Telemonitoring of lung function in COPD: the CHROMED study, a randomized clinical trial

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Running head: Telemonitoring of lung function in COPD: the CHROMED study

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At a Glance Commentary

Scientific Knowledge on the Subject: Despite observational studies suggesting that COPD exacerbation can be detected using a combination of symptoms and physiological measures, such as pulse and oxygen saturation, larger randomized controlled trials have not shown any effect of telemonitoring on time to first hospital admission (TTFH), hospitalization and quality of life. Tested tele-monitoring programs had a negligible impact on healthcare costs, and, in some cases, resulted in an increased healthcare utilisation.

What This Study Adds to the Field: This randomized controlled trial of 312 COPD patients is the first using only objective lung function data measured daily by the forced oscillation technique to prompt early intervention. Despite being feasible and well accepted by patients, this approach did not affect TTFH and quality of life. However, it significantly reduced healthcare costs, mostly due to a reduction in duration and frequency of subsequent hospitalisations, which was greatest in patients hospitalised the year before recruitment.

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org

Abstract

Rationale Early detection of COPD exacerbations using tele-monitoring of physiological variables might reduce the frequency of hospitalisation.

Objectives To evaluate the efficacy of home monitoring of lung mechanics by the forced oscillation technique (FOT) and cardiac parameters in older COPD patients with co-morbidities.

Methods This multicentre, randomized clinical trial recruited 312 GOLD grade II-IV COPD patients (median age 71 years [IQR:66-76], 49.6% grade II, 50.4% grade III-IV), with a history of exacerbation in the previous year and at least one non-pulmonary co-morbidity. Patients were randomised to usual care (n=158) or tele-monitoring (n=154) and followed for 9 months. All tele-monitoring patients self-assessed lung mechanics daily and in a subgroup with congestive heart failure (n=37) cardiac parameters were monitored. An algorithm identified deterioration, triggering a telephone contact to determine appropriate interventions.

Measurements and Main results Primary outcomes were time to first hospitalisation (TTFH) and change in EQ-5D utility index score. Secondary outcomes included: rate of antibiotic/corticosteroid prescriptions, hospitalisation, CAT, PHQ-9 and MLHF questionnaire scores, quality-adjusted life years and healthcare costs. Tele-monitoring did not affect TTFH, EQ-5D utility index score, antibiotic prescriptions, hospitalization rate and questionnaire scores. Tele-medicine was associated with fewer repeat hospitalizations (-54%, p=0.017). Previously hospitalised patients showed the greatest reduction in hospitalization rate (-53%, p=0.017) with large potential for cost savings (-3736€/patient/year, p=0.010).

Conclusions In older COPD patients with co-morbidities remote monitoring of lung function by FOT and cardiac parameters did not change TTFH and EQ-5D. However patients at risk of hospitalisation may benefit from this approach.

Keywords: Forced Oscillation technique, FOT, COPD exacerbation, Chronic Obstructive Pulmonary disease, Home monitoring, Chronic Obstructive Pulmonary Disease

Introduction

Chronic obstructive pulmonary disease (COPD) is common, impairs quality of life and is a leading cause of death worldwide[1]. Co-morbid conditions, such as cardiovascular disease often co-exist with COPD, leading to worse outcomes[2]. Both co-morbidity and increasing age are associated with less effective COPD self-management[3], more frequent hospitalisation[4] and higher mortality[5–7].

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines use frequency of exacerbation and hospitalization to stratify risk and direct treatment for COPD patients and consider exacerbation reduction as a core management goal[1]. Pharmacological therapy[1], pulmonary rehabilitation[8] and influenza vaccination[9] all reduce the exacerbation rate but their impact is modest. The use of remote tele-monitoring to detect exacerbations early is attractive as it might reduce exacerbation duration, severity and the need for hospitalization, a major driver of healthcare costs [10]. To date, most tele-monitoring studies in COPD have monitored symptoms and simple physiological measures, such as heart rate and oxygen saturation, alongside enhanced clinical support[11–15] and only a few included physiological measurements such as peak expiratory flow rate[16]. The outcomes of these studies have been disappointing, with limited evidence of health or economic benefit[12,17]. Moreover, none included objective, effort-independent measurements of pulmonary function.

The Forced Oscillation Technique (FOT) measures the mechanical properties of the lung during tidal breathing in a way that is simple to perform without supervision or effort, is operator independent and can be undertaken at home by COPD patients[18,19]. FOT can also detect changes in lung mechanics acutely after a bronchodilator[20] and during recovery from an exacerbation[21–23], making it a potentially attractive way to objectively define exacerbation events in a telemonitoring programme.

We hypothesised that, in older patients with both COPD and co-morbidities, remote respiratory monitoring using daily FOT measurements, with or without enhanced cardiac monitoring, would reduce the time to first hospitalization (TTFH), increase quality of life and reduce healthcare

costs. To test this hypothesis we conducted the CHROMED (Clinical tRials fOr elderly patients with MultiplE Disease) study, an international randomised controlled trial funded by the European Commission (CHROMED, project ID: 306093).

Methods

CHROMED was a multicentre, randomized unblinded parallel group clinical trial. Patients were recruited at six sites in five countries: Spain, UK, Slovenia, Estonia and Sweden (see ONLINE DATA SUPPLEMENT for details). The study was registered on ClinicalTrials.gov: NCT01960907.

Patients

We recruited patients aged 60 years or older, with a diagnosis of COPD GOLD grade II or higher[24], a history of acute exacerbation with or without hospitalization in the previous 12 months, a smoking history of ≥10 pack/years, and one or more documented non-pulmonary chronic conditions (see ONLINE DATA SUPPLEMENT). These included congestive heart failure (CHF), ischemic heart disease (IHD), hypertension, hyperlipidemia and clinically significant sleep disordered breathing. Patients with significant visual disturbance or mental health disorders that would make them unable to use the monitoring platform, a planned prolonged absence from home, living in areas not covered by a mobile data network or those unable to use the study equipment were excluded. Patients were clinically stable with at least 4 weeks elapsed since their last exacerbation.

All patients provided written informed consent and the protocol was approved by the ethical review boards of participating institutions.

Protocol

At recruitment, we recorded demographic data, measured spirometry before and 15 minutes after inhaling 200 μg salbutamol, and administered the St George's Respiratory Questionnaire

(SGRQ), the COPD Assessment Tool (CAT)[25], the EuroQoL EQ-5D questionnaire[26] and the Patient Health Questionnaire (PHQ-9)[27]. Patients with CHF or IHD also completed the Minnesota Living with Heart Failure Questionnaire (MLHFQ)[28].

Patients were shown how to use the study equipment and then randomized to intervention or control groups (1:1) using a concealed computer generated randomization sequence with a 4 element block design and stratified on a clinical centre basis. The intervention group used the CHROMED monitoring platform for nine months at approximately the same time each day. The platform comprised a device which measured within-breath respiratory mechanical impedance (RESMON PRO DIARY, Restech srl, Milan, Italy) using FOT, a touch-screen computer and a mobile modem. Patients with a diagnosis of CHF used an additional wearable device to assess blood pressure, oxygen saturation, heart rate and body temperature (WristClinic™ Medic4All, Switzerland) over a 4 minute period. FOT measurements were cleaned automatically from artefacts using previously published filtering rules[29] and automatically sent to the study server. An algorithm generated respiratory alerts if a trend of worsening was detected in at least one of the following FOT parameters measured at 5Hz: inspiratory resistance (Rinsp), inspiratory reactance (Xinsp) or the difference between inspiratory and expiratory reactance (ΔXrs), an index of the presence of tidal expiratory flow limitation[30,31]. Specifically, a worsening was deemed to occur when a statistically significant ($p<0.05$) linear increase of Rinsp or ΔXrs or a decrease of Xinsp and a correlation coefficient of at least 0.4 was detected in a time window of ten days including the current measurement (see ONLINE DATA SUPPLEMENT). Additional cardiac alerts were generated if blood pressure and/or heart rate and/or blood oxygen saturation and/or body temperature exceeded specific limits established in the baseline period on at least two consecutive days (see Table E2). Cardiac thresholds were adapted for each patient depending on baseline measurements. Missing FOT data were interpolated if at least 4 non-consecutive FOT measurements in the past 10 days were present. Cardiac measurements were analysed if at least 2 consecutive days of data were present. The alert triggered a contact with the

study nurse to determine the patient's clinical status and whether any intervention was required. After contact, a variety of actions were possible, ranging from no action to taking a course of antibiotics and/or corticosteroids or face-to-face assessment. We did not recommend specific criteria for hospitalisation, this decision being made on clinical grounds by the reviewing physician. Technical alerts were issued if no data were recorded for more than two days. When this occurred, the local site contacted the study patient. Patients in the control group received usual care according to their local practice.

Every three months, all participants were telephoned to establish their use of antibiotic/corticosteroids (moderate COPD exacerbations) and primary care resources, and to complete the EQ-5D questionnaire. Every two months, participants were telephoned and completed the CAT, PHQ-9 and MLHFQ questionnaires. Hospital admissions were identified from clinical records at the end of the trial. A detailed description of the study protocol is provided in the ONLINE DATA SUPPLEMENT.

Study outcomes

The pre-defined co-primary endpoints were TTFH and change in the EQ-5D utility index score. Secondary outcomes included moderate exacerbation rate, hospitalisation, final scores of the CAT, PHQ-9 and MLHFQ questionnaires. A cost-utility analysis was also performed to measure whether the intervention was cost-effective by comparing healthcare costs and quality-adjusted life years (QALYs) in the two groups. Costs were analysed with a healthcare system perspective and included hospital and primary care resources, remote follow-ups and management of medical alarms. Since the platform was still a prototype, the costs of the equipment and technical support could not be included (see ONLINE DATA SUPPLEMENT). We defined re-hospitalisation as any hospital admission that occurred during the study period after the first hospitalization.

Sample size

Two main outcomes were chosen for this study. Assuming that 60% of the study population would not be hospitalized at 9 months[32], a study population of 310 patients was calculated to detect a 25% increase in the TTFH with a type I error risk of 0.05 and a power of 80%. Moreover, using 0.73±0.22 as an estimate of the expected EQ-5D utility score in the study population[26] and anticipating a 10% drop out rate and 5% mortality rate, a sample size of at least 148 patients was needed to evaluate a minimum detectable difference of 15% of the EQ-5D utility score, with the same level of type I error and power used for TTFH.

Statistical analysis

Data are expressed as median and interquartile range (IQR) unless otherwise stated and were analysed by intention-to-treat. Time to first hospitalization used the Kaplan-Maier survival plot. Between-group significance was tested with the logrank test. Rates of prescription of antibiotics/corticosteroids (moderate exacerbations), hospital admissions and re-admission for COPD were calculated assuming a negative binomial distribution with number of events as the outcome, study group as single covariate and the logarithm of time of observation as offset variable[33]. Between-group comparisons are expressed as incidence rate ratios (IRR). We considered a p value below 5% to be significant for the primary outcomes and all other p values to be exploratory if the primary outcomes were negative.

An exploratory subgroup analysis was performed in patients with a potentially higher risk of hospitalization defined by: (1) a diagnosis of CHF and/or IHD, (2) COPD GOLD grade III and IV[24], (3) at least two exacerbations in the year preceding the study, and (4) at least one hospital admission due to a COPD exacerbation in the year before the study.

All statistical analyses were performed by using IBM SPSS Statistics (IBM SPSS, New York, NY, USA). A full description of the methodology used is reported in the ONLINE DATA SUPPLEMENT.

Results

Patients were recruited from Oct 15, 2013 to Jul 3, 2015. Of 326 patients screened, 14 declined to participate due to concerns about the equipment or inability to perform the measurements. A total of 312 patients (75 from UK, 80 from Estonia, 63 from Sweden, 61 from Spain and 33 from Slovenia) were randomized (154 intervention, 158 control). Of those, 109 (71%) in the intervention and 122 (77%) in the control group were successfully monitored for 9 months (Figure 1). Overall, 88% (IQR: 77%-95%) of the expected daily FOT measurements and 93% (IQR: 63%-98%) of the additional cardiac measurements for patients with cardiac co-morbidities were completed.

Baseline demographics

The groups were well matched for anthropometrics, disease severity, prior exacerbations, hospitalizations, co-morbidity and the season they entered the study (Table 1). Enrolled patients had a median age of 71 years, 97% had one or more co-morbidity which were predominantly cardiovascular, 49.7% had moderate, 37.2% severe and 13.1% very severe COPD[24]. All patients had exacerbated in the past year and 60.9% twice or more. Only 41.3% were hospitalized with a COPD exacerbation in the previous year.

Medical alerts

All the patients in the intervention group performed daily FOT measurements and 37 (24%) performed additional daily cardiac assessments. On average, 0.5 (IQR: 0.3–0.9) alerts/patient /month were generated based on FOT parameters, 1.1 (IQR: 0.8–1.4) alerts/patient/month by change in the cardiac parameters. Alerts were followed by a call from the study nurse within 1.4 ± 3.7 days of their generation. In 4039 days out of 36600 days of FOT monitoring (11%) and 1164 days out of 8406 days of cardiac monitoring (14%) the system could not generate any alerts due to missing

measurements. Missing data were primarily due to patient forgetfulness or being in vacation/out of the town (45%), bad coverage of the mobile network preventing a stable data transmission (35%), technical failure of the monitoring equipment (18%) and hospitalization of the patient (3%). In half of the respiratory alerts, patients reported one or more symptom changes, including increased breathlessness (66%), increased cough (42%), loss of energy (35%) and increased wheeze or chest tightness (28%). A similar proportion of cardiac alerts were symptomatic, with breathlessness (15%) and loss of energy (18%) the most frequent problems. Respiratory and cardiac alerts led to a change of treatment or face-to-face visit in 34% and 37% of cases, respectively. Further detail is shown in the ONLINE DATA SUPPLEMENT (Table E1).

Healthcare utilization defined exacerbations

In total, 38 (48%) hospital admissions in the intervention group had an alert in the preceding two weeks, and 21 (27%) were treated by the nurses/clinicians managing the alarm. Mean TTFH was 224 days (IQR: 209-240) in the intervention group and 254 days (IQR: 240-270) in the control group (p=0.342) (Figure 2). There was no difference between groups in the rate of moderate exacerbations (1.74 vs. 1.52, p=0.499), hospitalization (0.79 vs. 0.99, p=0.276) or the number of patients free from hospital admission (71% vs. 74%, p= 0.599) (Figure 3). Compared to control, intervention patients who were hospitalised during the trial (n=41 and 45, respectively) were less than half as likely to be re-hospitalized (IRR 0.46, p=0.017). The average length of hospital stay for all cause hospitalisation was 4.0 (IQR:1.0 - 9.0) days for the control group and 1.0 (IQR:1.0 - 6.7) day for the monitored group (p=0.045). The total days hospitalised in the two groups were 669 days in the control group and 359 in the monitored group. Patients provided with cardiac monitoring, generated 19 (24%) of the recorded hospital admissions.

Quality of life and health status

There were no significant between-group differences in the EQ-5D, CAT, or PHQ-9 scores at 9-month (Table 2) nor did the MLHF questionnaire scores differ in patients with CHF and/or IHD.

Cost effectiveness

There was no statistically significant change in QALYs between intervention and control groups (0.485 vs. 0.491, p=0.731; Table 2). There was a potentially significant reduction in the mean cost per patient in the intervention group compared to the control group (€3547 vs. €4831, p=0.011; Table 2).

Subgroup analysis

There were no significant differences between intervention and control group in the baseline characteristics of the subgroups (Table E4). There was no difference between treatments in TTFH and EQ-5D utility score at 9-months in any subgroup. However, monitored patients previously hospitalized for a COPD exacerbation showed a 53% reduction (p=0.017) in their observed hospitalization rate compared with the control group (Figure 3). There was no difference in QALYs between intervention and control groups in any subgroup. The mean cost per patient in the intervention group was lower than in the control group for all the analysed subgroups except for the subgroup with severe or very severe COPD. The largest differences were seen in patients with a previous hospitalization with COPD (€4147 vs. €6949, p=0.008) and those with cardiac comorbidities (€4237 vs. €6520, p=0.014).

Discussion

This is the first randomised trial to test whether daily tele-monitoring with objective measurements of resting lung function and cardiac variables (where appropriate) can detect COPD exacerbations early and reduce the chance of hospitalisation. Despite the acceptability of the monitoring system to patients, with a high adherence rate, its use did not affect overall TTFH, admission rate or patient's quality of life assessed by EQ5D. However, there was a potential for reduced healthcare costs, mostly due to a 54% decrease in repeat hospital admissions without any increase in other healthcare costs. The cost difference varied between patients, being greatest in those who were hospitalised in the previous year.

Although a few studies have suggested that combining symptoms and physiological variables, such as pulse and oxygen saturation, can identify COPD exacerbations[34], subsequent randomised trials have not shown any effect of monitoring on TTFH and/or patient's quality of life, similar to our findings[11–13,15,16]. However, while other trials recruited previously hospitalised patients, we studied COPD patients reporting two or more exacerbations in the previous year, i.e. a broader group of less severe patients. Although we saw no difference between groups in the time to first hospitalisation (our primary study end point), there was a difference in the mean duration of hospital stay and the total days hospitalised after an emergency admission in favour of the monitored patients. Exacerbation duration is an important determinant of the risk for future exacerbation and disease progression[35] and this may explain why patients who were hospitalised during the trial were significantly less likely to have a further hospitalisation when they were monitored. When we restricted our analysis to patients hospitalised in the year before enrolment, a group at higher risk of subsequent hospitalisation, there was a 53% reduction in hospitalisation rate in monitored patients. This effect on re-hospitalization may relate to the need for a run-in period to maximise the benefit of tele-monitoring or to a reduction in exacerbation severity during the first or subsequent

hospitalisations. This latter effect may result from earlier detection of exacerbations as there is evidence that earlier treatment decreases the duration of exacerbations[36].

We based respiratory alerts on daily measurements of lung mechanics by tidal oscillatory mechanics, thereby automating the system and reducing dependence on the patient's self-reported symptoms[37]. The CHROMED tele-monitoring system detected changes that preceded half the hospitalisations early enough to permit intervention Not all of these alerts identified events considered important by the clinical staff, although some alerts did precede subsequent hospitalisation, even when no extra treatment was given. Our data support other observations on the diversity of time course and response to treatment of COPD exacerbations[38,39].

Patients with COPD were able to perform daily lung function measurements during tidal breathing over an extended period with high adherence rate (88% recordings completed) and low drop out (73% completed the study). The attrition rate was similar between groups and little different to comparable clinical trials performed on similar patients and duration (23%[40], 50%[12] , 22%[11]). As there was no difference between study arms we can hypothesise that the attritions were mostly due to the multiple contacts for collecting questionnaires and the feeling of limitation in freedom to act induced by participating in a clinical trial rather than specific issues related to the monitoring procedures. The number of respiratory alerts per patients was roughly one every two months, a small number compared to other similar telemonitoring trials in which alerts were based on symptoms and/or other variables[11,12,41]. Compared to those studies, the monitoring system based on continuous self-evaluation of lung function by FOT led to neither a major increase in time burden for healthcare personnel nor an increase in drug prescriptions when compared to standard practice, allowing it to be incorporated into a clinical service. Despite being used in a smaller group of patients, the cardiac monitor generated more alerts (1 alert/patient/month instead of the 0.5 alert/patients/month generated by FOT monitoring), similar to other studies[11] that resulted in more changes in therapy. However, the number of hospitalisations in this group of patients was similar to the other patients.

At present, the economic benefit of tele-monitoring in COPD remains unclear [42], reflecting the difficulty in isolating the effects of tele-monitoring from educational interventions[43].It is important to be cautious when interpreting data from a trial whose primary end points were not met as is the case with CHROMED. Nonetheless, applying our pre-specified health economic analysis suggested that there was a reduction in the healthcare costs in the intervention arm, with an average saving of €1712 (27% lower) per patient per year, largely driven by a reduction in hospital costs. Although the additional costs for the hospital to manage the alerts were included in the analysis, the costs of the equipment and technical support were not included, as the CHROMED platform was still a prototype. Equipment and technical support costs tend to differ across countries and are often the result of a negotiation process between hospital and provider according different factors such as volumes. For tele-monitoring to be truly cost-effective the annual cost of equipment and technical support must be less than the annualized difference in costs between intervention and control groups. Using previously published values as an estimate of the yearly costs for installation, training and maintenance (€58)[17] and €53 for broadband contract (estimate from the trial), the system would be cost effective if the annual rental/purchase costs of the equipment were less than €1600 per patient.

Our exploratory subgroup analyses considered patients at greater risk of hospitalization, who might benefit more from tele-monitoring. Previously hospitalised patients showed the largest cost savings exclusive of equipment costs (3736 €/patient/year) suggesting that future studies should target this population. In patients with cardiac disease, there was a similar reduction in hospitalisation though this difference did not reach even notional significance.

Limitations of the study

The size and objective nature of the monitoring system are particular strengths of our study. However we were limited by the lower than expected number of hospitalisation and the variation in the pattern of healthcare between health care systems which precluded our mandating specific interventions in response to an alert. There may have been differences in the threshold for

hospitalization and we did not have an independent study endpoint committee to review the causes of death. Inevitably in a study of this kind both the participants and study team were unblinded to the nature of the intervention. However data about health care resource utilisation was obtained and analysed independently of the clinical study team.

To avoid bias from variation in costs across countries and improve its robustness, the economic evaluation was based on the costs of each intervention in a single country (UK)[44,45]. The actual magnitude of the cost savings should therefore be adjusted when different healthcare systems are considered. Moreover, the costs of the equipment and technical support should be carefully taken into account as and when the prototype platform is marketed. As a relatively small number of patients (24%) used the cardiac monitoring system, we cannot assess the cost effectiveness of this tool.

Conclusions

We found that tele-monitoring of older COPD patients, using forced oscillation methodology together with cardiac monitoring in patients with significant cardiac co-morbidities, was practical, well-tolerated and acceptable. Tele-monitoring did not influence TTFH, or our measure of general health status, the primary study outcomes. However, there were fewer exacerbations in patients with recent hospitalisations and fewer re-admissions in those who were hospitalised, changes which could translate into a health economic gain depending on the costs of any commercialised system. Whether cardiac monitoring in selected patients confers additional benefit is unclear and merits further study. Although ours was a negative clinical trial, it strongly suggests that using objectively defined criteria for clinical deterioration may be of value in COPD patients at risk of hospitalisation and this group should be the focus of future investigations.

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Declaration of interests

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Tables

Table 1 - Baseline characteristics of study patients.

	Control (n=158)	Intervention (n=154)
Gender, Male/Female	105/53	101/53
Age, median (IQR), years	71.0 (65.3, 76.0)	71.0 (66.0, 75.8)
BMI, median (IQR), Kg/m^2	26.9 (23.8, 31.6)	27.7 (24.5, 30.8)
Smoking History, median (IQR), pack/years	40.5 (30.0, 56.0)	40.0 (23.1, 50.0)
FEV1, median (IQR), L	1.32 (0.94, 1.77)	1.26 (0.96, 1.65)
FEV1, median (IQR), %predicted	50.4 (38.0, 63.9)	49.4 (37.1, 59.2)
FVC, median (IQR), L	2.52 (2.08, 3.07)	2.55 (2.01, 3.10)
FVC, median (IQR), %predicted	75.8 (63.0 89.7)	73.8 (61.8, 88.0)
FEV1/FVC, median (IQR), ratio	0.53 (0.42, 0.62)	0.53 (0.39, 0.63)
St. George's Respiratory Questionnaire, median (IQR), total score	50.9 (34.7, 63.4)	46.2 (35.6, 64.3)
No (%) of patient with only one exacerbation in the previous year	59 (37)	63 (41)
No (%) of patient with more than one exacerbation in the previous year	99 (63)	91 (59)
No (%) of patient with one exacerbation in the previous 3 months	66 (42)	50 (32)
No (%) of patient with more than one exacerbation in the previous 3 months	22 (14)	25 (16)
No (%) of patients hospitalized in the previous year	65 (41)	64 (42)
No (%) of patients hospitalized in the previous 3 months	21 (13)	22 (14)
No (%) of patient at GOLD stage (GOLD 2006)		
I	3 (2)	4 (3)
II	76 (48)	72 (47)
III	61 (39)	55 (36)
IV	18 (11)	23 (15)
Season recruited, No (%)		
Spring	8 (5)	7 (5)

Summer	17 (11)	13 (8)
Autumn	78 (49)	78 (51)
Winter	55 (35)	56 (36)
No (%) of patient with the following comorbidities		
Congestive heart failure (CHF)	13 (8)	18 (12)
Ischemic heart disease (IHD)	36 (23)	38 (25)
Congestive heart failure (CHF)+ischemic heart disease (IHD)	21 (13)	19 (12)
Hypertension	108 (68)	111 (72)
Sleep related disordered breathing	10 (6)	17 (11)
Osteoporosis	23 (15)	26 (17)
Hyperlipidaemia	92 (58)	82 (53)
No of comorbidities per patient	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)
Health status and depression questionnaires		
EQ-5D utility score, mean (SD)	0.663 (.225)	0.641 (.224)
EQ-5D VAS, mean (SD)	57.32 (20.72)	58.80 (17.76)
CAT score, mean (SD)	17.75 (8.42)	17.38 (7.87)
PHQ-9 score, mean (SD)	5.97 (5.79)	6.27 (5.69)
MLHF score, mean (SD)	27.82 (17.39)	31.83 (22.14)

Table 2 – Corticosteroids/antibiotics prescription rates, hospitalization and re–hospitalisation rates, cost per patient and health status and depression questionnaire results

All patients	**Control (n=158)**	**Intervention (n=154)**	**p value**
Prescription rate of systemic corticosteroids/antibiotics, events/year	1.515	1.735	0.499
Hospitalization rate, admission/year	0.99	0.79	0.276
No of patients free from hospital admission (%)	117 (74)	109 (71)	0.599
Length of hospitalization, median (IQR), days	4.0 (1.0, 9.0)	1.0 (1.0, 6.7)	0.045
Re-hospitalisation, IRR (95% CI)	0.46 (0.24 – 0.87)		0.017
EQ-5D	(n=153)	(n=150)	
Utility score (9-month), mean (SD)	.640 (.248)	.637 (.225)	0.915
VAS (9-month), mean (SD)	55.75 (21.17)	55.35 (18.46)	0.869
CAT	(n=154)	(n=150)	
Score (8-month), mean (SD)	17.17 (8.33)	16.76 (7.71)	0.665
PHQ-9	(n=155)	(n=150)	
Score (8-month), mean (SD)	6.35 (5.45)	6.71 (5.92)	0.606
MLHF	(n=33)	(n=35)	
Score (8-month), mean (SD)	33.99 (16.94)	34.75 (19.66)	0.887
Cost utility analysis	(n=153)	(n=150)	
QALYs (9-month), mean (SD)	.485 (.142)	.491 (.164)	0.731
Cost per patient (9-month), €, mean (SD)	4831 (10250)	3547 (5038)	0.011
Patients with CHF and/or IHD	**Control (n=70)**	**Intervention (n=75)**	
Prescription rate of systemic corticosteroids/antibiotics, events/year	1.82	2.19	0.499
Hospitalization rate, admission/year	1.40	0.73	0.067
No of patients free from hospital admission (%)	48 (69)	57 (76)	0.418
QALYs (9-month), mean (SD)	0.433 (0.192)	0.430 (0.185)	0.971
Cost per patient (9-month), €, mean (SD)	6520 (12575)	4237 (6154)	0.014
COPD severe and very severe	**Control (n=79)**	**Intervention (n=78)**	
Prescription rate of systemic corticosteroids/antibiotics, events/year	2,07	2,27	0.699
Hospitalization rate, admission/year	1.36	1.16	0.582
No of patients free from hospital admission (%)	52 (66)	48 (62)	0.693
QALYs (9-month), mean (SD)	0.484 (0.176)	0.473 (0.153)	0.68
Cost per patient (9-month), €, mean (SD)	5704 (10717)	4362 (6072)	0.116

Frequent exacerbators	**Control (n=99)**	**Intervention (n=91)**	
Prescription rate of systemic corticosteroids/antibiotics, events/year	2,06	2,22	0.645
Hospitalization rate, admission/year	1.36	0.90	0.133
No of patients free from hospital admission (%)	67 (74)	59 (65)	0.788
QALYs (9-month), mean (SD)	0.457 (0.191)	0.450 (0.145)	0.842
Cost per patient (9-month), €, mean (SD)	5798 (12221)	3847 (5778)	0.010
Hospitalized in the past year	**Control (n=65)**	**Intervention (n=64)**	
Prescription rate of systemic corticosteroids/antibiotics, events/year	1,95	1,72	0.779
Hospitalization rate, admission/year	1.88	0.85	0.017
No of patients free from hospital admission (%)	38 (58)	43 (67)	0.401
QALYs (9-month), mean (SD)	0.428 (0.203)	0.418 (0.172)	0.868
Cost per patient (9-month), €, mean (SD)	6949 (11870)	4147 (6482)	0.008

Figure 1 – CONSORT diagram showing the flow of patients throughout the study and reason for drop out

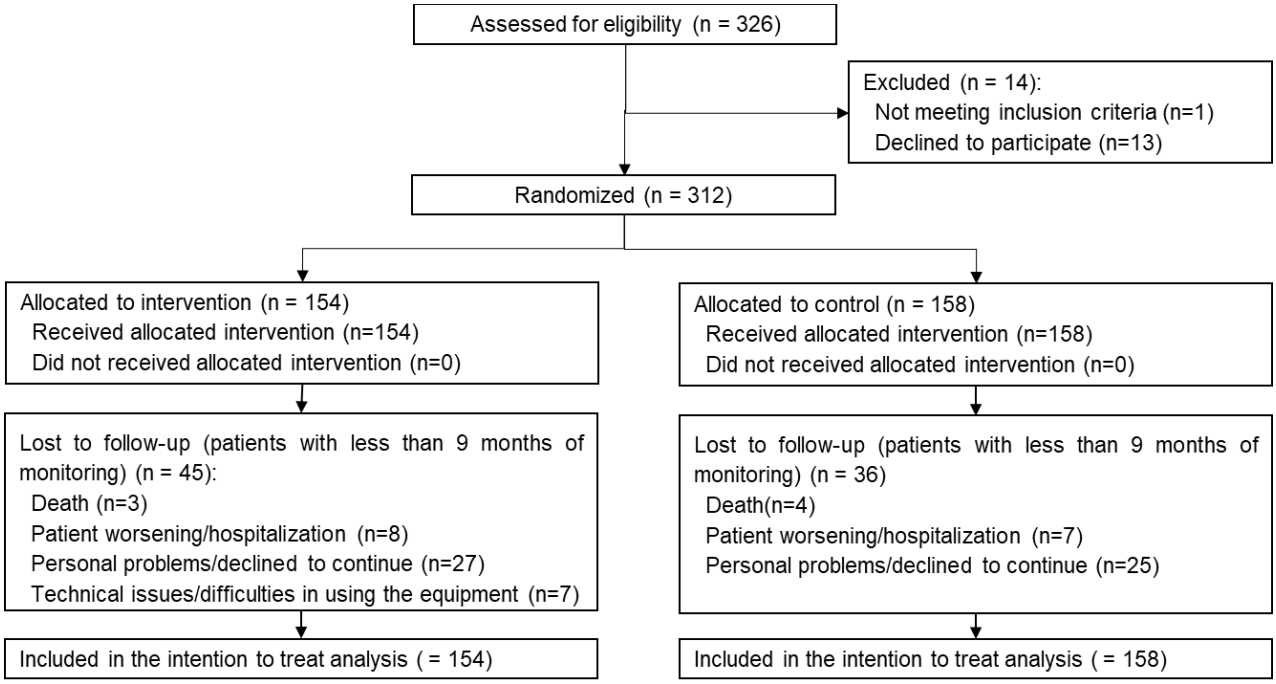
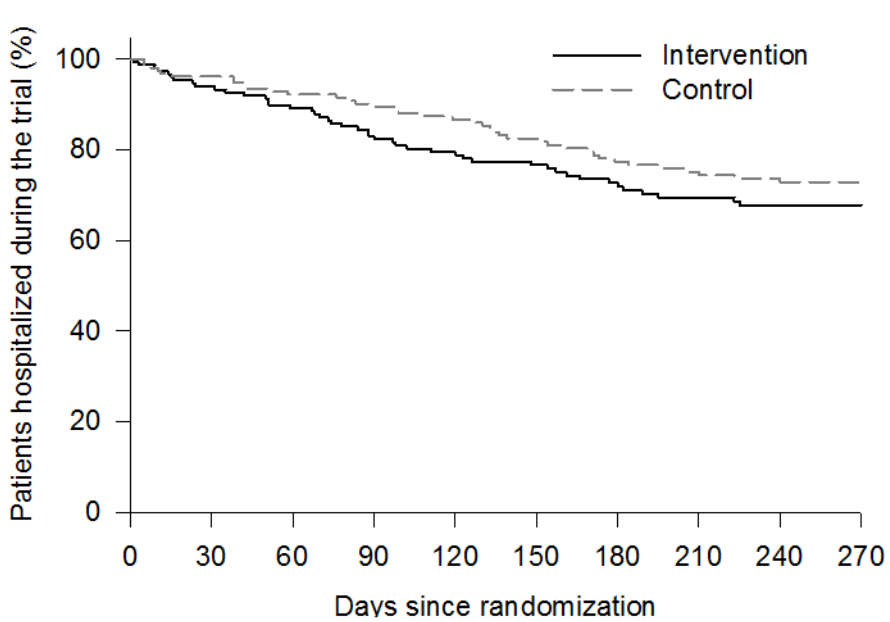


Figure 2 – Time to first hospital admission in control (continuous line) and intervention group (dashed, dark grey line). No significant difference was seen comparing the two groups.



Number of patients:										
Control	158	155	150	147	141	134	132	129	127	122
	100%	*98%*	*95%*	*93%*	*89%*	*85%*	*84%*	*82%*	*80%*	*77%*
Interventional	154	147	147	145	141	135	129	120	113	109
	100%	*95%*	*95%*	*94%*	*92%*	*88%*	*84%*	*78%*	*73%*	*71%*

Figure 3 – Incidence rate ratio (IRR) of hospitalizations (panel A) and systemic corticosteroids/antibiotics prescriptions (panel B) in all patients and exploratory subgroups.