Efficacy and costs of telehealth for the management of COPD: the PROMETE II trial

To the Editor:

Chronic obstructive pulmonary disease (COPD) is a significant and largely underdiagnosed cause of morbidity and mortality worldwide [1]. More long-term survivors with advanced disease have led to an ageing COPD population profile with an increased level of acute exacerbations, hospitalisations and polymorbidity [2].

Attention has been placed on identifying and validating innovative COPD care models, such as telehealth, particularly for high-cost patients with severe COPD and/or frequent acute exacerbations [3]. Early intervention during an exacerbation has been shown to reduce severity, duration and hospitalisation rates, and may lead to a slower decline in lung function and reduced clinical or social care costs [4].

Remote patient monitoring is often a key element of new care programmes as it permits the regular collection of physiological and symptomatic data from patients at home, which can be used to promptly identify exacerbations and initiate treatment [5].

Previously, the PROMETE I study confirmed the practicality of a telehealth intervention for severe COPD patients, and produced directional cost and clinical benefit data [6]. As a development and refinement of this study, the larger and longer PROMETE II project was designed. The primary objective was to reduce the number of COPD exacerbations leading to emergency department visits/hospital admissions with telehealth.

The study design of this second Madrid-based Project on Managing Chronic Obstructive Pulmonary Disease with Remote Patient Management (PROMETE II) study, was a multicentre, nonblind, randomised controlled trial of 12 months duration (figure 1). Patients were recruited in five hospitals, and randomised by block allocation within each centre: HU La Paz, HU La Princesa, Fundación Jiménez Díaz, HU 12 de Octubre and HU Rey Juan Carlos. The study protocol and procedures were approved by the Institutional Review Boards of each hospital, and all patients were required to provide their written informed consent to participate. The trial was registered at www.ClinicalTrials.gov NCT02499068. The research protocol of the PROMETE II trial is available upon request from the authors.

Inclusion criteria for study subjects were: patients aged 50–90 years, diagnosed with COPD [7], with severe airflow obstruction defined as the forced expiratory volume in the first second <50% of the predicted value, treated with chronic home oxygen therapy, and suffering two or more moderate or severe exacerbations in the previous year (with or without hospitalisation), but currently clinically stable (defined as 6 weeks without clinical symptoms since the last COPD exacerbation and separated by ⩾4 weeks after finalising treatment for the previous exacerbation).

Exclusion criteria were standard for COPD telehealth trials.

Our principal objective was to estimate the effectiveness of a home telemonitoring (HTM) strategy in managing patients with severe–very severe COPD when compared to routine clinical practice (RCP). The main variable was changes in the number of severe exacerbations, defined as those resulting in a hospital admission or a visit to the hospital emergency services.

@ERSpublications
In the PROMETE II trial, telehealth did not reduce COPD-related use of health services http://ow.ly/KL7t30jotNb

Cite this article as: Ancochea J, García-Río F, Vázquez-Espinosa E, *et al*. Efficacy and costs of telehealth for the management of COPD: the PROMETE II trial. *Eur Respir J* 2018; 51: 1800354 [https://doi.org/10.1183/13993003.00354-2018].

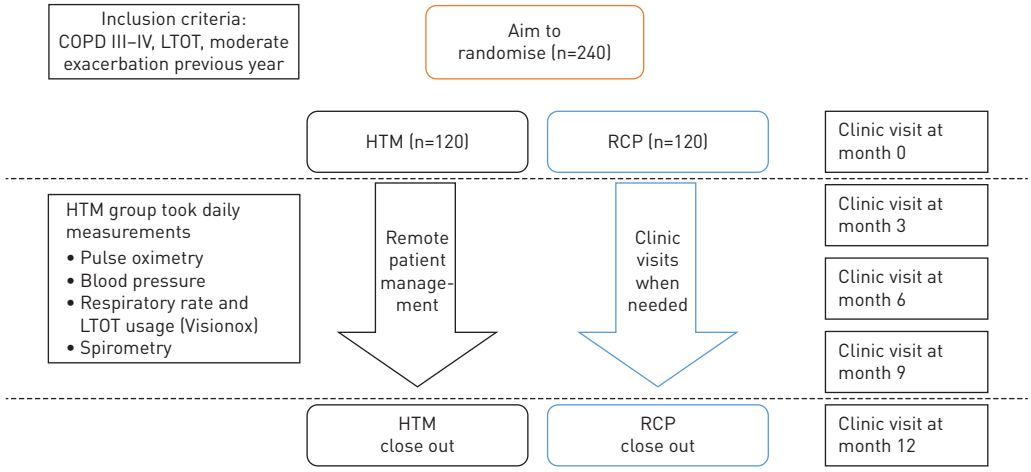

FIGURE 1 PROMETE II trial study design. COPD: chronic obstructive pulmonary disease; LTOT: long-term oxygen therapy; HTM: home telemonitoring; RCP: routine clinical practice.

The remote patient monitoring programme started with a nurse from the monitoring centre (MC) registering the participant in a dedicated data management portal. Once this was completed, the MC scheduled a home visit. The equipment given to each patient was a modem (2Net Hub; Qualcomm Life Inc., San Diego, CA, USA), a pulse oximeter (Onyx II; Nonin, Amsterdam, the Netherlands), a blood pressure gauge (A&D, Tokyo, Japan), a spirometer (Spirotel; MIR, Rome, Italy), and a respiratory rate and oxygen therapy compliance monitor (VisionOx; The Linde Group, Munich, Germany). After the first visit, the participant was given an aide-memoire instruction sheet detailing how to correctly measure the required physiological parameters.

Blood pressure, oxygen saturation, heart rate and spirometry were actively measured by the patient at home as per instructions whilst respiratory rate (and oxygen adherence) data were passively collected by the VisionOx device [8] connected to the oxygen feed from their main oxygen source. The information was sent to secure servers by the 3G modem that was provided free to the patient as part of the study equipment. The patient took measurements at the same time daily, at rest, and after having taken their prescribed medication and with oxygen therapy.

On their first day in the study, patients were required to perform the initial measurements of all the parameters under the supervision of the nursing staff. The values obtained over the first 4 days of the programme were taken as reference values (basal parameters) for each participant and titrated each alert configuration.

The information was received by the MC, which used a triage application to grade into a traffic light system according to severity: red, one or more measurements exceeded the pre-established limits; yellow, the measurements were missing either through not being performed or not being received; and green, all measurements made and within the limits predefined as acceptable.

Following Consolidated Standards of Reporting Trials (CONSORT) guidance [9], a sample size was estimated *a priori* of 240 patients to be recruited in the trial, *i.e.* 120 in each branch, to obtain 108 completers in each arm after 12 months of follow-up. Comparisons between proportions were made using Chi-squared or Fisher's exact tests as appropriate. For selected outcomes, the 95% confidence intervals were calculated. All analyses are presented intention-to-treat, unless otherwise stated. A p-value <0.05 was considered statistically significant.

Overall, 237 COPD patients were recruited, and 229 (96.6%) were randomised to HTM (n=115) or RCP (n=114). Given that only eight (3.4%) of all initially recruited participants were lost, it was considered unnecessary to conduct a CONSORT nonresponse study.

Participants had a mean±SD age of 71±8 years and 80% were men, and all demographic and clinical characteristics were evenly distributed by group, including education level, having a caretaker, modified Medical Research Council dyspnoea score, or number of COPD hospitalisations in the last year (all $p>0.05$).

There were no statistically significant differences in the primary efficacy analysis of the proportion of participants who had a severe exacerbation leading to a hospital admission or a visit to the hospital emergency department over the 12-month period (60% in HTM *versus* 53.5% in RCP, p=0.321) (table 1). Similarly, the mean number of exacerbations over the 12-month period was comparable between

groups (1.1 *versus* 0.9, p=0.1810), as was mean total duration of hospitalisation in the HTM group (18.9±16.1 days) compared to the RCP group (22.4±19.5 days, p=0.308), and time spent in the intensive care unit (6.0±4.6 *versus* 13.3±11.1 days, p=0.3490).

When Kaplan–Meier analysis of time to first exacerbation was performed, like in the primary analysis, these differences were not statistically significant (p=0.4195).

There were no differences by group in anxiety, depression, daily activity, EQ5D or COPD symptoms at 12 months (table 1), or throughout the study follow-up.

At month 12, the number of deaths was comparable between groups (12 *versus* 13). However, when "time to death" was measured in days, on average, participants in the HTM group stayed alive for 240.14 days during the follow-up period compared to those in the RCP group (157.13 days, p=0.2170), which is ~83 days longer.

Meta-analyses have produced conflicting results on the use of telehealth in severe COPD: the Cochrane review of 10 randomised controlled trials concluded telehealth did not significantly improve quality of life but could significantly reduce the risk of emergency department attendance and hospitalisation [10], whereas a more recent meta-analysis of 18 trials found no statistically significant quality of life benefits [11].

The original PROMETE study [6] showed a significant reduction in emergency department visits, hospitalisation, length of stay and mechanical ventilation rates. PROMETE II, as a validation of the first study, was larger and of longer duration. This required multiple recruiting hospitals, which made direct primary care management challenging from a resource and coordination standpoint. Whilst patient demographics and interventions remained comparable between the two studies, the reasons for these inconclusive findings in PROMETE II can only be speculative. Overall, our core results are nearly identical to a number of studies, including that by Pinnock *et al.* [12].

PROMETE II was a pragmatic trial designed as an intervention study to answer the question of effectiveness of telehealth in COPD management in the real world. Our study highlights the limitation of using telehealth as a stand-alone with physiological monitoring in the management of exacerbations of COPD. The main interpretation of our study results is that having only telehealth physiological monitoring of COPD patients will unlikely be of benefit. To date, no physiological measurements taken alone have been shown to assist in early recognition of disease worsening. These physiological changes (decrease in O_2 saturation, increases in respiratory rate, blood pressure, *etc.*) mostly reflect an exacerbation being severe and/or complicated, as opposed to an exacerbation being in an early stage. This consequently

TABLE 1 Primary and secondary end-point analyses

	HTM	RCP	p-value
Participants n	115	114	
Primary end-points			
All participants, ITT			
Participants who had at least one exacerbation[#] in the 12 months	69 (60.0%)	61 (53.5%)	0.321
Exacerbations in the 12 months	1.1±1.13	0.9±1.04	1.181
Only patients who reached month 12, PP			
Participants who had at least one exacerbation[#] in the 12 months	49 (56.3%)	43 (52.4%)	0.612
Exacerbations in the 12 months	1.0±1.13	0.9±1.09	0.472
Secondary end-points			
Duration of hospitalisation days	18.9±16.05	22.4±19.52	0.308
ICU admissions	3 (2.6%)	3 (2.6%)	0.991
Duration of ICU stay days	6.0±4.6	13.3±11.1	0.349
Presence of noninvasive ventilation	15 (13.0%)	16 (14.0%)	0.781
Presence of orotracheal ventilation	2 (1.7%)	3 (2.6%)	0.628
COPD symptoms at 12 months CAT index score	21.5±5.6	21.4±6.1	0.855
Goldberg Anxiety Subscale score at 12 months	0.9±1.9	1.0±2.0	0.911
Goldberg Depression Subscale score at 12 months	1.8±2.21	2.2±2.64	0.316
Daily activity at 12 months Barthel index	95.3±8.4	96.3±9.1	0.460
Quality of life EQ5D index score	0.80±0.2	0.79±0.2	0.895

Data are presented as n (%) or mean±SD, unless otherwise stated. Groups compared by Student's t-test for continuous variables and Chi-squared test for categorical variables. HTM: home telemonitoring; RCP: routine clinical practice; ITT: intention to treat; PP: per protocol; ICU: intensive care unit; COPD: chronic obstructive pulmonary disease; CAT: COPD Assessment Test. [#]: emergency department visit or hospitalisation.

does not permit the patient or healthcare professional to be alerted in time to intervene early and prevent further issues and/or complications such as hospital admissions.

In countries like Spain, where a well-developed health system ensures COPD patients have rapid, effective access to appropriate care, it may well prove challenging to demonstrate that telehealth further improves outcomes.

To conclude, remote patient management using this monitoring protocol in PROMETE II did not reduce the COPD-related ER visits or hospital admissions compared to RCP within 12 months.

Julio Ancochea[1], Francisco García-Río[2,3], Emma Vázquez-Espinosa[1], Ascensión Hernando-Sanz[4], Luis López-Yepes[4], Raúl Galera-Martínez[2,3], Germán Peces-Barba[3,5], Maria Teresa Pérez-Warnisher[3,5], Gonzalo Segrelles-Calvo[6], Celia Zamarro[6], Pablo González-Ponce[7], M. Inmaculata Ramos[8], Jose Ignacio Conforto[8], Syed Jafri[9] and Joan B. Soriano[1,10]

[1]Servicio de Neumología e Instituto de Investigación, Hospital Universitario de la Princesa (IISP), Universidad Autónoma de Madrid, Madrid, Spain. [2]Servicio de Neumología, Hospital Universitario La Paz, Universidad Autónoma de Madrid, Madrid, Spain. [3]Centro de Investigación en Red de Enfermedades Respiratorias, Madrid, Spain. [4]Servicio de Neumología, Hospital 12 de Octubre, Madrid, Spain. [5]Servicio de Neumología, Fundación Jiménez Díaz, Madrid, Spain. [6]Servicio de Neumología, Hospital Universitario Rey Juan Carlos, Móstoles, Spain. [7]Monitoring Centre for Remote Patient Monitoring, Linde Healthcare, Madrid, Spain. [8]Linde Healthcare, Madrid, Spain. [9]The Linde Group, Munich, Germany. [10]Methodological and Scientific Consultant, SEPAR, Spain.

Correspondence: Joan B. Soriano, IISP, Diego de León 62, 28006-Madrid (E), Spain. E-mail: jbsoriano2@gmail.com

This study is registered at www.ClinicalTrials.gov with identifier number NCT02499068.

Received: Dec 02 2017 | Accepted after revision: March 14 2018

Acknowledgements: We would like to thank the following staff from Fundación Teófilo Hernando (Madrid, Spain): Rocío Prieto, María Martínez, David Chong, Begoña Maestro and Arturo García. We would also especially like to thank all the participating patients and their families.

Author Contributions: J. Ancochea, F. García-Río, S. Jafri, M.I. Ramos and J.B. Soriano developed the research protocol; J. Ancochea, F. García-Río, E. Vázquez-Espinosa, A. Hernando-Sanz, L. López-Yepes, R. Galera-Martínez, G. Peces-Barba, M.T. Pérez-Warnisher, G. Segrelles-Calvo, G. Segrelles-Calvo and P. González-Ponce conducted all fieldwork; and all co-authors helped to draft this manuscript and approved its final version. All co-authors fulfil the Vancouver rules for authorship.

Conflict of interest: P. González-Ponce is an employee of Linde Healthcare. M.I. Ramos is an employee of Linde Healthcare. J.I. Conforto is an employee of Linde Healthcare. S. Jafri is an employee of The Linde Group.

Support statement: The study was sponsored by Fundación Teófilo Hernando, Universidad Autónoma de Madrid, with the support of Linde Healthcare. Funding information for this article has been deposited with the Crossref Funder Registry.

References

1 GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Respir Med* 2017; 5: 691–706.
2 MacNee W, Rabinovich RA, Choudhury G. Ageing and the border between health and disease. *Eur Respir J* 2014; 44: 1332–1352.
3 Tuckson RV, Edmunds M, Hodgkins ML. Telehealth. *N Engl J Med* 2017; 377: 1585–1592.
4 Wilkinson TMA, Donaldson GC, Hurst JR, *et al.* Early therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004; 169: 1298–1303.
5 Rabanales-Soto J, Párraga Martínez I, López-Torres J, *et al.* Tecnologías de la información y las comunicaciones: telemedicina. *Rev Clin Med Fam* 2011; 4: 42–48.
6 Segrelles Calvo G, Gómez-Suárez C, Soriano JB, *et al.* A home telehealth program for patients with severe COPD: the PROMETE study. *Respir Med* 2014; 108: 453–462.
7 Miravitlles M, Soler-Cataluna JJ, Calle M, *et al.* Spanish guideline for COPD (GesEPOC). Update 2014. *Arch Bronconeumol* 2014; 50: Suppl. 1, 1–16.
8 Yañez AM, Guerrero D, Pérez R, *et al.* Monitoring breathing rate at home allows early identification of COPD exacerbations. *Chest* 2012; 142: 1524–1519.
9 Begg C, Cho M, Eastwood S, *et al.* Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *JAMA* 1996; 276: 637–639.
10 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: e739–e749.
11 Gregersen TL, Green A, Frausing E, *et al.* Do telemedical interventions improve quality of life in patients with COPD? A systematic review. *Int J Chron Obstruct Pulmon Dis* 2016; 11: 809–822.
12 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.

Copyright ©ERS 2018