n=20)	8.2 (n=26)	-0.5	21.4 (n=45)	22.0 (n=39)	-0.6	14.6 (n=16)	21.4 (n=33)	-6.9
FEV1 (%)	47.7 (18.1)	48.4 (18.9)	-0.7	48.9 (18.3)	50.3 (19.8)	-1.4	47.7 (18.9)	45.7 (17.9)	2.1	45.1 (15.6)	47.7 (17.9)	-2.7
Missing (%)	18.5 (n=107)	19.8 (n=128)	-1.3	18.2 (n=47)	19.9 (n=63)	-1.7	21.4 (n=45)	15.8 (n=28)	5.6	13.6 (n=15)	24.0 (n=37)	-10.4

FVC (%)	70.4 (20.0)	73.3 (22.3)	-4.0**	71.2 (19.1)	75.4 (21.7)	-3.7	70.6 (21.3)	73.2 (24.6)	-2.6	66.4 (19.4)	73.3 (20.8)	-6.9**
Missing (%)	34.4 (n=199)	39.4 (n=255)	-5.0	31.0 (n=80)	38.0 (n=120)	-7.0	37.1 (n=78)	38.4 (n=68)	-1.3	37.3 (n=41)	43.5 (n=67)	-6.2
Comorbidities (%)												
Diabetes	10.2 (n=59)	9.9 (n=64)	0.3	8.9 (n=23)	9.8 (n=31)	-0.9	10.5 (n=22)	8.5 (n=15)	2.0	12.7 (n=14)	11.7 (n=18)	1.0
Coronary heart disease	32.7 (n=189)	31.8 (n=206)	0.9	32.6 (n=84)	32.3 (n=102)	0.3	36.2 (n=76)	34.5 (n=61)	1.7	26.4 (n=29)	27.9 (n=43)	-1.6
Mental health problem	4.8 (n=28)	4.8 (n=31)	0.1	4.3 (n=11)	5.1 (n=16)	-0.8	7.1 (n=15)	5.1 (n=9)	2.1	1.8 (n=2)	3.9 (n=6)	-2.1
Musculoskeletal disorder	24.9 (n=144)	29.4 (n=190)	-4.5	27.9 (n=72)	29.1 (n=92)	-1.2	22.4 (n=47)	31.1 (n=55)	-8.7	22.7 (n=25)	27.9 (n=43)	-5.2
Cancer	6.1 (n=35)	4.8 (n=31)	1.3	5.8 (n=15)	4.4 (n=14)	1.4	5.7 (n=12)	5.7 (n=10)	0.1	7.3 (n=8)	4.6 (n=7)	2.7
Missing (%)	8.1 (n=47)	7.9 (n=51)	0.3	1.9 (n=5)	2.2 (n=7)	-0.3	13.8 (n=29)	12.4 (n=22)	1.4	11.8 (n=13)	14.3 (n=22)	-2.5
Baseline PCS	37.5 (9.2)	37.7 (8.9)	-0.2	38.2 (9.1)	38.2 (9.2)	0.0	36.0 (9.10)	36.2 (8.4)	-0.2	37.8 (10.1)	37.9 (8.4)	-0.1
Missing (%)	23.9 (n=138)	25.5 (n=165)	1.6	0.0 (n=0)	0.0 (n=0)	0.0	31.9 (n=67)	37.9 (n=67)	-6.0	64.6 (n=71)	63.6 (n=98)	0.9
Baseline MCS	48.5 (11.6)	48.9 (11.2)	-0.4	49.9 (11.0)	50.6 (10.8)	-0.7	46.0 (12.3)	45.1 (11.6)	0.9	48.1 (11.5)	46.8 (11.0)	1.3
Missing (%)	23.9 (n=138)	25.5 (n=165)	1.6	0.0 (n=0)	0.0 (n=0)	0.0	31.9 (n=67)	37.9 (n=67)	-6.0	64.6 (n=71)	63.6 (n=98)	0.9

Data are mean (standard deviation) or proportion (number of patients)
All data is based on norms based scoring
THC: telehealthcare; UP: usual practice; Diff: difference
COPD: chronic obstructive pulmonary disease; FEV1(%): forced expiratory volume in one second of predicted normal; FVC(%): forced vital capacity
#Complete case: a case that have nonmissing values on MCS and PCS score at baseline and follow-up
##Lost-to-follow-up: cases that died, withdrew consent or did not return any study questionnaires after baseline
###Incomplete case: a case that is not lost to follow-up but has missing values on items in either PCS and MCS at baseline or follow-up
§ Variable has no missing values
*Fischer's exact test for differences in proportions of patients in telehealth group and usual practice group (at baseline, complete cases, lost-to-follow-up and incomplete cases), P < 0.05
**Mann-Whitney's test for differences in mean in telehealth group and usual practice group (at baseline, complete cases, lost-to-follow-up and incomplete cases), P < 0.05

3.1.1. Preliminary descriptive analysis of PCS and MCS summary scores

Table 2 presents descriptive statistics of PCS and MCS scores over time for the two analysis cohorts, complete cases (n=574) and available cases (n=1,225) in each treatment arm.

Table 2: Descriptive analysis of PCS and MCS summary scores.

	Primary analysis (n=1,225)#		Complete case analysis (n=574)	
	THC	UP	THC	UP
PCS at follow-up	34.6 (13.9)	34.7 (13.8)	38.3 (9.6)	38.1 (9.6)

MCS at follow-up	43.4 (17.2)	43.5 (17.3)	48.4 (11.2)	48.6 (11.4)
Difference in PCS scores from baseline to follow-up*	-2.6 (12.4)	-2.8 (11.9)	0.0 (7.1)	-0.1 (6.7)
Difference in MCS scores from baseline to follow-up*	-4.7 (16.5)	-5.3 (15.5)	-1.5 (10.6)	-2.0 (8.7)

Data are Mean (SD)
All data in based on norms-based scoring
PCS=physical component score; MCS=mental component score
THC: telehealthcare; UP: usual practice
*Follow-up score minus baseline score
#Primary analysis has imputed missing PCS and MCS summary scores

At follow-up, lower scores of mean PCS and MCS were represented in the primary analysis (n=1,225) compared with the complete case analysis (n=574). In the primary analysis, the raw mean difference in PCS scores from baseline to follow up was -2.6 (SD: 12.4) in the telehealthcare group and -2.8 (SD: 11.9) in the usual practice group. The raw mean difference in MCS scores in the same period were -4.7 (SD: 16.5) and -5.3 (SD: 15.5) for telehealthcare and usual practice, respectively (Table 2).

In the complete case analysis, the raw mean difference in PCS scores over time was 0.0 (SD: 7.1) in the telehealthcare group and -0.0 (SD: 6.7) in the usual practice group. The raw difference in MCS scores were -1.5 (SD: 10.6) and -2.0 (SD: 8.7) for telehealthcare and usual practice, respectively. A comparison of the raw differences in PCS and MCS scores between the two analysis cohorts' indicated that both complete cases and available cases scored lower HRQoL from baseline to follow-up, except for the telehealthcare group's PCS score from the complete case analysis, which score increased from baseline to follow-up (Table 2).

3.2. Primary analysis and complete case analysis

3.2.1. Adjusted outcomes

Table 3 presents adjusted mean difference in summary scores between treatment groups at 12-month follow-up for each analysis cohort.

Table 3: Adjusted mean difference in PCS and MCS summary scores between groups, 12-month follow-up.

	Primary analysis (n=1,225)#	ICC	Complete case analysis (n=574)	ICC
PCS (adjusted mean difference)*	0.1 (-1.4; 1.7)	0.0	0.2 (-0.9; 1.3)	0.0
MCS (adjusted mean difference)*	0.4 (-1.7; 2.4)	0.0	0.4 (-1.0; 1.7)	0.0

Data are Mean (95% CI)
All data is based on norms based scoring
Primary analysis have imputed missing PCS and MCS summary scores
*Adjusted mean differences are based on multilevel models controlling for all mentioned covariates and clustering.
Differences can be interpreted as the observed extra effect of telehealthcare compared to usual practice when all mentioned covariates and clustering are taken into account.
PCS=physical component score; MCS=mental component score; ICC=Intra-class coefficient

In the primary analysis (n=1,225), the adjusted mean differences in summary scores at 12-month follow-up were, PCS: 0.1 (95% CI, -1.4; 1.7) and MCS: 0.4 (95% CI, -1.7; 2.4). The overlapping confidence intervals indicated that differences between groups at 12-month follow-up were non-significant (Table 3).

In the complete case analysis (n=574), the adjusted mean differences in summary scores at 12-month follow-up were, PCS: 0.2 (95% CI, -0.9; 1.3) and MCS: 0.4 (95% CI, -1.0; 1.7). The adjusted outcomes indicated no evidence of statistically significant differences between groups at 12-month follow-up (all confidence intervals crossed 0) (Table 3).

3.2.2. Secondary analysis

We also performed a posteriori-defined subgroup analysis, which showed no statistically significant effect of the intervention in any of the defined subgroups. Tables 4 and 5 provide estimates of both adjusted mean differences in PCS and MCS summary scores, 95% confidence intervals and p-values for the total sample and for subgroups (Table 4, Table 5).

Table 4: Primary outcome and subgroup analyses of the COPD patients' socio-demographic characteristics: Adjusted mean differences in PCS and MCS summary scores for the total sample and subgroups, adjusted for respective baseline PCS or baseline MCS scores and age, gender, baseline FEV1, marital status, cancer and diabetes.

Socio-demographic characteristics								
Effectiveness	**PCS**	**PCS 95% CI**	**Wald test**	**ICC**	**MCS**	**MCS 95% CI**	**Wald test**	**ICC**
Total sample	0.1	[-1.4;1.7]	**P value**	0.0	0.4	[-1.7;2.4]	**P value**	0.0
Gender								
Female (54%)	-0.3	[-1.6;1.1]	0.6	0.0	-0.5	[-2.6;1.7]	0.3	0.0
Male (46%)	0.5	[-2.1;3.2]			-1.3	[-1.9;4.5]		
Age								
< 60 years (16%)	-0.5	[-4.0;3.1]	0.7	0.0	-0.1	[-4.3;4.1]	0.9	0.0
60-69 years (33%)	-1.2	[-3.2;0.9]			-0.7	[-3.7;2.3]		
70-79 years (38%)	1.0	[-1.9;3.9]			0.7	[-2.7;4.2]		
≥ 80 years (13%)	1.7	[-3.6;7.0]			2.2	[-5.0;9.3]		
Marital status								
Married/relationship (58%)	0.3	[-1.8;2.4]	0.7	0.0	1.0	[-2.2;4.2]	0.8	0.0
Single (23%)	-0.9	[-3.8;2.0]			-0.6	[-4.9;3.6]		
Widow/widower (19%)	0.9	[-2.6;4.3]			-0.5	[-4.9;4.0]		
Smoking status								
Non-smokers (66%)	0.4	[-1.6;2.5]	0.6	0.0	1.3	[-1.6;4.3]	0.2	0.0
Smoker (34%)	-0.4	[-2.8;1.9]			-1.5	[-4.3;1.4]		
Job status								
Full time job (5%)	-1.2	[-6.1;3.8]	0.8	0.0	6.0	[-12.6;0.6]	0.2	0.0
Part time job (7%)	-0.8	[-5.0;3.3]			0.8	[-5.2;6.9]		
No job (88%)	0.3	[-1.4;2.0]			0.7	[-1.7;3.2]		
Education								

Elementary school, 7th-10th grade (48%)	0.1	[-1.6;1.8]	1.0	0.0	0.7	[-2.0;3.4]	0.7	0.0
High school (2%)	0.6	[-7.9;9.0]			4.7	[-8.0;17.4]		
Skilled worker (34%)	0.8	[-1.8;3.4]			1.2	[-2.5;4.9]		
Short-term education (2-3 years) (8%)	-1.6	[-5.7;2.5]			-2.4	[-8.1;3.3]		
Middle-term education (3-5 years) (7%)	-0.5	[-6.4;5.5]			-4.3	[-10.2;1.6]		
Long-term education (5-8 years) (1%)	-0.8	[-18.7;17.1]			0.4	[-22.6;23.4]		

PCS=physical component score; MCS=mental component score; Mean difference; 95% confidence intervals
All data in based on norms-based scoring
Multilevel linear models controlling for baseline PCS or MCS score and age, gender, baseline FEV1, marital status, cancer and diabetes and clustering. Priori hypothesis was that adding telehealthcare to usual practice would improve patients' HRQoL relative to usual practice.

Table 5: Primary outcome and subgroup analyses of the COPD patients' health characteristics: Adjusted mean differences in PCS and MCS summary scores for the total sample and subgroups, adjusted for respective baseline PCS or baseline MCS and age, gender, baseline FEV1, marital status, cancer and diabetes.

Health characteristics								
Effectiveness	**PCS**	**PCS 95% CI**	**Wald test**	**ICC**	**MCS**	**MCS 95% CI**	**Wald test**	**ICC**
Total sample	0.1	[-1.4;1.7]	**P value**	0.0	0.4	[-1.7;2.4]	**P value**	0.0
COPD severity (GOLD 1-4)								
Mild, 1 (6%)	1.7	[-4.7;8.2]	0.7	0.0	0.6	[-6.8;8.1]	0.8	0.0
Moderate, 2 (38%)	-0,7	[-3.0;1.5]			-0.7	[-3.8;2.4]		
Severe, 3 (39%)	1.0	[-1.7;3.7]			1.5	[-2.1;5.1]		
Very severe, 4 (17%)	-0.6	[-4.8;3.5]			-0.2	[-5.2;4.8]		
COPD duration								
< 3.5 years (25%)	-0.7	[-2.9;1.6]	0.3	0.0	-1.0	[-4.4;2.4]	0.1	0.0
3.5-6 years (26%)	-1.6	[-4.6;1.4]			-2.0	[-5.7;1.6]		
7-10 years (26%)	0.5	[-2.8;3.8]			0.5	[-3.6;4.7]		
> 10 years (23%)	2.5	[-0.7;5.7]			4.0	[-0.2;8.2]		
Diabetes								
No (89%)	0.3	[-1.2;1.9]	0.4	0.0	0.3	[-1.8;2.5]	0.9	0.0
Yes (11%)	-1.4	[-5.3;2.4]			0.7	[-4.9;6.4]		
Heart disease								
No (65%)	0.1	[-1.5;1.6]	0.9	0.0	0.7	[-1.7;3.2]	0.6	0.0
Yes (35%)	0.3	[-2.6;3.2]			-0.3	[-3.7;3.1]		
Mental health problem								
No (95%)	0.3	[-1.3;1.9]	0.3	0.0	0.3	[-1.8;2.4]	0.8	0.0
Yes (5%)	-3.1	[-8.7;2.5]			1.5	[-6.2;9.2]		
Musculoskeletal disease								
No (70%)	0.1	[-1.7;1.8]	0.9	0.0	0.5	[-1.6;2.6]	0.7	0.0
Yes (30%)	0.2	[-2.0;2.5]			-0.1	[-3.5;3.3]		
Cancer								
No (94%)	0.0	[-1.4;1.5]	0.5	0.0	0.2	[-1.85;2.28]	0.6	0.0
Yes (6%)	2.1	[-4.7;8.9]			2.7	[-5.4;10.7]		
Number of comorbidities								

Yes (33%)	0.3	[-2.1;2.6]	0.1	0.0	0.3	[-2.8;3.4]	0.7	0.0
No (41%)	1.4	[-1.0;3.8]			1.0	[-2.2;4.2]		
2 or more (26%)	-2.0	[-4.9;1.0]			-0.7	[-4.3;2.9]		
Hypertension								
Yes (71%)	0.6	[-1.3;2.5]	0.3	0.0	0.4	[-2.1;2.9]	1.0	0.0
No (29%)	-1.1	[-3.7;1.4]			0.3	[-3.3;3.9]		
Tachycardia								
Yes (70%)	0.3	[-1.4;1.9]	0.8	0.0	0.1	[-2.0;2.2]	0.7	0.0
No (30%)	-0.2	[-3.3;3.0]			1.0	[-2.8;4.9]		
BMI								
< 25 (44%)	0.4	[-2.1;2.8]	1.0	0.0	0.5	[-2.9;3.7]	1.0	0.0
25-30 (34%)	0.2	[-2.5;2.9]			-0.1	[-3.8;3.6]		
> 30 (22%)	-0.4	[-4.5;3.6]			0.8	[-4.0;5.6]		

PCS=physical component score; MCS=mental component score; Mean difference; 95% confidence intervals
All data in based on norms-based scoring
Multilevel linear models controlling for baseline PCS or MCS score and age, gender, baseline FEV1, marital status, cancer and diabetes and clustering. Priori hypothesis was that adding telehealthcare to usual practice would improve patients' HRQoL relative to usual practice.

4. Discussion

The present study hypothesised that adding telehealthcare to usual practice would significantly increase patients' HRQoL [31]. This hypothesis was rejected. We found not statistical quality-of-life differences between groups in either the primary analysis, the complete case analysis or in any of the subgroups.

4.1. Interpretation of findings

Despite the non-significant differences, the mean differences in PCS and MCS scores at 12-month follow-up were larger for the control group than for the intervention group, which could indicate a faster deterioration over time for the controls than for the intervention patients. The largest mean difference was seen in MCS. If this is the case, it might be explained by the difficulty associated with affecting the physical QoL compared with the mental QoL. The slower decline in MCS for the telehealthcare group may be interpreted as a psychological benefit derived from using the Telekit.

Although the subgroup analysis indicated no statistically significant effects of the intervention in any of the posteriorly defined subgroups there was an indication of some positive effects on HRQoL within certain subgroups of the intervention group compared with usual practice. These trends towards positive effects on HRQoL should be further investigated.

4.2. Strengths and weaknesses

The present study was the first Danish large-scale trial established to remedy the lack of international evidence on HRQoL in patients with COPD who are receiving telehealthcare. A total of 1,225 participants from 26 municipality districts in the North Denmark Region were included in the analysis. The trial succeeded in establishing a fruitful cooperation between many stakeholders with different interests in the trial. The trial hence demonstrated the feasibility of intersectoral and interinstitutional collaboration towards a shared end, viz. the implementation of telehealthcare to improve COPD patients' HRQoL.

In contrast to the WSD [22–25], the TeleCare North trial compared the effects of telehealthcare with the effects of usual practice in COPD patients only. The design of the WSD was characterised by variability in terms of the employed technologies, the recruited sample, the type of intervention, and defined care pathways. Contrary to the WSD [40], the TeleCare North trial used a "clean" control group of COPD patients who received usual practice and no other forms of care.

The TeleCare North trial was based on the same concept as in previous Danish pilot studies [27–30,41] namely to increase patient empowerment and to detect disease deterioration through self-monitoring. In the present study, we attended to clarify the mechanisms that were supposed to provide effects. Organisational initiatives to further this concept, for example ensuring that patients had functional telehealthcare equipment, instructing patients how to use this equipment, and by gearing the organisation to rapidly respond to reported measures to prevent COPD exacerbations. That no significant effects of HRQoL were found, therefore cannot be attributed to patients' lack of equipment, a lack of instructions, or inadequate operational equipment.

In the trial, we found a considerable high attrition rate of 53% among participants with over half of the sample not providing follow-up data due to incomplete cases with missing data or loss to follow-up. Conducting a sensitivity analysis as a complete case analysis was therefore relevant in order to explore differences among complete and available cases. The high attrition rate may be attributed to disease progression and may have affected the findings of the trial. However, the consistency of results indicates that conclusions on findings are robust in spite of the high attrition rate. Further research is required to find explanations for high attrition rate among COPD patients.

The subgroup analysis was not pre-specified at the outset of the trial but was undertaken after the data collection of the trial. Because of the limitation noted, the findings of the post hoc subgroup analysis should be interpreted with caution irrespective of their significance.

We cannot rule out the influence of non-specific effects like a Hawthorne effect [42] or "natural history effects" [43], both of which could have influenced the intervention and the control group to some extent.

The potential presence of any such effects may explain why differences in HRQoL between the groups were difficult to detect.

The baseline variables used in the TeleCare North trial were not exhaustive; nor were all relevant variables included. At baseline, the FVC% indicated that the patients in the intervention group were poorer than the patients of the control group. It is widely known that QoL deteriorates with increasing severity of COPD [44]. This may also contribute to explaining why no significant differences in HRQoL were found between the groups. It would have been desirable to supplement the baseline variables with other clinical characteristics such as the Medical Research Council (MRC) dyspnoea score and with activities-of-daily-living measures to determine if the groups differed from each other in relation to their state of health. The number of selected baseline variables made it possible to classify the patients only according to the old GOLD classification (I-V). It would have been desirable to classify the patients according to the new GOLD classification (A-D) which is based on symptoms, airflow obstruction, and exacerbation history. Use of the new GOLD classification would probably have made it possible to establish more relevant subgroups [32].

The SF-36v2 was selected as an appropriate outcome measure because it is a useful, generic, and validated questionnaire for comparing differences between populations. It is possible, however, that generic questionnaires do not adequately measure the QoL issues that different groups of patients experience. It has been shown that the SF-36 is susceptible to ceiling and floor effects as it is applicable to a wide population of both healthy and sick individuals. It is possible that the SF-36v2 was not sufficiently sensitive to changes and to identifying outcome differences in patients with COPD [45]. This was also confirmed by Rixon et al. [25] who suggest that generic instruments are less sensitive to change related to telehealth than disease-specific instruments are. COPD is associated with symptoms that might have an impact on the patients' QoL, which makes it uncertain whether the generic questionnaires capture these aspects. Another alternative for measuring QoL could have been a more disease-specific questionnaire for COPD patients, such as the St. George' Respiratory Questionnaire (SGRQ) [46] and other QoL instruments such as the Chronic Respiratory Questionnaire (CRQ) [47]; the EQ-5D [48] or the Hospital Anxiety and Depression Scale (HAD) [49]. A study by Engström and colleagues [50] illustrated that a combination of generic and disease-specific questionnaires was the most suitable choice for measuring differences in COPD patients' HRQoL following an intervention. They argued that both disease-specific effects and the overall burden of the disease on everyday functioning and mental wellbeing should be considered. This was also confirmed in a review by Chen who recommended the use of both generic and disease-specific questionnaires in combination [45].

Another relevant consideration is whether QoL measures should be expected to change by implementation of telehealthcare. Two recent systematic reviews [18,51] found that the impact of telehealth on QoL in

patients with COPD is limited. However, the review suggested that active interventions may improve QoL outcomes in the telehealth group compared with usual care [18]. Based on this study's results and the literature [7,18,24,25], telehealthcare is not assumed to be convincing when looking at QoL as an isolated factor. However, QoL improvements may be expected over time [25] in active telehealthcare interventions where some kind of self-management skills training is an integrated part of the intervention [18].

The strategy of offering inclusion to all COPD patients who may benefit from telehealthcare in the whole region of North Denmark strengthens the generalisability of the findings. So does the use of minimal inclusion criteria and the 12-month-long continuous assessment of the patients. Given the significant differences between COPD and other chronic diseases, the findings should, however, not be applied to other chronic diseases.

The Region of North Denmark is fairly representative of the whole country of Denmark in terms of population and healthcare system. The findings are therefore generally applicable to the whole of Denmark and, at least partly, also to countries with similar healthcare systems such as the other Nordic countries.

4.3. Comparison with other studies

Our results demonstrate a further lack of any improvements in QoL following implementation of telehealthcare in COPD. The WSD is the only large-scale study of telehealthcare in COPD that we have come across. The findings from the WSD study by Cartwright and colleagues [24] indicated no improvement in HRQoL from telehealth, but some significant differences suggested that the telehealth group had a slower rate of deterioration over time compared with the control group.

Similarly, no statistical differences in the Telescot study [52] or the "The Virtual Hospital" trial [53] were identified between the control and intervention groups. The results of our study are consistent with the findings from these studies.

The review and meta-analysis by McLean et al. [7] is also relevant to consider; in contrast, their findings indicated possible impact of COPD patients' QoL. Another recent review by Cruz et al. [10] indicated inconsistency in HRQoL findings with most of the studies reporting no significant changes in HRQoL. However, the studies included in the reviews used different HRQoL instruments; and it has therefore been recommended to use similar HRQoL instruments in future studies to enable comparisons [7,10].

Nevertheless, the benefits in relation to QoL may be debated although telehealthcare seems unlikely to reduce QoL. One of our previous findings from the TeleCare North trial indicated that the intervention patients experienced enhanced control, freedom, security, and greater awareness of their COPD symptoms

when using the telehealthcare system [54]. These benefits are not underpinned by the present study's findings on HRQoL.

4.4. Implications for practice

Our findings indicate that adding telehealthcare to usual practice does not improve HRQoL in patients with COPD. We did not succeed in achieving the HRQoL effects we had hoped for, and the reduced HRQoL in both groups means that it is doubtful whether telehealthcare benefits patients' QoL. Therefore, policymakers and healthcare professionals should consider whether telehealthcare should be implemented to achieve other objectives than improving patients' HRQoL, i.e. saving costs, reducing mortality, affecting other outcome variables, etc.

Furthermore, it is relevant to explore other domains such as physical activity, psychological symptoms and different modes of telehealth application and interventions, which may be important in improving QoL. In addition, more research should be considered within more specific subgroups of COPD patients to assess whether telehealthcare has a particularly beneficial effect on QoL in some groups. It is possible that patients' QoL varies between subgroups. Knowledge of such variation is useful and may inform future implementation of telehealthcare allowing for targeting of specific patient subgroups.

4.5. Future directions

In the future, more research is needed into the underlying mechanisms behind this lack of an identifiable effect. More qualitative research is required to gain a deeper understanding of the mechanism and preconditions needed to improve patients' HRQoL by use of telehealthcare. A greater effort should be dedicated to studying the specific subgroups instead of the population as whole because telehealthcare systems likely fit some patients better than others. Furthermore, the COPD patients in the present trial were recruited from different municipalities, some of which might have been better at organizing telehealthcare than others. Large-scale studies are therefore not recommended until these underlying mechanisms have been further investigated.

Future studies should recognize telehealthcare as a complex intervention. Such studies should therefore be designed as a mix of randomised controlled trials and other research designs to fully assess complex interventions. It is possible that we have jumped too quickly to large-scale operational trials. Furthermore, research on the causal relationship between QoL and patients' socio-demographic and health characteristics is limited, indicating that a number of exploratory studies need to be performed within the TeleCare North trial in the future.

In conclusion, the findings of the present study indicate that the potential of telehealthcare for improving COPD patients' HRQoL is limited. However, it is assumed on the basis of these results that telehealthcare as an additional service alongside the existing clinical care does not lead to poorer QoL.

Acknowledgements

The participation of the Trial Administration Office, the general practitioners, hospitals, healthcare providers and patients in the North Denmark Region is acknowledged. Without their commitment to the implementation of the TeleCare North trial, it would not have been possible to do this study.

Declarations

Detailed description of intervention and comparator: The study protocol (DOI: 10.1186/1745-6215-15-178) is freely available and can be downloaded from: http://www.trialsjournal.com/content/15/1/178.

Details of contributors: Pernille Heyckendorff Lilholt (PHL), Flemming Witt Udsen (FWU), Ole Kristian Hejlesen (OKH), and Lars Holger Ehlers (LHE) conceived and designed the study and were responsible for its conduct. PHL and FWU managed the study and the data collection. The trial's Administration Office provided administrative support. FWU undertook the data analysis. PHL, FWU, OKH, and LHE interpreted the data. PHL prepared the first draft of the manuscript. OKH, FWU, and LHE revised and contributed to the manuscript. All authors read and approved the final manuscript.

Funding: This paper was funded by the North Denmark Region, the 11 municipalities in the North Denmark Region and by the Obel Family Foundation, the Danish Agency for Digitalization Policy and Strategy and the European Social Fund. The funding agencies had no influence on the design of the study, the analysis and interpretation, dissemination of results, or the shaping of the article. The article is based on the authors' views and not those of the sponsors.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work other than those detailed above; no financial relationships with any organisations that might have any interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethics approval: The trial was presented to the Danish Ethics Committee for Medical Research in the North Denmark Region and no ethical approval was needed. The trial has also been accepted by the Danish Data Protection Agency. All patients gave written informed consent for participation in this study and provided their approval for use of their data for research.

Data sharing: No additional data available.

Figure legends:

Figure 1: The Telekit system consists of a tablet, a blood pressure monitor, a fingertip pulse oximeter and a health precision scale

Figure 2: CONSORT diagram of the TeleCare North trial

References

1 Fletcher M, Upton J, Taylor-Fishwick J, *et al.* COPD uncovered: an international survey on the impact of chronic obstructive pulmonary disease [COPD] on a working age population. *BMC Public Health* 2011;**11**:1–13. doi:10.1186/1471-2458-11-612

2 Lõpez-Campos JL, Tan W, Soriano JB. Global burden of COPD. *Respirology* 2016;**21**:14–23. doi:10.1111/resp.12660

3 Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. *Lancet* 2007;**370**:765–73. doi:10.1016/S0140-6736(07)61380-4

4 Adeloye D, Chua S, Lee C, *et al.* Global and regional estimates of COPD prevalence: Systematic review and meta–analysis. *J Glob Health* 2015;**5**:1–17. doi:10.7189/jogh.05-020415

5 Goodridge D, Marciniuk D. Rural and remote care: Overcoming the challenges of distance. *Chron Respir Dis* 2016;**21**:21. doi:http://dx.doi.org/10.1177/1479972316633414

6 Annandale J, Lewis KE. Can telehealth help patients with COPD? *Nurs Times* 2005;**107**:12–4.http://www.ncbi.nlm.nih.gov/pubmed/21661486

7 McLean S, Nurmatov U, Liu JL, *et al.* Telehealthcare for chronic obstructive pulmonary disease: Cochrane Review and meta-analysis. *Br J Gen Pract* 2012;**62**:739–49. doi:10.3399/bjgp12X658269

8 Lundell S, Holmner Å, Rehn B, *et al.* Telehealthcare in COPD: A systematic review and meta-analysis on physical outcomes and dyspnea. *Respir Med* 2015;**109**:11–26. doi:10.1016/j.rmed.2014.10.008

9 Calvo GS, Hernández AS, Padilla DL, *et al.* Clinical Outcomes of Home Telemonitoring in Severe COPD. *iMedPub Journals* 2016;**1**:1–7.

10 Cruz J, Brooks D, Marques A. Home telemonitoring effectiveness in COPD: a systematic review. *Int J Clin Pract* 2014;**68**:369–78. doi:10.1111/ijcp.12345

11 Bolton CE, Waters CS, Peirce S, *et al.* Insufficient evidence of benefit: a systematic review of home telemonitoring for COPD. *J Eval Clin Pract* 2011;**17**:1216–22. doi:10.1111/j.1365-2753.2010.01536.x

12 Bowles KH, Baugh AC. Applying research evidence to optimize telehomecare. *J Cardiovasc Nurs* 2007;**22**:5–15.http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2874189&tool=pmcentrez&rendertype=abstract

13 Polisena J, Tran K, Cimon K, *et al.* Home telehealth for chronic obstructive pulmonary disease: a systematic review and meta-analysis. *J Telemed Telecare* 2010;**16**:120–7. doi:10.1258/jtt.2009.090812

14 Franek J. Home telehealth for patients with chronic obstructive pulmonary disease (COPD): an evidence-based analysis. *Ont Health Technol Assess Ser* 2012;**12**:1–

58.http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3384362&tool=pmcentrez&rendertype=abstract

15 Kitsiou S, Paré G, Jaana M. Systematic reviews and meta-analyses of home telemonitoring interventions for patients with chronic diseases: a critical assessment of their methodological quality. *J Med Internet Res* 2013;**15**:e150. doi:10.2196/jmir.2770

16 Ekeland AG, Bowes A, Flottorp S. Effectiveness of telemedicine: A systematic review of reviews. *Int J Med Inform* 2010;**79**:736–71. doi:10.1016/j.ijmedinf.2010.08.006

17 Pedone C, Lelli D. Systematic review of telemonitoring in copd: An update. *Pneumonol Alergol Pol* 2015;**83**:476–84. doi:10.5603/PiAP.2015.0077

18 Ulrik CS, Lomholt Gregersen T, Green A, *et al.* Do telemedical interventions improve quality of life in patients with COPD? A systematic review. *Int J Chron Obstruct Pulmon Dis* 2016;**Volume 11**:809. doi:10.2147/COPD.S96079

19 Bower P, Cartwright M, Hirani SP, *et al.* A comprehensive evaluation of the impact of telemonitoring in patients with long-term conditions and social care needs: protocol for the whole systems demonstrator cluster randomised trial. *BMC Health Serv Res* 2011;**11**:184. doi:10.1186/1472-6963-11-184

20 Hirani SP, Beynon M, Cartwright M, *et al.* The effect of telecare on the quality of life and psychological well-being of elderly recipients of social care over a 12-month period: the Whole Systems Demonstrator cluster randomised trial. *Age Ageing* 2014;**43**:334–41. doi:10.1093/ageing/aft185

21 Steventon A, Bardsley M, Billings J, *et al.* Effect of telecare on use of health and social care services: findings from the Whole Systems Demonstrator cluster randomised trial. *Age Ageing* 2013;**42**:501–8. doi:10.1093/ageing/aft008

22 Steventon A, Bardsley M, Billings J, *et al.* Effect of telehealth on use of secondary care and mortality: findings from the Whole System Demonstrator cluster randomised trial. *BMJ* 2012;**344**:e3874–e3874. doi:10.1136/bmj.e3874

23 Henderson C, Knapp M, Fernandez J-L, *et al.* Cost effectiveness of telehealth for patients with long term conditions (Whole Systems Demonstrator telehealth questionnaire study): nested economic evaluation in a pragmatic, cluster randomised controlled trial. *BMJ* 2013;**346**:f1035–f1035. doi:10.1136/bmj.f1035

24 Cartwright M, Hirani SP, Rixon L, *et al.* Effect of telehealth on quality of life and psychological outcomes over 12 months (Whole Systems Demonstrator telehealth questionnaire study): nested study of patient reported outcomes in a pragmatic, cluster randomised controlled trial. *BMJ* 2013;**346**:f653. doi:10.1136/bmj.f653

25 Rixon L, Hirani SP, Cartwright M, *et al.* A RCT of telehealth for COPD patient's quality of life: the whole system demonstrator evaluation. *Clin Respir J* 2015;:2–25. doi:10.1111/crj.12359

26 Fonden for Velfærdsteknologi. National handlingsplan for udbredelse af telemedicin. 2012. http://www.digst.dk/Digital-velfaerd/~/media/Files/Velfærdsteknologi/Telemedicinsk handlingsplan/Telemedicinsk handlingsplan-web.pdf

27 Haesum LKE, Soerensen N, Dinesen B, *et al.* Cost-utility analysis of a telerehabilitation program: a case study of COPD patients. *Telemed J E Health* 2012;**18**:688–92. doi:10.1089/tmj.2011.0250

28 Huniche L, Dinesen B, Grann O, *et al.* Empowering Patients with COPD using Tele-Homecare

Technology. 2010;:48–54. doi:10.3233/978-1-60750-563-1-48

29 Sorknæs AD, Madsen H, Hallas J, *et al.* Nurse tele-consultations with discharged COPD patients reduce early readmissions - an interventional study. *Clin Respir J* 2011;**5**:26–34. doi:10.1111/j.1752-699X.2010.00187.x

30 Sorknaes AD, Bech M, Madsen H, *et al.* The effect of real-time teleconsultations between hospital-based nurses and patients with severe COPD discharged after an exacerbation. *J Telemed Telecare* 2013;**19**:466–74. doi:10.1177/1357633X13512067

31 Udsen FW, Lilholt PH, Hejlesen O, *et al.* Effectiveness and cost-effectiveness of telehealthcare for chronic obstructive pulmonary disease: study protocol for a cluster randomized controlled trial. *Trials* 2014;**15**:178. doi:10.1186/1745-6215-15-178

32 GOLD: Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, And Prevention of Chronic Obstructive Pulmonary Disease. 2015. www.goldcopd.org

33 Davenport TE, Stevens SR, Baroni K, *et al.* Reliability and validity of Short Form 36 Version 2 to measure health perceptions in a sub-group of individuals with fatigue. *Disabil Rehabil* 2011;**33**:2596–604. doi:10.3109/09638288.2011.582925

34 Kosinski M, Dewy J. *How to Score Version Two of the SF-36 Health Survey*. 3rd ed. Quality Metric 2001.

35 Bentsen SB, Rokne B, Wahl AK. Comparison of health-related quality of life between patients with chronic obstructive pulmonary disease and the general population. *Scand J Caring Sci* 2013;**27**:905–12. doi:10.1111/scs.12002

36 Vickers AJ, Altman DG. Statistics notes: Analysing controlled trials with baseline and follow up measurements. *BMJ* 2001;**323**:1123–4. doi:10.1136/bmj.323.7321.1123

37 Faria R, Gomes M, Epstein D, *et al.* A Guide to Handling Missing Data in Cost-Effectiveness Analysis Conducted Within Randomised Controlled Trials. *Pharmacoeconomics* 2014;**32**:1157–70. doi:10.1007/s40273-014-0193-3

38 Ware J, Bayliss M, Rogers W, *et al.* Differences in 4-Year Health Outcomes for Elderly and Poor, Chronically III Patients Treated in HMO and Fee-for-Service Systems: Results from the Medical Outcomes Study. *J Am Med Assoc* 1996;**276**:1039–47. doi:doi:10.1001/jama.1996.03540130037027

39 Bjørner JB, Damsgaard MT, Watt T, Bech P, Rasmussen NK, Kristensen TS, Modvig J, Thunedborg K. *Dansk manual til SF-36*. København: : Lif 1997.

40 Ellis Tim. The Whole System Demonstrator Programme. York UK: 2009.

41 Dinesen B, Seeman J, Gustafsson J. Development of a program for tele-rehabilitation of COPD patients across sectors : co-innovation in a network Presentation of the Telekat case study. 2011;**11**.

42 Konstantinou GN. Pragmatic trials: how to adjust for the 'Hawthorne effect'? *Thorax* 2012;**67**:562–562. doi:10.1136/thoraxjnl-2011-200657

43 Bouchet C, Guillemin F, Briançon S. Nonspecific effects in longitudinal studies: impact on quality of life measures. *J Clin Epidemiol* 1996;**49**:15–20. doi:10.1016/0895-4356(95)00540-4

44 Zamzam M, Azab N, Wahsh R El, *et al.* Quality of life in COPD patients. *Egypt J Chest Dis Tuberc* 2013;**5**:36–40. doi:10.1016/j.ejcdt.2012.08.012

45 Chen T, Li L, Kochen MM. A systematic review: How to choose appropriate health-related quality of life (HRQOL) measures in routine general practice? *J Zhejiang Univ Sci* 2005;**6B**:936–40.

doi:10.1631/jzus.2005.B0936

46 Swigris JJ, Brown KK, Behr J, *et al.* The SF-36 and SGRQ: Validity and first look at minimum important differences in IPF. *Respir Med* 2010;**104**:296–304. doi:10.1016/j.rmed.2009.09.006

47 Guyatt GH, Berman LB, Townsend M, *et al.* A measure of quality of life for clinical trials in chronic lung disease. *Thorax* 1987;**42**:773–8. doi:10.1136/thx.42.10.773

48 The EuroQol Group. A New Facility for the Measurement of Health-Related Quality of Life. *Health Policy (New York)* 1990;**16**:199–208.

49 Aylard PR, Gooding JH, McKenna PJ, *et al.* A validation study of three anxiety and depression self-assessment scales. *J Psychosom Res* 1987;**31**:261–8. doi:10.1016/0022-3999(87)90083-3

50 Engström CP, Persson LO, Larsson S, *et al.* Health-related quality of life in COPD: why both disease-specific and generic measures should be used. *Eur Respir J* 2001;**18**:69–76.http://www.ncbi.nlm.nih.gov/pubmed/11510808

51 Liu L, Stroulia E, Nikolaidis I, *et al.* Smart homes and home health monitoring technologies for older adults: A systematic review. *Int J Med Inform* 2016;**91**:44–59. doi:10.1016/j.ijmedinf.2016.04.007

52 Pinnock H, Hanley J, McCloughan L, *et al.* Effectiveness of telemonitoring integrated into existing clinical services on hospital admission for exacerbation of chronic obstructive pulmonary disease: researcher blind, multicentre, randomised controlled trial. *Bmj* 2013;**347**:f6070. doi:10.1136/bmj.f6070

53 Jakobsen AS, Laursen LC, Rydahl-Hansen S, *et al.* Home-based telehealth hospitalization for exacerbation of chronic obstructive pulmonary disease: findings from 'the virtual hospital' trial. *Telemed J E Health* 2015;**21**:364–73. doi:10.1089/tmj.2014.0098

54 Lilholt PH, Korsbakke L, Hæsum E. Exploring User Experience of a Telehealth System for the Danish TeleCare North Trial. 2015;:301–5. doi:10.3233/978-1-61499-512-8-301

Figure 1: The Telekit system consists of a tablet, a blood pressure monitor, a fingertip pulse oximeter and a health precision scale.

180x119mm (300 x 300 DPI)

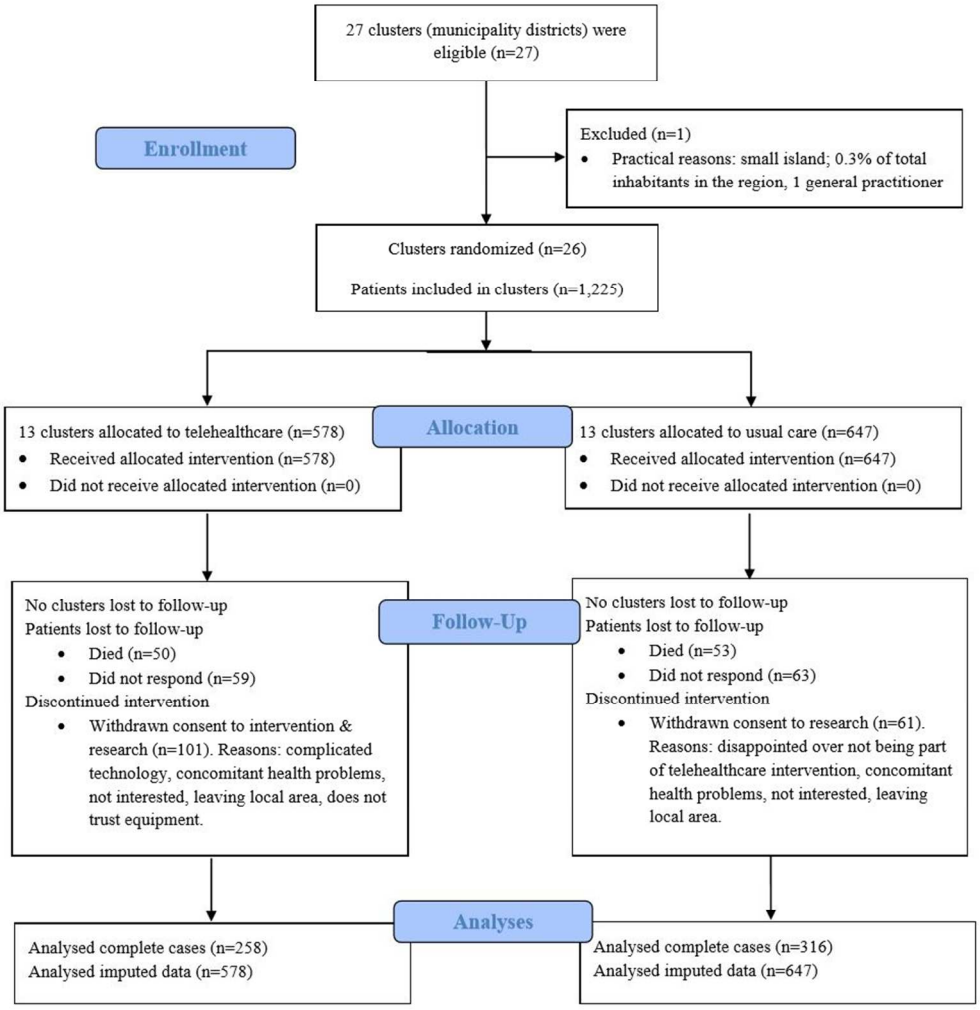

Figure 2: Consort diagram of the TeleCare North trial

83x86mm (300 x 300 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	p. 1 in protocol/p. 2 in manuscript
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	p. 1 in protocol/p. 2 in manuscript
	2b	All items from the World Health Organization Trial Registration Data Set	Clinicaltrials.gov
Protocol version	3	Date and version identifier	Original protocol
Funding	4	Sources and types of financial, material, and other support	p. 7 in protocol/p. 19 in manuscript
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	p. 7 in protocol/p. 19 in manuscript
	5b	Name and contact information for the trial sponsor	Clinicaltrials.gov, p. 19 in manuscript
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Not relevant

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Clinicaltrials.gov
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	p. 1-2 in protocol/p. 3-4 in manuscript
	6b	Explanation for choice of comparators	p. 4 in protocol, p. 6 in manuscript
Objectives	7	Specific objectives or hypotheses	p. 2/5 in protocol, p. 4 in manuscript
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	p. 2 in protocol/p. 4-5 in manuscript
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	p. 2-3 in protocol/p. 2 in manuscript
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	p. 2-3 in protocol/p. 5 in manuscript
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	p. 3-5 in protocol/p. 5-6 in manuscript
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Not relevant

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	p. 3-5 in protocol/ p. 6 in manuscript
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	p. 4 in protocol/p. 6 in manuscript
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	p. 5 in protocol/p. 7 in manuscript
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	p. 2-5 in protocol
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	p. 5 in protocol/p. 7 in manuscript
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	p. 3 in protocol/p. 5 in manuscript
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	p. 3-4 in protocol/p. 6 in manuscript
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	p. 3-4 in protocol/p. 6 in manuscript
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	p. 2-4 in protocol/ p. 5-6 in manuscript

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	p. 3-4 in protocol
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not relevant
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	p. 5 in protocol/p.7-8 in manuscript Clinicaltrials.gov
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	p. 5 in protocol Clinicaltrials.gov
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Clinicaltrials.gov
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	p. 5-6 in protocol/p. 7 in manuscript
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	p. 7 in manuscript
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	p. 5 in protocol/p. 7 in manuscript
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Clinicaltrials.gov

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Not relevant
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Not relevant
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	www.telecarenord.dk
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	p. 6 in protocol/ p. 20 in manuscript
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Not relevant
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	p. 3 in protocol/p. 5 in manuscript
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not relevant
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	www.telecarenord.dk
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	p. 7 in protocol/p. 19 in manuscript
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	p. 20 in manuscript
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not relevant

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	www.telecarenord.dk
	31b	Authorship eligibility guidelines and any intended use of professional writers	www.telecarenord.dk
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	The original protocol is open assess published
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	www.telecarenord.dk
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not relevant

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Table 1: CONSORT 2010 checklist of information to include when reporting a cluster randomised trial

Section/Topic	Item No	Standard Checklist item	Extension for cluster designs	Page No *
Title and abstract				
	1a	Identification as a randomised trial in the title	Identification as a cluster randomised trial in the title	p. 1 manuscript
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)[1,2]	See table 2	p. 2 manuscript
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	Rationale for using a cluster design	p. 3-4 manuscript
	2b	Specific objectives or hypotheses	Whether objectives pertain to the the cluster level, the individual participant level or both	p. 4 manuscript p. 4 protocol
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Definition of cluster and description of how the design features apply to the clusters	p. 4-6 manuscript p. 2-3 protocol
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		
Participants	4a	Eligibility criteria for participants	Eligibility criteria for clusters	p. 5 manuscript p. 2-3 protocol
	4b	Settings and locations where the data were collected		p. 6 manuscript p. 3 protocol
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Whether interventions pertain to the cluster level, the individual participant level or both	p. 5-6 manuscript p. 5 protocol

Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Whether outcome measures pertain to the cluster level, the individual participant level or both	p. 6-7 manuscript p. 5 protocol
	6b	Any changes to trial outcomes after the trial commenced, with reasons		
Sample size	7a	How sample size was determined	Method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a coefficient of intracluster correlation (ICC or *k*), and an indication of its uncertainty	
	7b	When applicable, explanation of any interim analyses and stopping guidelines		p. 7 manuscript p. 5 protocol
Randomisation:				
Sequence generation	8a	Method used to generate the random allocation sequence		p. 6 manuscript p. 3 protocol
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Details of stratification or matching if used	p. 6 manuscript p. 3 protocol
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level or both	p. 6 manuscript p. 3 protocol
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Replace by 10a, 10b and 10c	
	10a		Who generated the random allocation sequence, who	p. 6 manuscript p. 2-3 protocol

			enrolled clusters, and who assigned clusters to interventions	
	10b		Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete enumeration, random sampling)	p. 6 manuscript p. 2-3 protocol
	10c		From whom consent was sought (representatives of the cluster, or individual cluster members, or both), and whether consent was sought before or after randomisation	p. 3 protocol
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how		
	11b	If relevant, description of the similarity of interventions		p. 8-10 manuscript
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	How clustering was taken into account	p. 7-8 manuscript p. 5 protocol
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		p. 7-8 manuscript p. 5 protocol
Results				
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	For each group, the numbers of clusters that were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 2 manuscript

	13b	For each group, losses and exclusions after randomisation, together with reasons	For each group, losses and exclusions for both clusters and individual cluster members	Figure 2 manuscript
Recruitment	14a	Dates defining the periods of recruitment and follow-up		p. 6 manuscript p. 2 protocol
	14b	Why the trial ended or was stopped		
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Baseline characteristics for the individual and cluster levels as applicable for each group	Table 1 manuscript
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	For each group, number of clusters included in each analysis	p. 10 manuscript p. 3 protocol
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or k) for each primary outcome	p. 8-12 manuscript
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory		p. 12-14 manuscript
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms[3])		
Discussion				
Limitations	20	Trial limitations, addressing sources of potential bias,		p. 14-16 manuscript

		imprecision, and, if relevant, multiplicity of analyses		
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Generalisability to clusters and/or individual participants (as relevant)	p. 14-18 manuscript
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence		p. 14-18 manuscript
Other information				
Registration	23	Registration number and name of trial registry		p. 2 manuscript
Protocol	24	Where the full trial protocol can be accessed, if available		p. 18 manuscript
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders		p. 18-19 manuscript

** Note: page numbers optional depending on journal requirements*

Table 2: Extension of CONSORT for abstracts[1,2] to reports of cluster randomised trials

Item	Standard Checklist item	Extension for cluster trials
Title	Identification of study as randomised	**Identification of study as cluster randomised**
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	**Eligibility criteria for clusters**
Interventions	Interventions intended for each group	
Objective	Specific objective or hypothesis	**Whether objective or hypothesis pertains to the cluster level, the individual participant level or both**
Outcome	Clearly defined primary outcome for this report	**Whether the primary outcome pertains to the cluster level, the individual participant level or both**
Randomization	How participants were allocated to interventions	**How clusters were allocated to interventions**
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	
Results		
Numbers randomized	Number of participants randomized to each group	**Number of clusters randomized to each group**
Recruitment	Trial status[1]	
Numbers analysed	Number of participants analysed in each group	**Number of clusters analysed in each group**
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	**Results at the cluster or individual participant level as applicable for each primary outcome**
Harms	Important adverse events or side effects	
Conclusions	General interpretation of the results	
Trial registration	Registration number and name of trial register	
Funding	Source of funding	

[1] Relevant to Conference Abstracts

REFERENCES

1 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomised trials in journal and conference abstracts. *Lancet* 2008, 371:281-283

2 Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG at al (2008) CONSORT for reporting randomized controlled trials in journal and conference abstracts: explanation and elaboration. *PLoS Med* 5(1): e20

3 Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, Moher D. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004; 141(10):781-788.